Urinary Tract Symptoms: Microbiologic Evaluation In Rural Family Practice

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Abstract: In order to define the etiology of urinary symptoms in rural family practice, this study examines 106 patients (88 women, 18 men) who went to their family physicians in private practice or a resident-faculty practice with genitourinary symptoms. Evaluation of each patient included history, physical examination, urinalysis, and urine or cervical cultures for bacteria, *Mycoplasma*, and *Chlamydia*. Using agar plate culturing techniques, 37 patients (35 percent) were identified as having significant urine bacteria. *Chlamydia* was rarely associated with urinary tract symptoms. *Mycoplasma hominis*, however, was isolated and felt to be etiologic in 19 (22 percent) of the 88 symptomatic women ($P = 0.0026$). Older women (mean age 42 years, $P < 0.001$) with > 5 white blood cells per high-power field (WBC/hpf) on microscopic urinalysis ($P < 0.001$) were likely to have cystitis and significant bacteria on urine culture. Younger women (mean age 31 years, $P < 0.001$) with < 5 WBC/hpf ($P < 0.001$) had negative urine cultures and were likely to have *M. hominis* as a pathogen. These results demonstrate that the etiology of genitourinary symptoms seen in rural family practice may vary substantially from those seen in other patient care settings. (JABFP 1988; 1:39-45.)

Despite intensive investigation over the past 20 years, the etiology of genitourinary symptoms in patients seen in primary care settings remains only partially defined. Early studies established that the majority of patients with urinary tract infections were women: more than half of their urine cultures were negative, and no etiology could be found.[1-3]

Subsequent investigators demonstrated that vaginal infections were a substantial cause of urinary symptoms.[4,5] Low ($> 10^2$) colony forming unit/mL (cfu/mL) bacterial count, *Staphylococcus saprophyticus*, and *Chlamydia* have also been implicated as pathogens.[6,7] A recent comprehensive and sophisticated evaluation at the University of Washington clearly established that the etiology of urinary tract symptoms in women examined by their family physician varies dramatically from those seen in other ambulatory settings.[8]

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We designed this study to evaluate urinary symptoms among men and women patients in a rural family practice setting with the following three goals in mind:

1. To establish the etiology of urinary tract symptoms by using an in-depth history, physical examination, urinalysis, routine urine culture, and *Chlamydia* and *Mycoplasma* culturing.
2. To evaluate the family physician's ability to diagnose accurately urinary pathogens based on history, physical exam, and office-based laboratory testing.
3. To compare study results collected in the private practice setting with results collected in a family practice residency program.

At the outset, it should be recognized that some subsets of the population, i.e., symptomatic men, are sufficiently small so that generalizations are risky.

Methods

Study Practices

Family physicians from six group practices evaluated patients who came to their offices in Middle-

Table 1. *Characteristics of Female Etiologic Groups.*

	Cystitis Group	*Mycoplasma hominis*-Associated Group
Age (mean)*	42.3 years	31.5 years
Symptoms	(Percent)	(Percent)
Dysuria	84.3	66.7
Frequency†	93.4	64.6
Urgency	72.3	63.2
Nocturia	48.3	43.0
Vaginal burning	37.5	40.0
Cloudy/bloody urine	45.4	36.7
Unusual odor of urine	12.7	21.3
Flank pain	21.2	21.5
Urethral discharge	3.6	17.1
History of previous UTI†	72.8	50.0
"I think I have UTI"	72.1	54.0
Urine microscopic WBC/hpf†		
0–5	29.0	75.3
6–10	22.1	3.7
10–TNTC	3.4	5.7
TNTC	45.3	15.2

*Significantly different (t-test) for cystitis group versus *Mycoplasma hominis*-associated group, $P < 0.001$.

†Significantly different (chi-square) for cystitis group versus *Mycoplasma hominis*-associated group: for frequency, $\chi^2 = 3.99$, $P < 0.05$; for Hx of previous UTI, $\chi^2 = 4.7$, $P < 0.05$; for > 5WBC/hpf versus < 5WBC/hpf, $\chi^2 = 17.69$, $P < 0.001$.

sex County, Connecticut. These rural practices were located in towns with populations of 8,000 to 20,000; each practice consisted of two or three full-time family physicians in active clinical practice. Two resident-faculty office practices from the Middlesex Memorial Hospital Family Practice Residency Program were also enrolled. The hospital is a 400-bed community hospital serving Middlesex County, Connecticut, and sponsoring the residency program with 18 resident physicians and five full-time supervising family physician faculty.

Study Protocol

Symptomatic Patients

Each patient, regardless of age or sex, with one or more of the genitourinary symptoms listed in Table 1 was evaluated using a standardized approach, which included history, physical examination, routine urinalysis, cultures of uropathogens, and a clinical impression. Patients were excluded if any of the following conditions were present: indwelling urinary catheter, anatomic abnormality of the urinary tract, or chronic suppressive therapy for urinary tract infections. Upon presentation to the physician's office, the patient's initial symptoms were recorded by the receptionist or office nurse, and the physician completed the data collection form.

Clean-catch midstream urine specimens were collected from each patient. Nurses inoculated urine cultures on McConkey and blood agar plates and two dip-slide culture tubes (Uricult™). The dip-slides were immersed into the urine; the agar plates were inoculated using sterile disposable 0.01 mL inoculating loops.

After inoculation, the dip-slide culture tubes and one set of agar plates were incubated in the office incubator at 37°C. The agar plate cultures were read and quantified at the Microbiology Division of the University of Connecticut School of Medicine 24 hours after collection. Bacterial isolates were identified by standard methodology.

One of the dip-slide culture tubes from each patient was read the next day by the office physician; the second dip-slide was interpreted by a control physician, who had no knowledge of the first physician's reading or of the patient's complaints, physical findings, or urinalysis results.

Office physicians performed microscopic urinalysis on the centrifuged, clean-catch specimens and recorded the number of white blood cells per high-power field (WBC/hpf). Each physician also

completed potassium hydroxide (KOH) and hanging drop microscopic examinations for *Candida* and *Trichomonas* when clinically indicated. On the basis of the presenting complaints, physical findings, and results of microscopic examination, physicians recorded a clinical impression before culture results were available. The authors recognize that a KOH preparation is not definitive for vaginal candidiasis. However, this was the standard practice in these office settings.

Physicians obtained cultures for *Chlamydia* and *Mycoplasma* from the genitourinary epithelium during the physical examination, which included pelvic examination for women and rectal examination for men. Cultures were taken from the cervix and periurethral area of women and from the distal urethra of men. These specimens were inoculated into holding media, placed immediately on ice, transported to Middlesex Memorial Hospital, and placed in a −70°C freezer within two and one-half hours of collection.

On the following day, the *Mycoplasma* and *Chlamydia* cultures were shipped on dry ice to the Microbiology Division for incubation on specific culture media. *Chlamydia* were grown on hexosamide-treated McCoy cells. *Mycoplasma* were grown on solid and liquid phase growth media; positive cultures were interpreted as either *Ureaplasma urealyticum* or *Mycoplasma hominis*.

Asymptomatic Patients

A second group of patients (n = 20) who were asymptomatic (reporting for routine examinations) were evaluated in an identical manner. These patients had no urinary tract symptoms within six months, no evidence of vaginitis, had not taken antibiotics within 14 days, were not pregnant, and had an age/sex profile similar to the symptomatic patients.[7]

Diagnostic Criteria

Urinary Tract Infection

In women who were symptomatic, cystitis was defined as $> 10^2$ cfu/mL growth of a bacterium felt to be pathogenic. For men who were symptomatic, $> 10^5$ cfu/mL colony count was required.

In both cases, cultures were obtained using a clean-catch midstream specimen. None of the patients was catheterized. Colony count and organism identification were determined by the Microbiology Division at the University of Connecticut using the blood and McConkey agar plates. Results obtained using the dip-slide culture tube method were collected for comparison purposes.

Prostatitis

Symptomatic men were diagnosed as having prostatitis if they had findings specific to the prostate on physical examinations. In order to diagnose prostatitis, both tenderness and bogginess of the prostate needed to be present.

Abnormal Vaginal Examination (Vaginitis, etc.)

Women who were symptomatic were diagnosed as having an abnormal vaginal exam if any of the following were present: (1) *Candida*—vaginal secretions positive for yeast using standard potassium hydroxide preparation and microscopic examination; (2) Trichomonal vaginitis—vaginal secretions positive for *Trichomonas* using standard microscopic examination; (3) Cervicitis—clinical findings of inflammation and/or cervical discharge; (4) Vulvitis—clinical diagnoses based on physical examination findings of redness and tenderness in the vulvar area; (5) Nonspecific vaginitis (vaginosis)—abnormal, characteristically smelly, vaginal discharge associated with vaginal irritation. In addition, "clue" cells identified on microscopic examination were noted, if seen, but were not necessary in order to make the diagnosis; (6) Abnormal vaginal discharge—this finding was recorded if an abnormal vaginal discharge was seen without the presence of vaginal irritation. Smears of the vaginal discharge were negative for yeast and *Trichomonas* using microscopic examination.

Results

Demographics

Over the nine-month-study period, physicians examined and cultured 106 patients (88 women and 18 men) with genitourinary symptoms. Average age for all patients was 34.2 years. Average age for men was 39.8 years, and for the women it was 33.1 years. Forty-five percent of the symptomatic group reported that they were currently married; 29 percent had never been married. Sixty (56 percent) of the 106 symptomatic patients were from the private practice setting, and 46 (44 percent) were from the resident-faculty practice setting.

Table 2. *Findings Associated with Acute Genitourinary Syndromes in Women (n = 104).*

	Symptomatic (n = 88)			Asymptomatic
	Abnormal Vaginal Exam n = 34*	Cystitis > 10^2, n = 28	Negative Bacterial Culture Negative Physical Exam n = 26	n = 16
Voided urine > 10^2 bacteria on agar plates (n = 35)	7	28	0	0
Genitourinary cultures				
Chlamydia trachomatis (n = 2)	0	0	1	1
Ureaplasma urealyticum (n = 47)	19	8	7	7
M. hominis† (n = 20)	8	2	1	1

*Eleven monilial vaginitis, 10 abnormal vaginal discharge, nine nonspecific vaginosis, one trichomonas vaginitis, two cervicitis, one vulvitis.

†Significantly different (Fisher's exact test): for entire asymptomatic group (n = 20) versus entire symptomatic group (n = 106), $P = 0.0097$; for asymptomatic women (n = 16) versus women with negative physical exam and negative bacterial culture (n = 26), $P = 0.0026$; for women with nonspecific vaginosis and *M. hominis* versus *Candida* or *Trichomonas vaginalis*, $P = 0.0043$.

Average age for the 20 patients in the asymptomatic group (16 women, four men) was 37.2 years. Fifty-two percent of the asymptomatic group were currently married, and 20 percent had never been married.

Genitourinary Examination Findings

Thirty-four (38 percent) of the women with genitourinary symptoms were found to have abnormal vaginal findings (Table 2). Seven of these 34 women (20 percent) also had a positive culture for significant (> 10^2 cfu/mL) urine bacteria. Five of the 18 men with genitourinary symptoms were found to have prostatitis. Eleven had negative physical examinations and negative urine bacterial cultures (Table 2). The relatively few (18) symptomatic men in this study prompted us to exclude them from data summaries (Tables 1 and 2).

Agar Plate Bacterial Cultures

Of the total 106 symptomatic patients (both men and women), 37 (35 percent) were positive for significant urine bacteria using agar plate culturing techniques. Two of these 37 patients were men, and they grew > 1×10^5 cfu/mL. The remaining 35 women grew the following colony counts: 24 had > 1×10^5 cfu/mL, two had 5×10^4 cfu/mL, two had 2.5×10^4 cfu/mL, three had 1×10^4 cfu/mL, three had 2.5×10^3 cfu/mL, and one had 1×10^3 cfu/mL.

The laboratory identified *Escherichia coli* as the responsible organism in 80 percent of the positive cultures. Remaining positive cultures were interpreted as *Klebsiella* (six percent), *Proteus* (six percent), and *Staphylococcus saprophyticus* (six percent).

Dip-Slide (Uricult™) Cultures

Using the agar plate interpretations as the standard, family physicians utilized dip-slides to differentiate between positive and negative urine cultures ($\chi^2 = 34.8$; $P < 0.001$). Sensitivity was 90 percent, specificity 83 percent; predictive positive value was 64 percent, and negative predictive value equaled 96 percent. Compared to results of the laboratory-read agar plates, physicians correctly identified the responsible organism in 85 percent of the patients. *Klebsiella* was misread once by the family physicians as *E. coli*. *Staphylococcus saprophyticus* was misread once as enterococcus. *Proteus* was misinterpreted twice as a contaminated specimen.

The office physicians' ability to differentiate positive from negative dip-slide cultures compared favorably with the dip-slide cultures interpreted by the control physicians of the study group ($\chi^2 = 65.5$, $P < 0.001$). Sensitivity was 93 percent, specificity 83 percent; predictive positive value was 93 percent, and predictive negative value was 96 percent. Of considerable clinical interest, five patient cultures read by the laboratory as negative or skin contaminants on the agar

plates were read as $> 1 \times 10^5$ cfu/mL independently by both the family physician seeing that particular patient and the control physician reading the dip-slide at the research center.

Mycoplasma *and* Chlamydia *Cultures*

As shown in Table 2, *Ureaplasma urealyticum* (a *Mycoplasma* species) was present in symptomatic (45 percent) and asymptomatic (43 percent) women at approximately equal rates. *Chlamydia* was isolated rarely in either asymptomatic or symptomatic women. The laboratory identified *M. hominis* at statistically higher rates (Table 2) in these two symptomatic groups, compared to the respective asymptomatic group.

The distribution of *M. hominis* among women with abnormal vaginal findings (Table 2) is also of interest. *Ureaplasma urealyticum* was found to be randomly distributed through all diagnostic groups (*Candida*, trichomonal, nonspecific vaginitis), whereas seven of the eight *M. hominis* cultures were found in women with abnormal vaginal discharge or nonspecific vaginitis.

Thus, *M. hominis* was statistically more frequent among those with nonspecific vaginosis and abnormal vaginal discharge than with other vaginal diagnoses (Table 2). *M. hominis* was also significantly more common in symptomatic women with negative genitourinary exams and negative urine bacterial cultures than in asymptomatic women (Table 2).

In vitro laboratory testing indicated that the *M. hominis* isolated from symptomatic patients was sensitive to erythromycin and tetracycline and resistant to ampicillin, gentamicin, cephalosporins, metronidazole, and trimethoprim sulphamethoxazole.

Considering *Ureaplasma urealyticum* to be nonpathogenic, Table 1 relates the characteristics of the two etiologic groups generated by the results of this study. Mean age for cystitis group (42.3 years) is significantly older than the *M. hominis* group (31.5 years). Although women in the *M. hominis*-associated group tended to be single more frequently than the cystitis group, marital status was not significantly different. Women in the *M. hominis* group tended to have more negative responses (Table 1) to historical items, "frequency," and "history of previous urinary tract infection."

The two etiologic groups can also be distinguished (Table 1) on the basis of WBC/hpf on urine microscopic findings, which was completed by the office physicians. In particular, when testing for 0 to 10 WBC/hpf versus > 10 WBC/hpf, there is a significant difference between the groups ($\chi^2 = 7.34$, $P < 0.01$). Furthermore, for 0 to 5 WBC/hpf versus > 5 WBC/hpf, the groups are also different at a higher degree of significance ($\chi^2 = 17.69$, $P < 0.001$). Considering specificity, sensitivity, and predictive values, the 0 to 5 WBC/hpf versus > 5 WBC/hpf scheme better differentiates between the two etiologic groupings. In particular, for the 0 to 5 WBC/hpf versus > 5 WBC/hpf, sensitivity for predicting the *M. hominis*–associated group is 75 percent; the specificity is 71 percent; the predictive positive value is 83 percent, and the predictive negative value is 61 percent.

Physicians' Clinical Impressions

Physicians' clinical impressions (i.e., predicting a positive or negative culture), based on presenting symptoms, physical findings, and microscopic urinalysis, were highly correlated with ($\chi^2 = 21.4$, $P < 0.001$) a subsequent positive agar plate bacterial culture. Sensitivity was 92 percent, specificity 54 percent, predictive positive value was 51 percent, predictive negative value was 91 percent. Physicians were unable, however, consistently to predict the subsequent isolation of *Ureaplasma urealyticum*, *M. hominis*, or *Chlamydia*.

Residency Versus Private Practice Settings

No differences were noted for resident-faculty office practices versus private practice settings. In particular, the demographics, genitourinary examination findings, bacterial culture results, *Mycoplasma* or *Chlamydia* culture results, or physicians' clinical impressions were not found to be different between these two groups.

Discussion

From several vantage points, limitations in this study abound. In particular, the private practices and resident-faculty offices that were used as study practices are dedicated primarily to daily patient care, not to clinical research. Physicians and office staff conscientiously completed the study protocol amid their busy office practices. These factors limited total number of patients studied and analysis of some patient subgroups (i.e., men and residency versus private practice patient

groups). Additionally, transporting and handling (rapid specimen retrieval, freezing at −70°C) the *Mycoplasma* and *Chlamydia* cultures were technically cumbersome in our rural setting. Perhaps, a multicenter study (using several rural locales with cooperative study practices, community hospitals, and university hospitals) could generate larger patient numbers.

As documented in several previous studies, vaginal or cervical infection is a common cause of urinary symptoms in our study. The demographic characteristics, presenting signs and symptoms, physical findings, routine urinalyses, and standard bacterial culture results of this study are comparable to those reported in other studies conducted in a family practice setting.

Mond and coworkers noted that among symptomatic patients attending a general practice clinic, married women were four times more likely than single women to have significant bacteria on routine culture.[1] Similarly, older women in our study tended to have significant bacterial growth. The predictability of culturing significant bacteria based on a larger number of WBC/hpf on microscopic urinalysis is demonstrated in our study and others.[1,3,4]

Several investigators have shown that the dip-slide culture is highly accurate for colony count and organism identification.[9-12] Using dual and independent readings of the dip-slides, we have affirmed these findings and also have identified five patients with $> 1 \times 10^5$ cfu/mL bacteriuria that were read as negative on the McConkey and blood agar plates. Previous U.S. studies of symptomatic patients used a hospital laboratory as the source of bacterial colony count and organism identification. This study details the accuracy of U.S. physicians' interpretations of urine cultures on a day-to-day basis in their office practices using dip-slides.

When *Chlamydia* is considered as a possible pathogen in our study, three Seattle studies are relevant. Stamm, et al. and coworkers isolated *Chlamydia* in both symptomatic and asymptomatic patients and found this organism to be more common among the symptomatic group.[7] Brunham and colleagues, studying cervicitis in a venereal disease clinic, isolated *Chlamydia* frequently.[13] Conversely, we have noted few *Chlamydia* in either symptomatic or asymptomatic men or women, and Berg, et al. found *Chlamydia* to be an infrequent cause of urinary symptoms in the outpatient unit of the Family Practice Residency, University of Washington.[8] *Chlamydia* frequently causes urinary tract symptoms in some ambulatory settings, but apparently it is not seen frequently in family practice settings.

It should be noted that we cultured all patients entering the study regardless of clinical findings; Stamm, et al. excluded those with vaginal infection from his study group.[7] As Brunham, et al. found *Chlamydia* frequently among Seattle women with cervicitis and urethral syndrome, we frequently isolated *M. hominis* from cervical and periurethral areas among symptomatic women in rural Connecticut.[13] *Gardnerella vaginalis* has been demonstrated to be associated with vaginosis in a family practice setting; Berg, et al. did not culture patients for *M. hominis* or *Ureaplasma urealyticum*.[8] Our study isolated *M. hominis* frequently in patients with nonspecific vaginosis.

When reviewing *Mycoplasma* species as possible pathogens in other studies, Stamm, et al. found both *M. hominis* and *Ureaplasma urealyticum* commonly among both symptomatic and asymptomatic college students.[7] Our study documents that *M. hominis* is strongly associated with young symptomatic women in these rural family practices.

The clinical implication of this finding is that symptomatic women may be divided into one of two etiologic groups based on age and urine microscopic findings (Table 1). Antibiotic therapy for women in the *M. hominis*-associated group should be either erythromycin or tetracycline, since other antibiotics are not effective against *M. hominis*. Women in the cystitis group can be treated with a number of antibiotics, including ampicillin or trimethoprim sulfamethoxazole.

In conclusion, this study demonstrates that the etiology of genitourinary symptoms in rural family practices may differ substantially from the etiology in other patient care settings. Specifically, we have implicated *M. hominis* as a genitourinary pathogen among younger women patients with minimal pyuria. Further primary care studies in ambulatory settings should evaluate additional culturing and identification techniques and the effectiveness of therapeutic strategies based on etiology and patient characteristics.

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References

1. Mond NC, Percival A, Williams JD, Brumfist W. Presentation, diagnosis and treatment of urinary-tract infection in general practice. Lancet 1965; 1:514-9.
2. Gallagher DJA, Montgomerie JZ, North JDK. Acute infections of the urinary tract and the urethral syndrome in general practice. Br Med J 1965; 1:622-6.
3. Brooks D, Maudar A. Pathogenesis of the urethral syndrome in women and its diagnosis in general practice. Lancet 1972; 2:893-8.
4. Komaroff AL, Pass TM, McCue JD, Cohen AB, Hendricks TM, Friedland G. Management strategies for urinary and vaginal infections. Arch Intern Med 1978; 138:1069-73.
5. McCue JD, Komaroff AL, Pass TM, Cohen AB, Friedland G. Strategies for diagnosing vaginitis. J Fam Pract 1979; 9:395-402.
6. Stamm WE, Counts GW, Running KP, Fihn S, Turck M, Holmes KK. Diagnosis of coliform infections in acutely dysuric women. N Engl J Med 1982; 307:463-8.
7. Stamm WE, Wagner KF, Amsel R, et al. Causes of the acute urethral syndrome in women. N Engl J Med 1980; 303:409-15.
8. Berg AO, Heidrich FE, Fihn SD, et al. Establishing the cause of genitourinary symptoms in women in a family practice. JAMA 1984; 251: 620-5.
9. Maskell R. A controlled trial of the use of dip slides in general practice for the diagnosis of urinary infection. J Clin Pathol 1973; 26:181-3.
10. McDonald PJ, Furness ET, Beasley NV. Dip-slide diagnosis of urinary tract infection. Med J of Aust 1972; 1:20-3.
11. Ellner PD, Papachristos T. Detection of bacteriuria by dip-slide. Routine use in a large general hospital. Am J Clin Pathol 1975; 63:516-21.
12. Bailey MJ, Neary JTF, Notelovitz M. The Uricult dip-slide in significant bacteriuria. S Afr Med J 1972; 46:1323-6.
13. Brunham RC, Paavonen J, Stevens CE, et al. Mucopurulent cervicitis—the ignored counterpart in women of urethritis in men. N Engl J Med 1984; 311:1-6.