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No pathogen-specific sign or symptom predicts the etiology of monomicrobial nongonococcal urethritis in men

Stephen J. Jordan[1,2], **Evelyn Toh**[2], **James A. Williams**[1], **Lora Fortenberry**[2], **Michelle LaPradd**[3], **John D. Ryan**[2], **David E. Nelson**[2], **Teresa A. Batteiger**[1]

[1]Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

[2]Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, Indiana

[3]Department of Biostatistics, Richard M. Fairbanks School of Public Health, Indianapolis, Indiana

Abstract

Identifying pathogen-specific signs or symptoms of nongonococcal urethritis (NGU) could improve syndromic management accuracy. We evaluated NGU signs and symptoms in 220 men with single-pathogen infections (*Chlamydia trachomatis*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, or *Ureaplasma urealyticum*) or idiopathic urethritis. No individual sign or symptom accurately predicted the infectious etiology.

Summary:

We evaluated whether pathogen-specific signs and symptoms could inform pathogen-directed NGU treatment in men. No sign or symptom reliably differentiated infection with any NGU-associated pathogen. Pathogen-directed treatment will require point-of-care molecular tests.

Keywords

Nongonococcal urethritis; pathogen-specific treatment; signs; symptoms; syndromic management

Introduction

Nongonococcal urethritis (NGU) is a common diagnosis in men. NGU is strongly associated with *Chlamydia trachomatis* (CT) and *Mycoplasma genitalium* (MG) and may be associated with *Trichomonas vaginalis* (TV) and *Ureaplasma urealyticum* (UU).[1] Frequently, no infectious agent is identified in men with NGU; this has been termed idiopathic urethritis (IU).[2] NGU is diagnosed by documenting objective evidence of urethritis (Gram stain of urethral secretions with an increase in polymorphonuclear leukocytes per high-power field [PMN/HPF], the presence of PMN in urine, or discharge on physical exam) and excluding the presence of Gram-negative intracellular diplococci.[3] The CDC-recommended test for

[#]**Corresponding Author**: Teresa A. Batteiger, Emerson Hall, Suite 421, 545 N. Barnhill Drive, Indianapolis, Indiana 46202-5124. Phone: 1 (317) 274-8115. Fax: 1 (317) 274-1587. tbatteig@iu.edu.

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identifying NGU-associated pathogens is the use of nucleic acid amplification tests (NAAT).[4] However, NAAT results may be delayed hours to days, and no FDA-approved point-of-care (POC) assay currently exists to guide same-visit treatment decisions.

The standard clinical approach to NGU combines syndromic management with empiric antimicrobial treatment. Syndromic management of NGU involves evaluation for urethritis signs (e.g., discharge and/or meatal erythema) and symptoms (discharge, dysuria, urethral tingling/burning, etc.). Once NGU is confirmed by physical examination and/or Gram stain, empiric NGU treatment is initiated with first-line antibiotic regimens (azithromycin or doxycycline) while awaiting pathogen confirmation by NAAT testing.[3]

First-line NGU treatment regimens are ineffective against some NGU-associated pathogens including TV and macrolide-resistant MG. In the absence of pathogen-specific treatment facilitated by POC diagnostic assays, an alternative approach might be the identification of pathogen-specific signs and/or symptoms. A limited number of studies have examined the association between the signs or symptoms of urethritis and NGU-associated pathogens and have provided inconsistent results.[5–7] To explore further the possible associations between specific signs and symptoms and specific NGU pathogens, we identified symptomatic men with documented monomicrobial NGU or idiopathic urethritis and collected detailed signs and symptoms data. Our objective was to assess if the presence of any sign or symptom was significantly associated with a specific NGU pathogen.

Materials and Methods

The study population was symptomatic men ≥18 years of age who presented to the Marion County Public Health Department (MCPHD) Bell Flower STD Clinic in Indianapolis, Indiana, and enrolled in the Idiopathic Urethritis Men's Project (IUMP) study.[8, 9] The study was approved by the Indiana University-Purdue University Indianapolis (IUPUI) Institutional Review Board and MCPHD. Men with symptomatic NGU (>5PMN/HPF without evidence of Gram-negative intracellular diplococci) were identified and referred for study. After written consent was obtained, a physical exam was performed, and a first-catch urine specimen was collected for detection of NG, CT, MG, TV and UU by NAAT. NGU was defined as ≥5 PMN/HPF on Gram stain of urethral secretions and/or the presence of a urethral discharge. Men were asked if they had specific urethritis symptoms including discharge, dysuria, burning/tingling, itching, lesions, and meatal erythema. We also collected demographic and sexual behavioral data. Men who tested negative for all five pathogens were classified as having idiopathic urethritis (IU). For this analysis, we excluded the following: NAAT+ for *N. gonorrhoeae*, indeterminate NAAT result, or >1 pathogen detected. Men with NGU were treated with azithromycin 1gm once orally. The frequencies of the observed signs and symptoms were compared using the Chi-square test or Fisher's exact test. A *P*-value <0.05 was considered statistically significant. Only groups with N≥5 were evaluated. All analyses were performed using SAS® version 9.3.

Results

Two hundred twenty men enrolled in the IUMP from August 4, 2016, to July 25, 2019, and were included in this analysis (Table 1). The median age was 28 years (range 18–64), 66% were African American, 91% were non-Hispanic, and 85% identified as heterosexual. Eighty-five percent (N=188) reported symptoms of urethritis as their reason for clinic attendance. The most common urethritis symptom that resulted in clinic attendance was discharge (87%, N=192), followed by burning/tingling (38%, N=83), and dysuria (31%, N=68). Itching, meatal erythema, and lesions were rarely reported or observed. On physical examination, 89% were circumcised (N=195), 96% (N=212) had discharge, and 7% (N=16) had meatal erythema.

Of the 220 men, 81(37%) had CT, 39 (18%) had MG, 10 (5%) had TV, and 20 (9%) had UU; 70 (32%) men had IU. We stratified the men into four different monomicrobial groups and an IU group and assessed whether specific urethritis symptoms (discharge, dysuria, burning/tingling, lesions, or itching), urethritis signs (discharge or meatal erythema), or discharge characteristics (severity and color) were differentially associated with any of the groups. We excluded the symptoms of meatal erythema and lesions/other due to an insufficient number of observations. The most common pathogen-stratified symptom in men with urethritis was discharge, followed by dysuria, burning/tingling, and itching (Figure 1A). On exam, urethral discharge was very common (range: 90–100% across the five groups), while meatal erythema was much rarer (5–15%) (Figure 1B). The most common discharge quantity was “small” (44–70%), followed by “minimal” (6–44%), and then “moderate” (11–33%) (Figure 1C). “Copious” discharge was rarely observed (0–8%). The most commonly reported discharge color was clear/colorless (67–81%), followed by white (10–23%), and then yellow (0–10%).

Comparing these five NGU groups, no statistically significant differences were identified in the relative frequencies of patient-reported urethritis symptoms. Additionally, in men with urethral discharge on exam, no pathogen-specific differences in discharge amount or color were identified.

Discussion

Our study objective was to assess whether pathogen-specific signs and/or symptoms of NGU could be identified in symptomatic men with monomicrobial infections or IU in order to improve empiric treatment efficacy by increasing the pre-test probability for specific pathogens. No pathogen-specific signs or symptoms were identified, which highlights the urgent need for POC molecular tests.

Pathogen-directed therapy could improve both NGU treatment outcomes and antibiotic stewardship by identifying pathogens for which first-line regimens are ineffective, preventing unnecessary antibiotic exposure, shortening the time to appropriate treatment, and the development of persistent or recurrent urethritis. Considered a cause of persistent urethritis, TV is intrinsically resistant to azithromycin and doxycycline. Although TV infections are relatively rare in men (national U.S. prevalence estimates are <1%),[10] in some

high-risk populations TV has been identified in up to 20% of men with acute NGU.[11] MG is associated with persistent urethritis due to increasing resistance to first-line NGU regimens.[12, 13] Further, the prevalence of MG treatment failures associated with azithromycin are increasing and is reported to be approaching 40%.[14] Pathogen-directed therapy can help decrease the time to administration of appropriate antibiotics for azithromycin- or doxycycline-resistant bacterial organisms, reducing risk for STI transmission, and maximizing stewardship of alternate antibiotic regimens, such as moxifloxacin (the sole approved drug in the U.S. for treatment of macrolide-resistant MG).

The lack of pathogen-specific signs or symptoms suggests that urethral inflammation may be non-specific and that acute-phase urethral immune responses against different NGU-associated pathogens are similar. Nevertheless, the physical exam plays a major role in assessing potential STI cases, and our results do not discount its importance in the evaluation of patients with suspected NGU. This was demonstrated in a study by Tuddenham & Ghanem, who reported that, had the physical exam been omitted, the appropriate STI diagnosis would have been missed in >10% of symptomatic men, 4.5% of STI contacts, and 2.7% of asymptomatic men.[15] Therefore, although the physical exam remains an important tool in the categorization of STI and complications, our study highlights the inadequacy of both the history and physical exam at predicting the etiology of NGU. POC molecular tests are urgently needed to guide same visit clinical decision making.

Our study findings agree with those of Sena et al and disagree with those of Ito et al and Wetmore et al, both of whom reported differences in NGU signs/symptoms by pathogen, especially for MG.[5–7] It is possible that differences in patient populations (e.g., the Ito et al study was predominantly in heterosexual Japanese men) or perhaps pathogen virulence may explain these results. Also, we cannot exclude that our study was underpowered to detect a difference.

Our study had several strengths. First, our use of five-pathogen testing to identify men with mono-infection-associated NGU was a strength of this analysis. Additionally, our analysis eliminated men with mixed infections, which reduced the risk of false-positive results due to poorly characterized interactions between pathogenic organisms. Our analysis also considered various signs and symptoms that may be associated with urethritis in order to robustly test whether NGU etiologies could be accurately predicted. A limitation of our study included our analysis that relied on a single-center cohort of men presenting to a public STD clinic. As a result, our results may be less generalizable to other patient populations and/or clinical settings. Also, our study utilized a strict inclusion criterion of ≥5 PMN/HPF on urethral swab smear to define NGU and we did not evaluate men with mild urethral inflammation (i.e., 2-5 PMN/HPF).

In conclusion, signs and symptoms of NGU are not pathogen-specific and cannot accurately predict the etiology in men with monomicrobial NGU. While the physical examination remains critical to diagnosing NGU and other syndromes, pathogen-specific NGU management will require the development and implementation of POC molecular tests.

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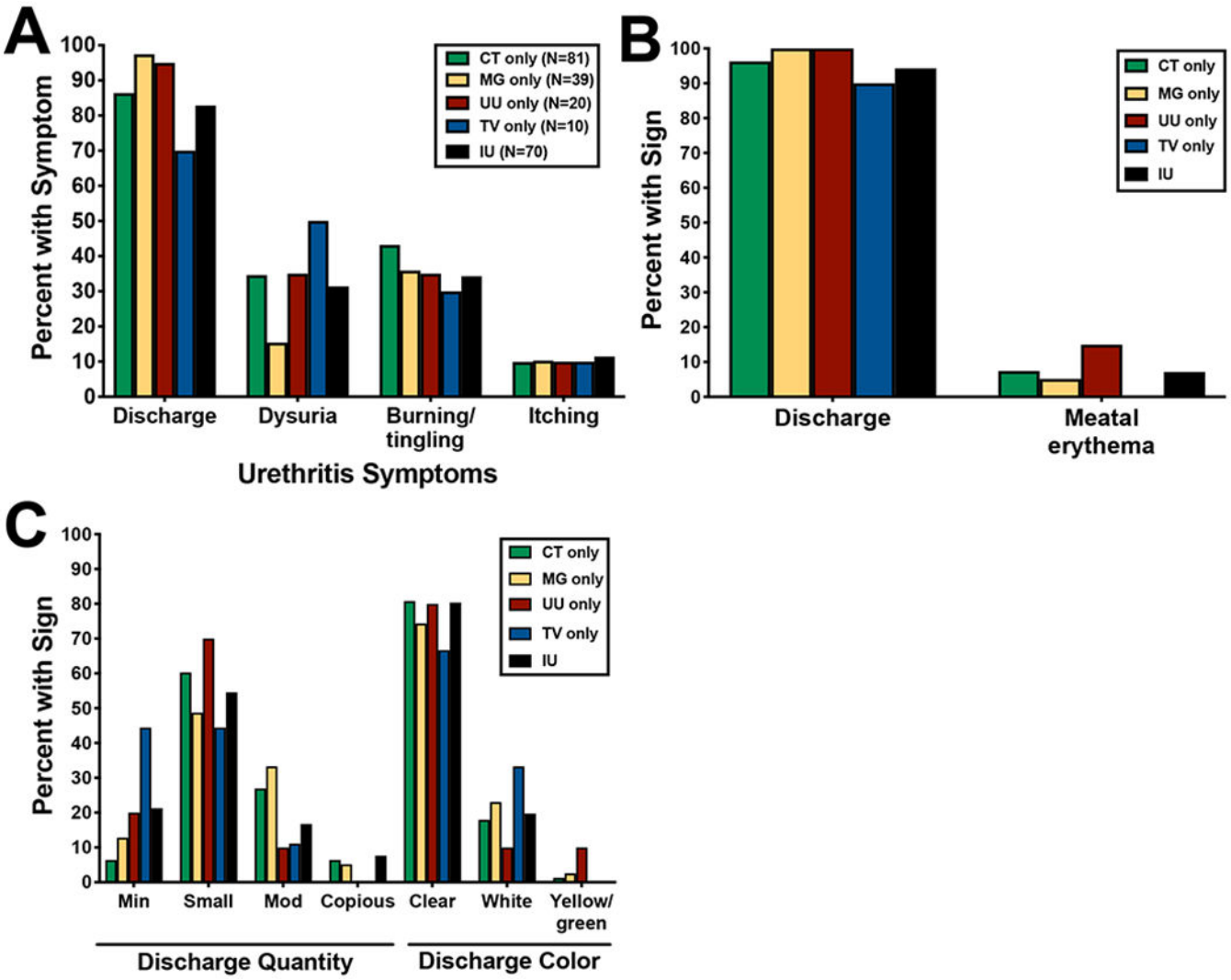

Figure 1. Percent NGU cases with urethritis symptoms and signs, stratified by pathogen and IU.

(A) Frequency of NGU symptoms by group. (B) Frequency of NGU signs by group. (C) Frequency of discharge amount and color by group. Significance was evaluated by Chi-square or Fisher's exact test. Significance set at $P<0.05$. No significant differences were observed. Symptoms with $N\leq5$ were excluded.

Table 1.

Study participant characteristics (N = 220)

Characteristic	
Age, median (IQR)	28 (24 – 35)
Race, *n* (%)	
African American	146 (66%)
Caucasian	42 (19%)
Other	32 (16%)
Ethnicity	
Hispanic	18 (9%)
Non-Hispanic	186 (91%)
Sexual Orientation	
Homosexual	18 (8%)
Heterosexual	187 (85%)
Bisexual/other[a]	15 (7%)
Reason for visit	
Having symptoms	188 (85%)
Worried has STI	24 (11%)
Contact to STI	5 (2%)
Routine check up	3 (1%)
Reported Lifetime Sexual Behaviors	
Lifetime Partners, median (IQR)	12 (6 – 25)
Received oral sex	212 (97%)
Vaginal sex	202 (93%)
Insertive anal sex	123 (56%)
Prior STI Diagnosis	
Gonorrhea	86 (41%)
Chlamydia	122 (57%)
Trichomoniasis	32 (16%)
NGU	94 (45%)
Reported Symptoms	
Discharge	192 (87%)
Dysuria	68 (31%)
Burning/Tingling	83 (38%)
Itching/lesions	1 (0%)
Meatal erythema	1 (0%)
Physical Exam	
Circumcised	195 (89%)
Discharge	212 (96%)

Characteristic	
Meatal erythema	16 (7%)

Abbreviations: IQR, interquartile range; STI, sexually transmitted infection; PMN/HPF, polymorphonuclear neutrophils per high-power field.

[a] Includes pansexual and asexual