Features of Urethritis in a Cohort of Male Soldiers


Of 400 cases of urethritis in male soldiers enrolled in a behavioral intervention project, the etiology of 69% was defined at study enrollment, as well as the etiology of 72% of 25 repeated episodes involving 21 men during the first 78 days of active follow-up (5% of the cohort). Chlamydia trachomatis (36%), Neisseria gonorrhoeae (34%), and Ureaplasma urealyticum (19%) were the most common causes of infection identified at enrollment and during subsequent visits (44%, 28%, and 12%, respectively). By univariate analysis, patients with repeated infection (“repeaters”) were significantly more likely to report a history of sexually transmitted disease (STD; relative risk [RR], 3) and sex with sex workers (RR, 4) than were nonrepeaters. By multivariate analysis, only STD history was significant (RR, 2.8). Characteristics of repeaters in this cohort suggest that specific patterns may be used to establish screening “profiles” of potential repeaters, by which such individuals might be targeted for aggressive intervention at the time of the initial diagnosis.

Persons at high risk for acquiring urethritis and other sexually transmitted diseases (STDs) frequently are members of socially, demographically, and geographically defined sexual networks that have been termed core groups [1]. The existence of core groups has been validated through demonstration of spatial and demographic clustering of gonorrhea [2-4] and syphilis [5], although the evidence is less compelling for chlamydia [6, 7] and other STDs. Features of core groups empirically defined to date include social marginalization (e.g., sex workers, street gangs, and drug addicts), a male-to-female ratio >1, young age, and an urban setting.

One of the central tenets of the core group model holds that a relatively small group of individuals contributes disproportionately to the overall community STD burden [6, 8, 9]. Within this group are so-called high-frequency transmitters who sustain disease in the population through their activities, which exceed a disease-specific critical threshold for rate of partner exchange [10]. The “success” of an individual high-frequency transmitter depends upon his or her ability to avoid or resist cure (i.e., failure to be identified as infected, failure to access treatment, or microbiological treatment failure), frequency of sexual activity (number of acts as well as number of partners), or both. It has been hypothesized that access to and identification of high-frequency transmitters is critical to disruption of the core and subsequent control of STDs in the population [9, 11].

Within the high-frequency-transmitter group are those persons who were repeatedly STD clinic patients (“repeaters”) as a consequence of their frequent STD exposures. The ability to profile STD repeaters, and thereby more effectively target these individuals for aggressive behavioral and other interventions, has potential utility for conserving scarce clinic resources, as well as for facilitating community STD control. Recently, a behavioral intervention project was conducted at our military STD clinic that involved active-duty Army soldiers [12]. The prospective nature of this project afforded an opportunity to...
identify short-term repeaters among members of the volunteer pool and to explore demographic and behavioral characteristics of these individuals, compared with those study participants who did not repeat as clinic clients during the study. In addition, the inclusion of biological markers as outcome measures in this study allowed us to describe the microbial etiologies associated with urethritis, both at initial enrollment and at the time of repeat visits.

Patients and Methods

Patients. Four hundred active-duty male soldiers presenting to the Fort Bragg Epidemiology and Disease Control (EDC) Clinic from December 1994 through January 1996 with signs and/or symptoms of acute urethritis who were not known to be HIV-positive, had at least 2 months remaining on-station at Fort Bragg, and had provided informed consent were consecutively enrolled in a behavioral intervention study, as described elsewhere [12]. In brief, 3 single-session preventive interventions for reducing HIV/STD risk behaviors were evaluated in a quasi-experimental pre-/postevaluation design. Standard clinic care alone was compared against standard care combined with 1 of the 3 interventions: health-risk appraisal, interactive video, and targeted situational behaviors.

Demographic, behavioral, and microbiological data were obtained at the time of study entry. The sample was composed of relatively young men (median age, 23 years; range, 18–43 years) who were predominantly single, with a skew toward high school–level education and the lower enlisted military ranks. The majority (56.8%) were black, 34.8% were white, and 4.5% were Hispanic/Latino; 3% fell into other racial/ethnic categories [13]. Ninety-four patients recruited to enroll in the study declined to participate; no differences between volunteers and refusers were seen [13].

Follow-up visits were scheduled for ~2 weeks and 2 months after study enrollment. Behavioral and microbiological data were obtained at each follow-up visit. Those individuals who developed signs or symptoms of an STD at other than scheduled return-visit intervals (interim or unscheduled clinic visits) were evaluated in the same way. All study participants received 1 g of directly observed azithromycin orally at study enrollment, and those for whom a diagnosis of gonorrhea was confirmed also received 250 mg of ceftriaxone intramuscularly. Contact-tracing and clinical management of disease acquired during the study were performed according to clinic routines and Centers for Disease Control and Prevention guidelines in effect at the time [14].

Microbiological diagnoses. Neisseria gonorrhoeae infection was diagnosed by visualization of gram-negative intracellular diplococci on gram-stained smears of urethral exudate, by culture of urethral swab specimens on modified Thayer-Martin agar, or both. Chlamydia trachomatis was identified by detection of antigen in urine by use of the Syva Microtrak II EIA kit (Syva, San Jose, CA) and by amplification of DNA in urine with the LCx C. trachomatis assay (Abbott Laboratories, Abbott Park, IL), according to the manufacturers’ instructions. Both assays were performed on each urine specimen. For the purpose of this study, Chlamydia positivity was defined as positivity of either or both tests.

Trichomonas vaginalis was sought through inoculation and microscopic examination of a commercially available self-contained cultivation system by use of patient urethral swabs (Biomed In-Pouch Test, Biomed Diagnostics, San Jose, CA), according to the manufacturer’s instructions.

Swabs for Ureaplasma urealyticum culture were placed in 1 mL of pleuro-pneumonia–like organism (PPLO) broth (with arginine and urea) and then were placed in liquid nitrogen until cultured. At the time of culture, specimens were thawed and inoculated into PPLO broth (with arginine and urea) and then were incubated at 35°C. Broths demonstrating a color change were used to inoculate PPLO agar plates. Plates were incubated at 35°C in an anaerobic jar with a GasPak generator (BBL Becton Dickinson Microbiology Systems, Cockeysville, MD). Colonies of U. urealyticum were identified by the appearance of dark-brown colonies after addition of ureaplasma spot-test reagent.

Subjects were screened for syphilis with the Rapid Plasma Reagin test (Becton Dickinson Microbiology Systems). Evidence of infection with HIV was sought by EIA with Western blot confirmation (of repeatedly positive samples), according to methods and standards adopted by the US Army [15, 16].

Diagnosis of genital herpes simplex virus infection was made by clinical observation only. No attempts were made to culture or otherwise identify viruses, Mycoplasma genitalium, or other potential causes of urethritis. Nongonococcal urethritis was diagnosed when at least 5 WBCs per oil-immersion field (1000×) could be visualized in examination of urethral exudate and when no specific etiology for urethritis could be found.

We defined a “repeater” as any study participant who returned for either a scheduled or unscheduled visit during the project interval and had STD diagnosed again. To avoid confusion with response to initial antimicrobial therapy, interim visits that occurred within 2 weeks were not considered repeated visits. Antimicrobial therapy was administered at the time of each visit for recognized STD.

All repeated visits of study subjects who were followed for the duration of the behavioral intervention study were recorded. However, consistent with guidelines established for analysis of behavioral parameters in the parent study [12], only those visits that occurred within 78 days of each volunteer’s enrollment date were considered for analysis.

Statistical methods. Relationships between infectious etiologies and demographic variables were evaluated with χ² analyses. Attempts were made to obtain samples for all microbiological assays at each visit. However, technical problems occasionally arose (e.g., misplaced samples and specimen contamination) that precluded the determination of complete microbiological profiles for all individuals. Proportions reported therefore reflect only those results available for analysis. Values reported for race/ethnicity include only white, black, and Hispanic/Latino soldiers, owing to the small numbers in other categories. Age groupings were selected empirically, to allow for analysis of variables at intervals reflective of the clinic population (most clinic clients were aged <35 years).

Univariate analyses to determine relationships between behavioral factors and STD repeater status were conducted by use of χ² tests. Only those behavioral data obtained at the time of enrollment were used for these comparisons. Logistic regression was then performed to adjust for specific demographic factors (age, race/eth-
nicity, military rank, and marital status). All analyses were performed with SAS software (version 6.2; SAS Institute, Cary, NC).

**Results**

**Etiology at enrollment.** Of the 400 study volunteers, an etiology for urethritis could be found at the time of enrollment for ~70% (277/400). *C. trachomatis* and *N. gonorrhoeae*, found in 142 (35.5%) and 138 (34.5%) of individuals, respectively, were the 2 most frequently identified pathogens (table 1). These agents accounted for 40% and 39%, respectively, of the total 356 agents found. *U. urealyticum* was recovered from 76 soldiers (19%; 21% of all agents). We were unable to document a single case of *T. vaginalis* infection in the study cohort at enrollment. No evidence of active syphilis or HIV infection was detected in any subject.

A single pathogen was detected in 205 individuals (51.2%), 2 pathogens were found in 65 (16.2%), and 3 pathogens were found in 7 (1.8%). Among those from whose specimens a single pathogen was identified, *N. gonorrhoeae* was found in 79 (38.5%), *C. trachomatis* in 81 (39.5%), and *U. urealyticum* in 45 (22.0%). Among those from whose specimens 2 pathogens were recognized, the largest proportion had coinfection with *N. gonorrhoeae* and *C. trachomatis* (41 [63.1%] of 65), whereas *C. trachomatis* and *U. urealyticum* were found in 13 individuals and *N. gonorrhoeae* and *U. urealyticum* were present together in 11 persons.

Infection due to *N. gonorrhoeae* was significantly associated with younger age ($\chi^2 = 21.919; P < .001$). This was the pathogen predominantly identified in soldiers aged <20 years (52% of 31 organisms), but it was relatively less frequent in older age groups (table 2). *C. trachomatis* accounted for about one-third of identified agents in soldiers aged <25 and >34 years and represented >45% of pathogens (41/88) found in individuals aged 25–34 years. However, no specific age-related pattern was found ($\chi^2 = 6.685; P = .153$). Similarly, *U. urealyticum* infection was not associated with age ($\chi^2 = 5.504; P = .239$).

A strong association with race/ethnicity was found for both *N. gonorrhoeae* ($\chi^2 = 46.346; P < .001$) and *U. urealyticum* ($\chi^2 = 13.235; P = .001$) but not for *C. trachomatis* ($\chi^2 = 5.443; P = .066$). Among black soldiers with urethritis, *N. gonorrhoeae* was identified in 48%, *C. trachomatis* in 40%, and *U. urealyticum* in 15% (table 3). Among white soldiers, *N. gonorrhoeae* was found in 15%, *C. trachomatis* in 31%, and *U. urealyticum* in 30%. In the “other” race/ethnicity grouping (in which 16 of 19 were Hispanic/Latino), *N. gonorrhoeae* was found in 21%, *C. trachomatis* in 16%, and *U. urealyticum* in 12%.

The risk ratio for black soldiers versus white soldiers for *N. gonorrhoeae* was 5.39 (95% CI, 3.2–9.1); for *C. trachomatis*, 1.49 (95% CI, 0.9–2.3); and for *U. urealyticum*, 0.4 (95% CI, 0.2–0.7). Of the 138 cases of gonorrhea diagnosed, 81% involved black soldiers and 16% involved white soldiers. Of the 142 cases of *C. trachomatis* infection diagnosed, 66% involved black soldiers and 32% involved white soldiers; of the cases of *U. urealyticum* infection diagnosed, 42% involved black soldiers and 55% involved white soldiers.

**Repeated episodes.** At the time of study closure, a total of 27 STD repeaters had been identified. Four of these 27 were excluded from analysis, because their visits occurred beyond our maximum-allowable 78-day follow-up period. Repeated visits for 2 additional individuals were considered to be due to genital herpes simplex virus infection. Because it could not be determined whether these infections were primary or recurrent episodes, they were also excluded from analysis.

Within 78 days of enrollment, 25 repeated visits were recorded for the 21 individuals evaluated (5% of the study cohort). Seven repeated episodes were noted during scheduled follow-up visits: 1 at the 2-week visit and 6 at the 2-month visit. Fourteen episodes were diagnosed at unscheduled (interim) visits. In the case of 1 individual, repeated episodes were detected at both a scheduled (2-month) visit and an unscheduled visit. Repeated visits were evenly distributed among the 4 behavioral-intervention groups assessed in the parent study [12] ($\chi^2 = 1.837; P = .607$).

Among the subset of repeaters, 18 were seen once, 2 were seen twice, and 1 was seen 3 times during the follow-up period. The time interval for visits ranged from 14 to 64 days after enrollment.

An etiology was found for 18 (72%) of 25 repeated episodes. A single pathogen was identified in 15 (60%), and 2 pathogens were found in 3 (12%). *C. trachomatis* and *N. gonorrhoeae* were the most frequently identified pathogens at repeated visits (table 1). No infections were due to *T. vaginalis*, and no episodes of syphilis or HIV infection were observed during the follow-up period.

**Behavioral factors.** Univariate analyses yielded no differences between repeaters and nonrepeaters with respect to age, pay grade (rank), marital status, education attainment, or living arrangement. Race/ethnicity proved marginally significant ($P = .045$). Similarly, there were no differences noted for a va-
The most commonly recognized causes of urethritis in men are *N. gonorrhoeae*, *C. trachomatis*, and *U. urealyticum*, although a variety of other agents are recognized as probable (e.g., *T. vaginalis*, *M. genitalium*, and herpes simplex virus) or possible (e.g., *Mycoplasma hominis*) etiologic agents of this condition [17, 18]. Consistent with observations made previously in other populations, *N. gonorrhoeae*, *C. trachomatis*, and *U. urealyticum* were the most frequent causes of urethritis in men in this military cohort. *N. gonorrhoeae* was found to be strongly associated with younger age and black race, whereas *C. trachomatis* was not linked to either age or race/ethnicity. *U. urealyticum* was found most frequently among white study enrollees. It is surprising that *T. vaginalis* was not found in any soldiers in this population. We believe this latter finding to be valid, inasmuch as *T. vaginalis* was infrequently identified by either wet mount or culture of specimens from women attending the Fort Bragg EDC Clinic during the time interval surrounding this study. We have no explanation for this phenomenon.

Concurrent infection with multiple pathogens was a relatively frequent finding (18% overall) in our study cohort. It is not surprising that *N. gonorrhoeae* and *C. trachomatis* accounted for the majority of coinfections, but *U. urealyticum* infection, in concert with both *N. gonorrhoeae* and *C. trachomatis* infections, was a relatively frequent occurrence. These findings validate the public health policy of providing antimicrobial coverage for *C. trachomatis* (and other causes of nongonococcal urethritis) concurrent with specific therapy against *N. gonorrhoeae* [14].

We identified *C. trachomatis* as the most prevalent pathogen associated with urethritis in this cohort of men, both as a single agent and in association with others in multiple infections. *C. trachomatis* is widely recognized as the most common bacterial cause of STDs in the United States, owing in large part to its often asymptomatic occurrence in both men and women, as well as its relatively persistent nature in genitalurinary infections [19–21]. Our findings lend continued support to the need for targeting this pathogen through screening and for aggressive contact-tracing efforts in order to reduce the consequences of chronic disease and sequelae.

Five percent of soldiers with urethritis who enrolled in the behavioral intervention study repeated as STD clinic attendees during an 11-week follow-up period. We were able to define an etiology for the new STD in nearly three-fourths of repeated episodes. Comparison of pathogens identified during initial and repeated STDs in this subset of soldiers revealed frequent (2/
coincidence of agents, suggesting either reinfection by the sexual partner from whom the initial STD was acquired or infection from a person sharing similar risk factors for specific-pathogen acquisition (i.e., another member of this person’s core group). Future efforts to more precisely identify etiologic agents (e.g., with pulse-field gel electrophoresis, ribotyping, polymerase chain reaction–restriction fragment length polymorphism, or single-strand conformation polymorphism) could prove very useful for elucidating this phenomenon.

It is difficult to assess the relative magnitude of repeated infection observed in this study. Comparable rates of short-term repeated STDs in military or civilian populations could not be found in a literature review. However, a 9.4% repeated infection rate for gonorrhea was recorded over 6 months in Denver [22], a 13.5% repeated infection rate for gonorrhea was seen within 8–9 weeks among inner-city women in Kansas City [23], and an 11.6% monthly incidence of repeated gonococcal and chlamydial infections was seen among female control subjects in a spermicide study in Birmingham, Alabama [24]. It is probable that if our follow-up period extended an additional 3–6 months, repeated infections among our study cohort would mirror rates reported in these other studies.

Urethritis is among the most prevalent conditions for which care is rendered in the United States and is the most common clinical diagnosis for men seeking care at STD clinics [7, 25–27]. The economic impact of STDs is staggering [26–28]. Thus, by inference, the costs associated with diagnosis and treatment of urethritis are substantial, particularly for those segments of the health care system most frequently associated with management of the condition (e.g., public or community-based clinics) and least able to bear the burden.

It is clear that individuals with repeated infections contribute disproportionately to the overall STD clinic burden [3, 9, 22, 29–33]. The ability to identify early those individuals who are likely to become reinfected would thus provide a potential avenue to channel clinics’ limited prevention and screening resources more effectively. Previous studies of gonococcal reinfection have focused predominantly on demographic characteristics (young age, male sex, lower socioeconomic status, minority race, single marital status, and unemployment) [9, 30, 31, 34, 35] and geographic characteristics [3, 22] for defining this core. Lundin et al. found in 1977 that social and psychological characteristics of repeaters were distinct from those of nonrepeaters [36].

We identified specific behavioral markers that, in this limited study, differentiated repeaters from nonrepeaters during a short follow-up interval. In our population, a history of multiple sex partners or sex with sex workers was significantly associated with repeated infection, and a history of >10 lifetime partners increased risk marginally. The positive predictive values of the 2 variables significantly associated with repeated infection in this study were relatively low (10% and 16%, respectively). With a longer follow-up interval (and presumably higher absolute rate of repeated infection), however, these variables would probably become much more useful as predictors in a population with similar overall disease prevalence.

These findings provide a potential focus for screening STD clinic patients and should be confirmed in a prospective study to determine the effect of behavioral screening and targeted intervention on overall repeated-STD rates.

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References