Expanding the Spectrum of Pathogens in Urethritis: Implications for Presumptive Therapy?

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(See the article by Yokoi et al. on pages 866–71)

Neisseria gonorrhoeae was formally identified in 1879 by the German physician and bacteriologist Albert Neisser. However, the first documented reference to gonococcal infection dates to the book of Leviticus, which recommends abstinence for 7 days for those with a “running issue” (typically attributed to gonorrhea) [1, 2], making it the “oldest” recognized sexually transmitted infection. Although gonorrhea prevalence in the United States has been steadily decreasing since the mid-1970s, it was still the second most commonly reported infectious disease in 2005, and the rate of 115.6 cases per 100,000 population represented the first increase in >5 years. From 2000 through 2005, rates in the western United States increased by 42% [3]. Because of increasing fluoroquinolone resistance, cephalosporins are now recommended for therapy [4]. Untreated gonococcal infections are associated with pelvic inflammatory disease and related sequelae in women (e.g., tubal factor infertility, ectopic pregnancy, and chronic pelvic pain), as well as increased risk for acquisition and transmission of HIV infection [5].

Postgonococcal urethritis—urethritis that persists after successful eradication of laboratory-confirmed gonococcal infection—is reported to occur in 21%–69% of men treated with antibiotics that target gonorrhea [6–9]. These estimates, however, date from the late 1970s. Since that time, very little research has been done on this syndrome, despite the identification of several new etiologies of urethritis. Mycoplasma genitalium, first identified in 1980, has been associated with urethritis in almost all studies that used nucleic acid amplification tests to identify this organism [10]. Two of 3 studies that have differentiated Ureaplasma urealyticum into newly recognized distinct species showed that U. urealyticum biovar 2 but not Ureaplasma parvum was associated with non-gonococcal urethritis [11–13].

In this issue of Clinical Infectious Diseases, Yokoi et al. [14] evaluate the role of these newly identified organisms in postgonococcal urethritis, providing the first etiologic study of this syndrome in 30 years. These investigators report on 390 men with documented gonorrhea attending the Department of Urology at Toyota Memorial Hospital in Toyota, Japan, over a 6-year period. At enrollment, 30.8% of the patients were coinfected with either Chlamydia trachomatis, M. genitalium, and/or U. urealyticum biovar 2.

Two hundred ninety-one patients (84%) who received diagnoses of gonorrhea returned for a follow-up visit 7–10 days after treatment with either a cephalosporin or spectinomycin; 35.7% of these patients had postgonococcal urethritis, defined as ≥5 polymorphonuclear leukocytes per high-power field in a Gram-stained urethral smear specimen with no observed gram-negative intracellular diplococci. C. trachomatis was detected at enrollment in nearly one-half of these men (49%); M. genitalium was detected in 9.6%, and U. urealyticum biovar 2 was detected in 12.5%. Both M. genitalium and U. urealyticum biovar 2 were strongly and independently associated with postgonococcal urethritis, adjusting for chlamydial infection.

What are the clinical implications of these findings? First, the study provides additional support for treating men who receive diagnoses of gonorrhea for concurrent chlamydial infection, as recommended by the Centers for Disease Control and Prevention [15]. However, Yokoi et al. [14] also found that 13.5% of men with postgonococcal urethritis had negative test results for C. trachomatis but positive results for M. genitalium and/or U. urealyticum biovar 2. On the basis of these findings, Yokoi and colleagues concluded that men with gonorrhea should receive presumptive therapy that is effective against all 3 organisms.
This recommendation raises 2 questions. First, is the prevalence of these newly identified organisms among men with gonorrhea sufficiently high to merit potentially adjusting the presumptive therapy for urethritis? Although 13.5% of Japanese men with gonorrhea had M. genitalium and/or U. urealyticum biovar 2 identified [14], prevalence may vary by population. Systematic surveillance of these “new” organisms would better define prevalence, but commercial diagnostic assays are not yet available. However, given the increasing evidence linking these organisms with urethritis, cervicitis, and female upper reproductive tract infections [10], the answer to the first question may be yes. The second question logically follows: what should that treatment be?

Although Yokoi et al. [14] do not describe recommended treatment regimens for C. trachomatis in Japan, the Centers for Disease Control and Prevention and the World Health Organization recommend either azithromycin (1 g orally in a single dose) or doxycycline (100 mg orally twice daily for 7 days) [15, 16]. The choice of regimen is typically based on cost or compliance concerns. Unfortunately, doxycycline may not be an ideal treatment for M. genitalium infection. The microbiologic cure rate for M. genitalium infection that is associated with doxycycline treatment was low in 4 recent studies, ranging from 35% to 44% [17–20], and the most recently released Centers for Disease Control and Prevention treatment guidelines indicate that “azithromycin and doxycycline are highly effective for chlamydial urethritis; however, infections with M. genitalium may respond better to azithromycin” [15, p. 36, 18]. Although 1 small study reported a 94% microbiologic cure rate associated with doxycycline therapy [21], this appears to be the exception rather than the rule.

Although the few comparative studies suggest that azithromycin therapy is more effective than doxycycline therapy [19, 20], Bradshaw et al. [22] observed a 28% treatment failure rate subsequent to the standard 1-g single-dose regimen of azithromycin among Australian men with M. genitalium–positive nongonococcal urethritis. Because of concerns about treatment failure, some clinicians recommend an extended 5-day regimen of azithromycin, consisting of 500 mg on the first day, followed by 250 mg for 4 days [18]. However, even this extended regimen resulted in microbiologic failures in the Australian men with M. genitalium, and M. genitalium was eradicated only after treatment with moxifloxacin (400 mg/day for 10 days) [22]. Considering the high cost of moxifloxacin, limited available data, and potential for emergence of further resistance, this regimen should probably be reserved for cases of treatment failure.

Other antibiotics that may be effective against C. trachomatis are similarly problematic. Although gatifloxacin was effective in a study involving Japanese men [23], it was removed from the US market in May 2006, subsequent to reports of increased risk for dysglycemia [24]. Rifalazil (25 mg/day), which is not currently available in the United States, was very effective against C. trachomatis but was <50% effective against M. genitalium at a 5-week test-of-cure [25].

Few data exist on antimicrobial susceptibilities of U. urealyticum biovar 2 and U. parvum, but several studies have evaluated response of undifferentiated Ureaplasma species to tetracyclines and azithromycin in men with urethritis. Microbiologic cure rates ranged from 45% to 77%, with similar rates for both drugs [26–29]. A small number of observational studies involving women suggest that U. urealyticum biovar 2 isolates may exhibit reduced susceptibility to tetracyclines relative to U. parvum [30–32], but further studies are needed. No data are available on susceptibilities of these 2 species to azithromycin.

Although Japan does not currently recommend presumptive therapy for chlamydial infection for men with gonorrhea, this practice is routine in the United States and many other countries [15, 16]. Because of accumulating evidence that doxycycline therapy may not be sufficiently effective against M. genitalium and U. urealyticum biovar 2, should azithromycin be recommended over doxycycline as presumptive therapy for urethritis? Double-blind, randomized trials to determine which of these drugs is optimal for M. genitalium, U. urealyticum biovar 2, U. parvum, and idiopathic urethritis are ongoing, but results will not be available until early 2010. In the absence of definitive data, evidence such as that from Yokoi et al. [14] somewhat shift the balance to favoring azithromycin therapy. The major downside to azithromycin is cost. Although the drug is now off-patent, it remains substantially more expensive than doxycycline in the United States. Thus, the choice of therapy for urethritis must still be individualized, based primarily on considerations of cost to patients and programs, patient preference, and efforts to optimize compliance.

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References


