Diagnosis and Treatment of Urethritis in Men

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Received March 28, 1983

Gonococcal and nongonococcal urethritis are the most common sexually transmitted diseases in men. Failure to control these infections is a result of improper treatment of index cases and their sexual contacts. The proper management of urethritis in men is reviewed.

Sexually transmitted diseases (STDs) are epidemic in the United States [1,2]. Recent publicity has focused on herpes genitalis and the lethal acquired immunodeficiency syndrome (AIDS). Interest in these incurable diseases has overshadowed the continued importance of more traditional STDs. Urethritis remains the most common acute manifestation of STD in men. Two million cases of gonorrhea and 2.5 million cases of nongonococcal urethritis (NGU) are estimated to occur annually in the U.S. [1,2]. Over the last decade, advances have been made in defining the etiology, epidemiology, and complications of NGU. Despite this progress, many practitioners still equate all urethral symptoms with gonorrhea and the requisite for intramuscular penicillin. In a recent editorial, Brandt underscored the immediate need for well-trained front-line practitioners to “combat the STD epidemic of the 1980’s and 1990’s” [1]. At present, less than six teaching hours are devoted to STDs in an average four-year medical school curriculum [1].

The intent of this publication is to review the proper management of the male patient with urethral symptoms. The critical management steps are summarized as follows:

1. Confirm the presence of urethritis by detecting polymorphonuclear leukocytes in the urethral exudate.
2. Differentiate gonococcal urethritis (GU) from NGU by Gram stain of an endourethral specimen.
3. Initiate empiric antibiotic therapy based on Gram stain findings, likelihood of medication compliance, and the probability of antibiotic resistance or extragenital sites of infection.
4. Trace and treat all sexual contacts of patients with GU or NGU.
5. Document symptom resolution, disappearance of urethral inflammation, and bacteriologic cure after treatment.

IS URETHRITIS PRESENT?

Dysuria localized to the mid or terminal urethra and spontaneous or expressible urethral discharge are the hallmarks of urethritis. Less specific symptoms include...
urethral itch and, rarely, urinary frequency and urgency. Urethritis may be asymptomatic, detected only by the presence of pyuria in up to 22 percent of cases [3]. Fever, flank pain, or pain occurring only with ejaculation are not features of urethritis, but implicate a prostatic or upper urinary tract origin.

In examining the urethra for evidence of inflammation, two points are noteworthy. First, no moisture is normally expressible from the urethral meatus except immediately following micturition or during sexual arousal. Second, urination less than two hours prior to examination may wash away abnormal urethral exudate. Indeed, in patients with urethritis the amount of detectable urethral exudate has been demonstrated to increase directly with the interval since micturition [3]. If urethral symptoms exist without detectable exudate, and recent voiding has occurred, a second examination two hours post void may prove fruitful.

Polymorphonuclear leukocytes (PMNs) must be present in a urethral smear (customarily Gram-stained) to diagnose urethritis. The minimum number of PMNs that is abnormal is unknown, but greater than 4 PMNs per oil immersion field (970 ×) is considered diagnostic [3]. An adequate specimen for smear is readily obtainable if urethral discharge is spontaneous. In the absence of spontaneous discharge, the urethra should be milked from the base of the penis toward the glans. If no exudate is expressible, an endourethral specimen should be obtained with a narrow-tipped calcium alginate swab inserted at least 1 cm into the urethra. The swab is then rolled gently over a glass slide for staining; vigorous streaking may destroy cellular morphology.

Another useful technique for localizing inflammation to the urethra requires the collection of divided urines for quantitative leukocyte counts. Two urine receptacles are given to the patient. The first 10 ml of urine is voided into one receptacle (first voided urine), and the remainder of the void is directed into the second receptacle. Ten ml of urine is then harvested from the second receptable, and the two 10 ml specimens are centrifuged and compared under high power (400 ×) for leukocytes in the sediment. Greater than 15 PMNs per high-power field in the first voided urine sediment, with a lesser number in the second sediment, confirms the presence of urethritis [4]. Equal numbers of PMNs in both sediments suggests cystitis, prostatitis, or upper urinary tract inflammation. This technique is particularly helpful when expressible discharge is absent, and adequate endourethral swabbing cannot be performed.

On occasion, despite urethral complaints, discharge is absent and PMNs cannot be detected in the urethral smear or urine sediment. Contact with urethral irritants, such as detergents or spermicides, may be causative. In addition, "venerophobia" following a new sexual contact may result in excessive scrutiny and misinterpretation of normal urethral sensations that occur during voiding and ejaculation. In such cases, reassurance and a follow-up examination are all that are necessary. However, because objective findings of urethritis may be evanescent, the label of functional urethral symptoms should be withheld until thorough serial examinations have been performed [5].

ETIOLOGIES

Once the presence of urethritis has been confirmed, specific causes should be considered. A comprehensive list of infectious etiologies of male urethritis is presented in Table 1. Microorganisms that can be recovered from the urethra, but are not pathogens (despite earlier claims), include Mycoplasma hominis, Gardnerella
MALE URETHRITIS: DIAGNOSIS AND TREATMENT

TABLE 1

Infectious Etiologies of Male Urethritis

| % Infectious Urethritis | References |
|-------------------------|------------|
| I. Gonococcal Urethritis (GU) | 30-50       | [6]         |
| II. Nongonococcal Urethritis (NGU) | 50-70       | [7,8]       |

| % NGU | References |
|-------|------------|
| Chlamydia trachomatis | 40-50 | [7-9] |
| Ureaplasma urealyticum* | 20-30 | [10-13] |
| Unknown agent(s) (tetracycline-suppressible) | 20-25 | [14] |
| Trichomonas vaginalis | 5 | |
| Herpes simplex | rare | [3,8,16] |
| Candida albicans | rare | [3,8,16] |
| Endourethral syphilitic chancre | rare | [17] |
| Condylomata accuminata | rare | [18] |

*Etiologic role controversial

vaginalis, Corynebacterium genitalium and pseudogenitalium, cytomegalovirus, and coliforms [3,10].

Traditionally, urethritis has been classified as gonococcal or nongonococcal. This distinction arose because gonococci are readily identifiable by urethral Gram stain and culture, whereas the agents of NGU are not. Nonspecific urethritis (NSU) is an obsolete term previously used to describe the 95 percent of NGU not caused by Candida albicans, Trichomonas vaginalis, or Herpes simplex [7]. Since Chlamydia trachomatis is now known to cause 40-50 percent of NGU, the term NSU, which implies no specific etiology, should be abandoned.

GONOCOCCAL URETHRITIS

The descriptive term gonorrhea: the “flow of seeds,” was coined by the Greek physician Galen in 130 A.D. More than seventeen centuries later, Neisser discovered the diplococcus that now bears his name. Neisseria gonorrhoeae is a non-motile, Gram-negative, aerobic bacterium that characteristically grows in pairs or diplococci (long axis apposed and adjacent sides flattened). The organism causes 30-50 percent of male urethritis. Gonococcal isolation rates are highest (60-70 percent) in urban males of lower socioeconomic status [6]. In contrast, less than 10 percent of urethritis in university students is gonococcal in origin [19]. Other characteristics of GU include an abrupt onset of dysuria and urethral discharge three to four days after exposure. Discharge is purulent in over 90 percent of cases, and a spontaneous urethral “drip” occurs in 30-40 percent. For comparison, discharge is purulent in only 20-25 percent of NGU, and is rarely spontaneous (< 5 percent) [6].

Despite these suggestive features, GU cannot be reliably distinguished from NGU on clinical grounds alone. A urethral Gram stain or culture is required. If typical, intracellular Gram-negative diplococci (GND) are present on urethral Gram stain, 98 percent of cultures will grow gonococci. When no intra- or extracellular GND are present, 99 percent of cultures will be negative. Approximately 15 percent of Gram stains are equivocal, revealing extracellular GND only. Only 10 percent of equivocal
smears will be culture-positive. Overall, few diagnostic tests in medicine are as safe, simple, inexpensive, and accurate as the urethral Gram stain is in symptomatic urethritis [6]. Accordingly, it should be employed in the diagnostic evaluation of all patients with urethritis.

A urethral Gram stain that demonstrates intracellular GND warrants treatment of the patient and his sexual contacts for gonorrhea. Urethral culture is optional unless Gram stain findings are equivocal or penicillin resistance is suspected. For health department reporting purposes, a Gram stain diagnosis of GU is sufficient.

Several treatment options for uncomplicated GU exist and are listed in Table 2, along with specific advantages and disadvantages for each regimen listed [20]. Cure rates for GU approach 95 percent for all regimens listed [21]. The likelihood of medication compliance and the probability of extraurethral gonococcal infection (pharynx or rectum) should influence the antibiotic choice.

For non-compliant patients, single-dose therapy with parenteral penicillin G or oral amoxicillin/ampicillin is preferable. In the penicillin-allergic, non-compliant patient, single-dose spectinomycin is the treatment of choice. For compliant pa-

| Regimen (not listed in order of preference) | Advantages | Disadvantages |
|---------------------------------------------|------------|--------------|
| 1. Aqueous Procaine Penicillin G: 4.8 million units IM (2 sites) plus probenecid 1.0 g p.o. | 1. Single-dose therapy 2. Effective against anorectal and pharyngeal infection; treatment of choice in homosexual men 3. Eradicates incubating syphilis | 1. Painful IM infection 2. Possible penicillin anaphylaxis: 1/10,000 [12] 3. Possible procaine reaction (psychosis): 1/1,000 [12] 4. No activity against concomitant C. trachomatis infection |
| 2. Ampicillin/Amoxicillin: ampicillin 3.5 g p.o. or amoxicillin 3.0 g p.o. either with probenecid 1.0 g p.o. | 1. Single-dose therapy 2. No injection 3. Eradicates incubating syphilis 4. Lower incidence of anaphylaxis vs. IM route | 1. Ineffective against anorectal and pharyngeal infection 2. No activity against concomitant C. trachomatis infection |
| 3. Tetracycline: 500 mg p.o. QID for 7 days | 1. Effective against concomitant C. trachomatis infection 2. Effective for pharyngeal infection 3. Eradicates incubating syphilis | 1. Requires compliance 2. Ineffective against anorectal infection in men |
| 4. Spectinomycin: 2.0 g IM | 1. Single-dose therapy for penicillin-allergic patient 2. Effective against anorectal infection 3. Effective against penicillinase-producing strains (PPNG) | 1. Ineffective against pharyngeal infection 2. No activity against concomitant C. trachomatis infection 3. Does not eradicate incubating syphilis |
tients, tetracycline is highly effective and has the unique advantage of preventing most postgonococcal urethritis (PGU) [12]. Seventeen to 32 percent of patients with GU are co-infected with *C. trachomatis* [8,15,22]. When co-infected patients are treated with an antibiotic other than tetracycline, over 80 percent develop PGU [8,12]. If initial treatment is with tetracycline, less than 10 percent develop PGU. To prevent PGU and to insure gonococcal eradication, single-dose anti-gonococcal therapy with ampicillin/amoxicillin, followed by one week of tetracycline, has been recommended for widespread use [20]. However, the efficacy and safety of this combined regimen have not been established.

Homosexual men with GU who practice fellatio and rectal intercourse often have pharyngeal and rectal gonococcal infection. For these extraurethral sites of infection, parenteral penicillin G is the most effective regimen. Ampicillin/amoxicillin and spectinomycin are not effective for pharyngeal infection [23,24], and a 15 percent failure rate has been reported for rectal infection in men treated with tetracycline [25]. For penicillin-allergic patients with pharyngeal and rectal infection, nine tablets of trimethoprim-sulfamethoxazole (80 mg/400 mg) as a single daily dose, for five days, is indicated.

Penicillinase-producing *N. gonorrhoeae* (PPNG) was first recognized in 1976 [26–28]. From 1976–1979, fewer than 400 cases were reported annually in the U.S., with most cases being acquired in endemic areas in Southeast Asia or West Africa [29]. Starting in 1980, sustained domestic spread of imported PPNG occurred, which resulted in a dramatic increase in reported cases from 328 in 1979 to 9,208 in 1982 [CDC: Venereal Disease Control Division]. Currently, PPNG is concentrated in the indigent populations of large cities: New York, Miami, and San Diego. Gonococcal infection acquired in a PPNG endemic area or persistent GU after treatment should raise the suspicion of PPNG infection.

Spectinomycin 2.0 g intramuscularly is the treatment of choice for PPNG; only one well-documented case of spectinomycin resistance has been reported [30]. Limitations of spectinomycin include inadequate activity against pharyngeal PPNG infection, incubating syphilis, or concomitant *C. trachomatis* infection. Alternatives to spectinomycin include cefoxitin 2.0 g intramuscularly plus probenecid 1.0 g by mouth or cefotaxime 1.0 g intramuscularly without probenecid. As with spectinomycin, neither cefoxitin nor cefotaxime has activity against pharyngeal PPNG or *C. trachomatis* infection. Most PPNG are tetracycline-resistant; therefore, tetracycline must be added to spectinomycin to prevent PGU [31]. For pharyngeal PPNG infection, trimethoprim-sulfamethoxazole (80 mg/400 mg) nine tablets daily, for five days, is the only treatment option.

Treatment of all heterosexual and homosexual contacts of men with GU is essential. In the U.S., gonorrhea has been erratically controlled because treatment of asymptomatic sexual contacts remains inconsistent. This inconsistency preserves a vast human reservoir of *N. gonorrhoeae* and sustains the occurrence of two million cases annually. Asymptomatic gonococcal infection is not limited to women. Thirty to 50 percent of male contacts of women with acute pelvic inflammatory disease have asymptomatic urethral infection, and 20–30 percent of male homosexuals are rectal gonococcal carriers [32,33]. The only means of reducing carrier and transmission rates is by widespread empiric treatment of all sexual contacts of index cases. Once treated, follow-up cultures to detect treatment failure are mandatory. In addition to a urethral culture, homosexual men should have rectal and pharyngeal cultures to exclude persistent extragenital infection. For heterosexual women, cervical and rectal cultures are indicated.
Chlamydia trachomatis

Chlamydialae are unique, tetracycline-sensitive, bacterial pathogens. The inability of these organisms to synthesize ATP obliges intracellular energy parasitism for growth and replication. The species C. trachomatis causes 40–50 percent of NGU [8–10,13]. Evidence linking C. trachomatis to NGU includes: significantly higher isolation rates from patients with NGU compared to controls, serotype-specific IgM antibody production in acute urethral infection, and resolution of urethritis after eradication of the organism with antimicrobial therapy [8–10,13].

Diagnosis of C. trachomatis urethritis requires isolation of the organism in tissue culture or detection of antibody production by microimmunofluorescence [34]. Since neither of these techniques are widely available, a presumptive diagnosis is made by excluding GU with urethral Gram stain and culture. Compared to GU, C. trachomatis urethritis is characterized by a longer incubation period [35], more gradual symptom onset, clear or no discharge in greater than 90 percent of cases [6], and a link with higher socioeconomic status [19].

Complications of C. trachomatis urethritis in men include Reiter’s syndrome in 1–2 percent [36,37], epididymitis in 3 percent, and prostatic involvement in 20–30 percent (largely asymptomatic) [7,13]. In addition, urethral stricture may result from chronic C. trachomatis infection [7,16].

Serious consequences of C. trachomatis infection in women and neonates have been identified. Chlamydia trachomatis can be recovered from the endocervix of most female sexual contacts of men with C. trachomatis NGU [7,13]. Although infection is largely asymptomatic, purulent cervicitis [38], cervical dysplasia [39], pelvic inflammatory disease (PID) [40,41], perihepatitis [42,43], and the acute urethral syndrome [44,45] may develop. Five percent of women are estimated to harbor C. trachomatis, and recent data (culture and serology) implicate it as the cause of 20–35 percent of PID in the U.S. [2,9].

Vertical transmission of C. trachomatis was first recognized in 1910 by Linder, who demonstrated identical intracytoplasmic inclusions in maternal cervical scrapings and conjunctival scrapings from neonates with inclusion conjunctivitis [46]. Screening data currently indicates that 10 percent of pregnant women have cervical C. trachomatis infection [2]. Sixty to 70 percent of infants passing through an infected birth canal become infected [47]. Manifestations of neonatal infection include acute follicular conjunctivitis, nasopharyngitis, serous otitis media, and infant pneumonia [48,49]. Prospectively observations have demonstrated that 35–50 percent of exposed infants develop conjunctivitis and 10–20 percent develop pneumonia. Vertically transmitted C. trachomatis is now recognized as the most common cause of pneumonia in the first six months of life [47]. Furthermore, a tenfold greater incidence of perinatal death has been reported in the offspring of C. trachomatis infected women compared with uninfected controls [50].

The potential morbidity and mortality of C. trachomatis infection demand an aggressive approach to the treatment and control of NGU.

Ureplasma urealyticum

Ureplasma urealyticum, formerly T-strain mycoplasma, is a minute coccobacillary bacterium identified by its ability to hydrolize urea and form tiny, 15–30 μm diameter colonies on agar medium ("T" for tiny colonies). Whether U. urealyticum
is a cause of NGU remains unsettled [11]. The organism has been recovered more frequently and in greater quantity (colony-forming units/ml) from men with non-chlamydial NGU compared to asymptomatic controls [13,51,52]. However, isolation rates from sexually active men without urethritis approach 65 percent [13]. It has been postulated that only certain strains of *U. urealyticum* are pathogenic. The report of urethritis developing in two investigators who inoculated themselves with purified strains of *U. urealyticum* isolated from patients with NGU substantiates this hypothesis [53]. Overall, evidence links *U. urealyticum* to 15–25 percent of NGU [11,13].

No practical means are available to differentiate *U. urealyticum* from *C. trachomatis* urethritis. But, since both organisms are routinely sensitive to tetracycline and erythromycin, differentiation is not required for initial therapy.

*Other Causes of NGU*

*Trichomonas vaginalis* is a rare cause of male urethritis. In a consecutive series of 113 men with NGU, *T. vaginalis* was noted in the urine sediment of only one patient [8]. Even when urethral infection occurs, it is largely asymptomatic [54,55]. Because of its rarity, *T. vaginalis* need not be routinely considered in the initial evaluation of men with urethritis. If suspicion is raised by known contact with vaginal trichomoniasis, the motile protozoan can be detected with 80 percent sensitivity by examination of the morning urine sediment. A culture of the urethral exudate or urine sediment for trichomonas is indicated when microscopic examination is negative and clinical suspicion remains high [56].

*Herpes simplex, Candida albicans, and condylomata accuminata* rarely, if ever, cause urethritis without some extraurethral manifestation visible on the penis.

In 20–25 percent of NGU, no known pathogen can be recovered from the urethra [8,13,14,57]. Culture-negative NGU occurs with greatest frequency among homosexual and bisexual men. Recent data suggests that the causative agent is tetracycline-suppressible. Bowie et al. demonstrated that 44 of 46 patients with NGU who had negative cultures for *C. trachomatis* and *U. urealyticum* responded to minocycline therapy [14]. Although the initial response rate was excellent, over 50 percent of responders developed recurrent urethritis after cessation of treatment, indicating that therapy was not always curative.

**TREATMENT OF NGU**

If polymorphonuclear leukocytes, but no intracellular Gram-negative diplococci (GND) are present on urethral Gram stain, the presumptive diagnosis of NGU can be made. Tetracycline 500 mg four times a day for seven days is the treatment of choice. This regimen will also effectively treat the 10 percent of gonococcal urethritis in which urethral Gram stains are negative (intracellular GND absent). *Chlamydia trachomatis* is uniformly tetracycline-sensitive, and tetracycline-resistant strains of *U. urealyticum* are rare. As noted, the agent responsible for culture-negative NGU also appears to be tetracycline-responsive. Collectively, these three agents account for greater than 90 percent of NGU, which correlates with the 90 percent response rate of NGU to tetracycline [58]. Spectinomycin and sulfonamides are less effective for NGU because *C. trachomatis* is spectinomycin-resistant and *U. urealyticum* is sulfonamide-resistant. Penicillin, ampicillin, and amoxicillin are ineffective, having no activity against either *C. trachomatis* or *U. urealyticum*. The tetracycline analogues, doxycycline 100 mg twice a day or minocycline 100 mg every day, can be
substituted for four-times-a-day tetracycline, but expense is greater and a 15 percent incidence of vestibular toxicity has been reported with minocycline [14]. All sexual contacts of men with NGU should be treated with tetracycline (unless contraindicated). For pregnant contacts, erythromycin 500 mg four times a day for seven days should be substituted. Treatment of contacts will reduce reinfection of index cases, eliminate carriers, and prevent the more serious manifestations of *C. trachomatis* infection in women and infants. Asymptomatic *C. trachomatis* infection has been documented to persist in women for over a year [59]. This chronic carrier state constitutes the major source of horizontal and vertical *C. trachomatis* infection. Failure to recognize and eradicate this reservoir has led to an epidemic of chlamydial diseases in the U.S. [2].

**PERSISTENT AND RECURRENT NGU**

Despite proper treatment, persistent and recurrent NGU are common. In a recent study of 289 men treated with minocycline for NGU, urethritis persisted on therapy in 8 percent and recurred after completion of therapy in 22 percent. Combined persistence and recurrent rates were 19 percent, 32 percent, and 52 percent for *C. trachomatis* urethritis, *U. urealyticum* urethritis, and culture-negative urethritis, respectively [14]. Little information exists on the proper management of persistent or recurrent urethritis.

Urethritis that persists on tetracycline may result from infection with *T. vaginalis* or a tetracycline-resistant strain of *U. urealyticum*. A saline mount of the urethral exudate or morning urine sediment should be performed to detect trichomonads. Whenever possible, the patient's sexual partner should be examined for vaginal trichomoniasis. If trichomonads are detected in either partner, both should be treated with metronidazole 2.0 g orally, in a single dose (contraindicated in pregnancy). When *T. vaginalis* is not detected, a seven-day course of erythromycin 500 mg four times a day is indicated for the possibility of tetracycline-resistant ureaplasma infection [60].

Optimal management of recurrent NGU remains undefined. Extending initial therapy beyond seven days does not prevent recurrences [14]. Reinfection from a new or untreated sexual partner must always be excluded. If reinfection is possible, retreatment of the patient and his contacts is warranted. Relapse from a persistent nidus of infection within the prostate has also been postulated to be a cause of recurrent NGU. For this reason, erythromycin, which has better prostatic penetrance than tetracycline, is recommended for recurrent NGU [16]. A dose of 500 mg four times a day for one to two weeks should be prescribed.

For all cases of urethritis that persist unaffected by antibiotic therapy, cystoscopy to exclude urethral stricture, diverticulum, or neoplasm is imperative.

**SUMMARY APPROACH**

Urethral PMNs must be detected to diagnose urethritis. If PMNs and intracellular Gram-negative diplococci (GND) are seen on urethral Gram stain, treatment of the patient and his sexual contacts for gonorrhea is warranted. The choice of antigonoococcal therapy should depend on the likelihood of medication compliance and the probability of antibiotic resistance or extragenital infection. Of the recommended treatment regimens, only tetracycline will prevent postgonococcal urethritis. If PMNs, but no intracellular GND are present on urethral Gram stain, treatment of the patient and his sexual contacts with tetracycline or erythromycin for NGU is in-
dicated. Differentiation between *C. trachomatis*, *U. urealyticum*, and culture-negative urethritis is impractical and will not alter initial therapy. Regardless of the initial treatment for GU or NGU, all patients should be reexamined after treatment to document cure. Patients with persistent GU should be cultured and treated for PPNG infection with spectinomycin. For persistent NGU, *T. vaginalis* infection must be excluded. If trichomonas infection is not detected, erythromycin is indicated for tetracycline-resistant ureaplasma infection. For recurrent NGU, retreatment of the patient and his sexual partners with erythromycin for one to two weeks is recommended. Urethritis unresponsive to antibiotic therapy should prompt an anatomic evaluation of the urethra.

ACKNOWLEDGEMENTS

I am indebted to Deanna Carbone and Betsey Pesapane for secretarial assistance in preparation of this manuscript.

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