Urethritis is defined as the presence of leukorrhea and urethral inflammation [1]. It is clinically characterized by discharge of mucoid or purulent material and by dysuria. Urethritis has been traditionally differentiated as gonococcal or nongonococcal urethritis (NGU) as the basis for treatment strategies. From a clinical management perspective, further etiologic differentiation of NGU has not been possible technically. A number of different organisms have been associated with NGU. *Chlamydia trachomatis* was long considered to be the cause of the largest subgroup of diagnosable cases of NGU, followed by *Ureaplasma* species [2, 3]. However, identification of specific NGU pathogens is not routinely pursued since the recommended therapies against *Chlamydia* species and the other with the MEDLINE 2000 computerized database of the U.S. National Library of Medicine. The terms *urethritis* (as subject) and *NGU, Chlamydia urethritis*, and *treatment* (as key words) were searched for in titles and abstracts. Two hundred and five citations were found. The search was then limited to articles in the English language with abstracts and concerning human subjects; this reduced the number of citations to 114. Citations were then selected from this group on the basis of clinical and/or management issues.

In this article we review the recent literature on diagnosis and treatment of NGU, focusing on the etiology, treatment, and recommended laboratory tests for acute NGU, the etiology and management of recurrent NGU, and partner notification strategies. We also review the rationale for changes proposed in the 1998 STD treatment guidelines and discuss how these may be applied in a variety of clinical settings, including specialized STD clinics and primary health care practices.

**Methods**

A search of the literature from 1992 to 1996 was conducted with the MEDLINE 2000 computerized database of the U.S. National Library of Medicine. The terms *urethritis* (as subject) and *NGU, Chlamydia urethritis*, and *treatment* (as key words) were searched for in titles and abstracts. Two hundred and five citations were found. The search was then limited to articles in the English language with abstracts and concerning human subjects; this reduced the number of citations to 114. Citations were then selected from this group on the basis of clinical orientation and methodology (i.e., study design, number of subjects, selection criteria, and sampling design) and consideration of etiologic and/or management issues.

We included only those studies that evaluated for multiple etiologies of NGU. For example, studies of the epidemiology and treatment of chlamydial urethritis were not included, as they are addressed in the background article on *Chlamydia* for the 1998 STD treatment guidelines. Additional citations from earlier time periods were used to answer questions not addressed in the current literature. Articles were summarized, including methodologies, predictor and outcome variables, results, and conclusions. These findings were presented at the 1997 Sexually Transmitted Disease (STD) Treatment Guidelines Consultants’ Meeting in February 1997. Conclusions were drawn and recommendations for revisions of the STD treatment guidelines were made.
Table 1. Microbiological causes of nongonococcal urethritis (NGU; >5 WBCs/high-power field).

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients studied</th>
<th>Chlamydia</th>
<th>Ureaplasma</th>
<th>Mycoplasma hominis</th>
<th>Mycoplasma genitalium</th>
<th>Trichomonas</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5]</td>
<td>452</td>
<td>15</td>
<td>28</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>[6]</td>
<td>149</td>
<td>31</td>
<td>42</td>
<td>89</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>[7]</td>
<td>122</td>
<td>19²</td>
<td>4²</td>
<td>2²</td>
<td>26³</td>
<td>3³</td>
<td>12 GC²</td>
</tr>
<tr>
<td>[9]</td>
<td>52</td>
<td>27*</td>
<td>31*</td>
<td>4*</td>
<td>25³</td>
<td>8 GC²</td>
<td></td>
</tr>
<tr>
<td>[10]</td>
<td>103</td>
<td>41</td>
<td>NT</td>
<td>NT</td>
<td>24¹</td>
<td>NT</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. The studies considered were those in which multiple etiologies were assessed. GC = gonococcal; NT = not tested for.
* Determined by culture.
² Determined by EIA.
³ Determined by PCR.

Results

Etiology of NGU

In reviewing the literature, we identified six articles [5–10] and one letter [11] that evaluated the etiology of NGU, with studies including large numbers of men (52 ≤ n ≤ 452) and using more sensitive and specific diagnostic techniques than were previously available. Results of five of these studies are listed in table 1. We also included three additional articles [12–14] from earlier time periods or with a more limited etiologic focus to expand information presented on Trichomonas vaginalis urethritis.

The more recently available nucleic acid amplification techniques employed in these studies for diagnosis of chlamydia infection have a much higher sensitivity and specificity than cell culture for diagnosis of the etiology of NGU [15–17]. For example, in the study by Jaschek et al., cell culture, once considered the “gold standard” for the diagnosis of chlamydial infection, detected only 68% of Chlamydia-positive urethral samples, compared with a 95% detection rate by the urine PCR test [16].

Surprisingly, Chlamydia was found to account for a relatively small proportion of cases of NGU. In the three largest studies, all of which predominantly involved subjects from STD clinics and the use of standardized case definitions for NGU, chlamydia infection was found in 19%–31% of patients (table 1) [5–7]. In the largest study in which etiology was determined as part of a multicenter treatment trial, only 15% of NGU was chlamydial and regional variation was noted; the lowest rates were in the Northwest, where a Chlamydia-control program has been in place since 1988 [18, 19]. In the same three studies, Ureaplasma urealyticum was detected in 9%–42% of cases. Therefore, even under the best of circumstances, up to two-thirds of gram stain–documented NGU is not due to these two organisms. These findings have led to the consideration of other possibilities.

Mycoplasma genitalium is a recently characterized, slowly growing organism. The first reports of its isolation in cultures of urethral swabs from men with NGU were published in 1981 [20]. The controversy surrounding its pathogenicity in cases of urethritis is due to the numerous failed attempts to isolate M. genitalium from men with NGU [9, 10, 21]. The advent of PCR testing has enabled investigators to detect small quantities of M. genitalium DNA [22]. M. genitalium was found to bestudies including large numbers of men (52 ≤ n ≤ 452) and using more sensitive and specific diagnostic techniques than the pathogen responsible in 15%–25% of NGU cases by PCR testing [7, 9, 10, 11]. In the recent case-control studies reviewed, M. genitalium was isolated significantly more frequently in the symptomatic NGU cases than in the nonurethritis (control) cases [9–11]. M. genitalium was not isolated from anatomical sites other than the urethra, such as the throat or rectum. The investigators in these studies concluded that Mycoplasma was likely to be a cause of NGU. Nevertheless, these investigations were based only on cross-sectional studies and on isolated case reports. Therefore, until more data are available, the relationship between M. genitalium and NGU cannot be considered causal.

T. vaginalis, a protozoan parasite, infects the urogenital tract and is recognized as a common cause of urogenital disease, particularly among infected women [23, 24]. Traditional expert opinion cites that infected men are usually asymptomatic and that morbidity arises primarily from infection of their sex partners. However, the lack of a sensitive test for T. vaginalis in most clinical settings has prevented diagnosis of trichomoniiasis as one of the etiologies of urethritis [25]. T. vaginalis may play a greater role in the etiology of NGU than previously suspected. Borchardt et al. found the prevalence of T. vaginalis to be 12% when utilizing the InPouch TV culture system (BioMed Diagnostics, San Jose, CA) and only 3% when utilizing the traditional wet-mount-examination method in a cross-sectional study of 204 men examined at an STD clinic [8]. This study illustrates the poor sensitivity of the traditional wet-mount test for trichomoniiasis in males.

With use of modified Diamond’s culture medium, Krieger et al. recovered T. vaginalis from urethral swab and first-void-urine specimens from 22% of 147 men who had sexual exposure to trichomoniiasis and from 6% of 300 randomly selected
Chlamydia

Chlamydia, 35% of the NGU cases [7]. In a multicenter study using cell compared to urethral cell cultures [29, 30]. Urine-based direct

unnounced in areas with

cases. No identi®ed NGU etiology has been particularly pro-

examined NGU etiology found

thral swabs, in which

Chla-

mydia

from

men presenting to an STD clinic [13]. T. vaginalis was isolated from 18% of 123 men with nonchlamydial NGU, 11% of 82 men with gonococcal or chlamydial urethritis, and 8% of 242 men without urethritis.

Hoosen et al. identified T. vaginalis, by means of culture with modified Diamond’s medium and by wet mount of urethral swabs, in 14.7% of 55 male patients with persistent urethritis [14]. These rates of trichomonas NGU, which are higher than previously reported, suggest that trichomoniiasis could be a cause of acute and persistent urethritis that does not respond to traditional antimicrobial therapy. Although popular belief posits that most trichomonas NGU cases resolve spontaneously by 2 weeks without treatment, one study documented spontaneous resolution in only 36% of 20 untreated asymptomatic men who remained sexually abstinent during a mean of 16 days [12, 26].

Despite the improved diagnostic capabilities, the proportion of NGU cases without an identified etiology has been increasing. Janier et al. found 20% of patients with NGU to be infected with indeterminate pathogens (Haemophilus parainfluenzae, group B streptococci, Gardnerella vaginalis, Mycoplasma hominis, other Streptococcus species, Staphylococcus aureus, and Candida albicans), while no pathogens were recovered in 35% of the NGU cases [7]. In a multicenter study using cell culture of urethral swabs for isolation of Chlamydia, seven of the participating centers isolated Chlamydia from <20% of men with acute NGU, whereas only two centers isolated Chla-

mydia from >30% of men presenting with acute NGU [5]. This contrasts with previous studies using cell culture of ure-

thral swabs, in which C. trachomatis accounted for 35%±45% of acute NGU cases [3]. Five of the six studies reviewed that examined NGU etiology found C. trachomatis in <35% of cases. No identified NGU etiology has been particularly pronounced in areas with Chlamydia-control programs.

Laboratory Diagnosis

Gram staining. Although gram staining is still widely used to diagnose urethritis, the question arises as to the relevance of the microscopic definition of urethritis if new diagnostic capabilities can isolate STD pathogens in asymptomatic men and/or in men who may not meet the microscopic criteria for NGU. Recent studies evaluating the etiology and treatment of NGU have continued to rely on gram staining to define this syndrome and to identify gram-negative diplococci [5, 7, 9–11]. One of these studies evaluated the utility of urethral-smear gram staining and leukocyte count of centrifuged first-void urine to diagnose urethritis in men presenting to an STD clinic [7]. Etiologic results were obtained in all cases, regardless of symptoms and smear results. At least one STD pathogen was isolated from the urethra of 46% of men with urethral discharge but who did not meet the microscopic definition of urethritis. In addition, at least one STD pathogen was isolated from the urethra of 16% of men with neither urethral discharge nor microscopically evident urethritis.

Etiologic Diagnosis

Chlamydia. Until the recent development of nucleic acid–based diagnostic tests, tissue culture of urethral swab speci-
mens was the “gold standard” for diagnosing chlamydial infection. Problems with this method involve patient discomfort, expense, labor, strict transport requirements, and time to comple-
tion of test (up to 72 hours). In addition, there appears to be a difference in culture sensitivity between the male urethral and female endocervical specimens (50%–85% vs. 70%–85%, respectively) [16, 27, 28]. This discrepancy has been postulated to be due to the less efficient sampling of the male urethra. A smaller swab is used and the urethra has a smaller surface area to be sampled.

Urine-based diagnostic tests decrease costs and time to test completion. They also prevent the discomfort associated with urethral sampling and may thereby improve patients’ acceptance of diagnostic testing. The urine EIA, although promising when released, proved to have an unacceptably low sensitivity of only 53% for detecting Chlamydia in first-void urine, as compared to urethral cell cultures [29, 30]. Urine-based direct fluorescent antibody (DFA) tests appear to be more effective. In one study, a urine DFA test appeared to be more sensitive than a urethral DFA test, regardless of time after voiding (90% sensitivity via urethral DFA test vs. 83% sensitivity via urethral DFA test) [31].

DNA amplification testing via both urethral and urine speci-

mens has superior sensitivity and specificity in comparison with all other available tests for etiologic diagnosis of NGU [15–17, 27, 28, 31, 32]. As previously mentioned, M. genitalium has been consistently detected from the urethra only by PCR techniques [9, 10, 21, 22]. In a study looking at chlamydial infection among sexual contacts, PCR identified 50% more infected individuals than culture, with a greater increase in the yield of positive tests among males than among females [28]. The frequency of isolation of Chlamydia from male partners of infected females rose from 42% by culture to 68% by PCR. Half of the men in this study were asymptomatic, making PCR an attractive diagnostic method for etiologic identification of asymptomatic urethritis, especially with use of urine specimens.

The disadvantage of any nonculture test is the inability to differentiate active infection from cured infection. For example, after bacterial lysis, DNA fragments may persist and give a false-positive result. A study of 33 adolescent females with chlamydial infection diagnosed by both PCR and ligase chain reaction (LCR) urine tests showed that all follow-up PCR and LCR tests were negative by 15 days following therapy [33]. However, the time period for this “carryover” is still not well defined. This disadvantage must be weighed against the advantage of patients’ acceptance of a urine-based test over urethral
swabbing, improved power of detection of both symptomatic and asymptomatic disease, and eradication of latent infection that could lead to transmission.

*Trichomonas.* The original studies of Krieger et al. found that culture of urethral scrapings in Diamond’s medium was the most sensitive technique for diagnosis of urethral trichomoniasis [12, 34]. However, use of this technique is limited by lack of availability and the discomfort associated with urethral swab sampling. Recently, the self-contained InPouch TV culture medium has become available. A cross-sectional study of 204 men examined at an STD clinic identified 24 cases of *T. vaginalis* by InPouch TV urine culture; only 3 were found by the standard wet-mount technique [8]. The InPouch TV urine culture is a simple and highly sensitive test. Unlike most of the diagnostic tests already described, this test can be performed in an office and offers the advantage of using urine rather than a urethral specimen.

*Ureaplasma and mycoplasma infections.* Diagnosis of these requires specialized media and laboratory and transport facilities. Since in many cases it is difficult to ascertain whether the organism is a pathogen or a commensal, specific diagnosis is not recommended except in a referral or research setting.

### Diagnostic and Management Strategies

Documentation of urethritis is essential when patients present with dysuria, burning, and frequency, since these symptoms may be due to etiologies other than treatable STDs. If mucoid or purulent discharge is not evident on examination, then either a positive leukocyte esterase test (LET) of first-void urine or a gram stain of FVU can document the syndrome. The gram stain offers the opportunity to differentiate gonococcal urethritis from NGU. Gram stains are not available in most clinical practice settings such as ambulatory care clinics, offices, and emergency departments. Therefore, clinicians must rely on documentation of discharge by examination or by a positive LET to fulfill the criteria for urethritis. This is a problem because of clinicians’ desire to establish objectively the presence of urethritis and an etiologic diagnosis. There is also a clinical and public health imperative to provide effective treatment at the time of the visit.

New etiologic diagnostic tests with very high sensitivities and specificities have demonstrated that asymptomatic urethritis is more common than previously suspected. Table 2 lists all the studies reviewed that distinguish urethritis etiologies in terms of symptomatology and/or microscopic findings. Between 5% and 58% of urethritis cases in these citations were asymptomatic and between 5% and 38% of cases had microscopic findings of <5 polymorphonuclear leukocytes (PMNs) per hpf on a gram stain or <10 WBCs/hpf in a spun urine specimen. How do we then define urethritis if standard definitions have proven to be insensitive screens for identification of STD pathogens?

### Table 2. Data from the reviewed studies in which the etiology of urethritis was determined on the basis of symptomatology and/or microscopic findings.

<table>
<thead>
<tr>
<th>Characteristic distinguishing etiology, reference</th>
<th>Organism</th>
<th>Method of detection</th>
<th>No. of patients with characteristic/total no. infected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation of STD pathogens; no signs or symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td>Chlamydia</td>
<td>Urine PCR</td>
<td>32/79 (40.5)</td>
</tr>
<tr>
<td>[7]</td>
<td>Chlamydia</td>
<td>Culture, EIA</td>
<td>7/28 (25.0)</td>
</tr>
<tr>
<td>[10]</td>
<td>Ureaplasma</td>
<td>EIA</td>
<td>3/15 (20.0)</td>
</tr>
<tr>
<td>[9]</td>
<td>Chlamydia</td>
<td>DFA test</td>
<td>2/40 (5.0)</td>
</tr>
<tr>
<td>[12]</td>
<td>Ureaplasma</td>
<td>Culture</td>
<td>4/18 (22.2)</td>
</tr>
<tr>
<td>&lt;5 WBCs/hpf on gram stain of urethral smear or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 WBCs/hpf on gram stain of FVU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[31]</td>
<td>Chlamydia</td>
<td>DFA test</td>
<td>4/78 (5.1)</td>
</tr>
<tr>
<td>[7]</td>
<td>Chlamydia</td>
<td>Culture, EIA</td>
<td>8/28 (28.6)</td>
</tr>
<tr>
<td>[10]</td>
<td>Ureaplasma</td>
<td>EIA</td>
<td>5/15 (33.3)</td>
</tr>
<tr>
<td>[12]</td>
<td>Trichomonas</td>
<td>Culture</td>
<td>19/50 (38.0)</td>
</tr>
</tbody>
</table>

NOTE. DFA = direct fluorescent antibody; FVU = first-void urine; hpf = high-power field; STD = sexually transmitted disease.

### Treatment

Stamm et al. compared a single 1-g dose of azithromycin to a 7-day course of doxycycline in a randomized, double-blind, multicenter trial of empirical treatment for NGU [5] (table 3). These patients were also evaluated for infection by culture for *C. trachomatis* and *U. urealyticum* (*Neisseria gonorrhoeae* was excluded by culture). Clinical cure rates were comparable among the 248 patients in the azithromycin-treated group (90%) vs. the 123 in the doxycycline-treated groups (89%). Patients were reevaluated for infection at 2 and 5 weeks after study enrollment. Clinical cure rates were similar in the two groups when stratified for presence or absence of *C. trachomatis* and *U. urealyticum* prior to treatment. Adverse reactions, mostly gastrointestinal, were mild to moderate and occurred in 23% of azithromycin-treated and 29% of doxycycline-treated patients.

A lower dose of azithromycin did not prove effective for the treatment of NGU. In a study of 11 men who were administered a single 500-mg dose of azithromycin for treatment of NGU, only 4 were cured, the therapy of 3 failed, and 4 were lost to follow-up by 4 weeks after treatment [32].

Although the theoretical advantage of a single-dose treatment for NGU appears obvious, studies comparing rates of both symptomatic and etiologic cure of NGU do not prove an advantage over a 7-day course of doxycycline [5, 35–37] (table 3). Cost of therapy is an important issue, especially in the
Table 3. Data from prospective studies of therapy for nongonococcal urethritis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial design</th>
<th>Therapy</th>
<th>Chlamydia</th>
<th>Ureaplasma</th>
<th>Total: any or no pathogen isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5]</td>
<td>Randomized,</td>
<td>Azithromycin (1 g stat)</td>
<td>At 2 w, 36/38 (95); at 5 w, 27/30 (90)</td>
<td>At 2 w, 67/92 (73); at 5 w, 37/71 (52)</td>
<td>At 2 w, 222/248 (90); at 5 w, 171/193 (89)</td>
</tr>
<tr>
<td></td>
<td>controlled</td>
<td>vs. Doxycycline (100 mg b.i.d. for 7 d)</td>
<td>At 2 w, 26/28 (93); at 5 w, 23/23 (100)</td>
<td>At 2 w, 22/34 (65); at 5 w, 17/30 (57)</td>
<td>At 2 w, 110/123 (89); at 5 w, 84/89 (95)</td>
</tr>
<tr>
<td>[35]</td>
<td>Randomized,</td>
<td>Azithromycin (1 g stat)</td>
<td>73/79 (92)</td>
<td>30/35 (86)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>nonblinded</td>
<td>vs. Doxycycline (100 mg b.i.d. for 7 d)</td>
<td>68/69 (99)</td>
<td>20/25 (80)</td>
<td>...</td>
</tr>
<tr>
<td>[6]</td>
<td>Randomized,</td>
<td>Minocycline (100 mg daily for 7 d)</td>
<td>At 4 w, 19/19 (100)</td>
<td>At 4 w, 15/24 (63)</td>
<td>At 4 w, 58/65 (88)</td>
</tr>
<tr>
<td></td>
<td>controlled</td>
<td>vs. Doxycycline (100 mg b.i.d. for 7 d)</td>
<td>At 4 w, 21/21 (100)</td>
<td>At 4 w, 12/19 (63)</td>
<td>At 4 w, 61/74 (82)</td>
</tr>
</tbody>
</table>

public health sector, where funds are limited. In a 1995 study by Stamm et al. [5], the cost of azithromycin therapy was 10 times that of doxycycline.

Other therapeutics do not appear to offer any advantage over doxycycline or azithromycin for the treatment of NGU. Minocycline was shown to be as effective as doxycycline in curing both chlamydial NGU and nonchlamydial NGU in a randomized controlled trial [6]. Both treatment courses were 7 days. Although adverse effects occurred more frequently in the doxycycline treatment group than in the minocycline treatment group in this study, earlier studies documented severe adverse effects, including vestibular dysfunction with the administration of minocycline [38, 39]. Therefore, this therapy is not widely used.

Studies of ofloxacin and clarithromycin demonstrated efficacy equivalent to that of doxycycline for treatment of chlamydial and nonchlamydial NGU, but sample sizes were small ([40] and personal communication, W. McCormick). The efficacy and safety of a 7-day course of sparfloxicin were comparable to those of doxycycline in a double-blinded randomized multicenter study of 725 men with clinically diagnosed NGU and >5 PMNs/hpf on urethral microscopy who were tested by culture for N. gonorrhoeae, C. trachomatis, U. urealyticum, and M. hominis [41]. A 3-day sparfloxacin course was associated with a lower C. trachomatis eradication rate than were both of the 7-day courses of therapy.

In all of these studies, cure rates and relapse rates differed by etiology, although not by therapy. For example, Stamm et al. demonstrated 94% microbiological cure at 2 weeks, with little difference at 5 weeks’ follow-up, in cases of chlamydial urethritis. In contrast, the microbiological cure rates for patients with ureaplasma urethritis were lower: 71% at 2 weeks and 53% at 5 weeks [5]. Romanowski reported similar endpoints at 4 weeks’ follow-up, with a 100% cure rate for chlamydial urethritis and 63% for ureaplasma urethritis [6]. An older study examining the prevalence of tetracycline-resistant U. urealyticum revealed persistence of NGU in three of six men infected with Ureaplasma strains for which the MICs were >256 μg/mL at 6–8 days after initiation of treatment with minocycline [42]. This is an important point to keep in mind, since the prevalence of nongonococcal nonchlamydial pathogens in cases of NGU is increasing.

Discussion

Management: Is the Term NGU Obsolete?

Over the last decade, sensitive diagnostic tests for chlamydia infection have become widely available. The development of noninvasive urine nucleic acid amplification tests has made the screening of males feasible. The epidemiology of NGU is changing, with a decline in the proportion of cases resulting from chlamydial infection, particularly in areas with well-established chlamydia screening programs. The question then arises as to the need for new terminology defining urethritis, i.e., gonococcal, chlamydial, and nongonococcal/nonchlamydial urethritis.

Differentiation between chlamydial and nonchlamydial urethritis is important because of the different public health approaches to control, such as partner notification and management of treatment failure. However, regulatory and cost restrictions prohibit access in most clinical settings to gram staining and nucleic acid amplification testing. How, then, can widespread diagnostic screening for urethritis be implemented, given the reality of current limitations in most clinical settings?
Diagnosis: Documentation of Urethritis

Ideally, patients with urethral complaints should have urethritis documented by gram staining and diagnostic testing for *N. gonorrhoeae* and *C. trachomatis*. If gonococcal infection is presumptively diagnosed with gram staining, then routine treatment includes cotreatment for chlamydia infection. If urethral inflammation is seen but gram-negative diplococci are not observed, attempts should be made to differentiate between chlamydial urethritis and nonchlamydial NGU. This is facilitated by testing for *Chlamydia*. Unfortunately, sensitive rapid (stat) tests to diagnose chlamydial infection are not yet available. Nevertheless, identification of a specific causal pathogen may improve patients’ compliance and increase the success of partner-notification efforts. Diagnostic information can also provide information on prognosis and the likelihood of recurrence.

Treatment

On the basis of the recent literature, it appears that among treated patients with chlamydial urethritis, a high cure rate is ensured if they are compliant with the appropriate antibiotic regimen. Conversely, for patients with nonchlamydial NGU, relapse rates can be expected to be up to 50% after 2 months. Knowledge of etiology also helps discern whether patients are at continued risk. For example, recurrence of chlamydial infection would more likely be due to reexposure or continued high-risk activity than to treatment failure.

Because of the lack of availability of tests, assessment for trichomonas infection is routinely indicated only for patients with urethritis (gonococcal, chlamydial, or nongonococcal/non-chlamydial) who do not fully respond to therapy. Many practitioners prefer to treat these patients empirically because treatment with metronidazole is inexpensive.

Public Health Approach: Partner Notification

Partner referral for presumptive treatment is recommended for cases of chlamydial urethritis and will be increasingly important as state and local health departments develop and expand *Chlamydia*-control programs. In contrast, partner referral is not routinely recommended for cases of nonchlamydial NGU. Many of the organisms implicated in nonchlamydial NGU, such as *Mycoplasma* and *Ureaplasma*, are also found as commensals. Thus, sexual transmission cannot always be assumed. In addition, the large proportion of cases in which no specific etiology is identified has been problematic for public health intervention. Most experts believe that partner referral is not routinely indicated for nongonococcal, nonchlamydial urethritis.

The current guidelines have attempted to address these issues through the following principles:

1. Etiologic definition of urethritis (for gonorrhea and chlamydial infection) is desired in all cases, even if treatment is given. Diagnosis facilitates the public health surveillance (reporting) process and also facilitates the referral of sex partners for treatment.

2. If gram staining is not available, urethritis should be documented by physical examination or by a positive urine LET. With few exceptions (adolescents being the most prominent example), the diagnosis should not be made on the basis of symptoms alone.

3. When a diagnosis of urethritis is made, syndromic treatment strategies are recommended if gram staining is not available. In most cases, this would be treatment for gonococcal and chlamydial urethritis. Practitioners in areas with extremely low gonorrhea rates may not have to treat for gonorrhea. This decision should be made in consultation with local health authorities.

4. Partner referral or other interventions for sex contacts should be instituted on the basis of a positive test for gonorrhea or chlamydial infection. There are situations, however, in which syndromic treatment is given and diagnostic tests are not performed. In these cases, partner referral and similar treatment of the partner are recommended.

Conclusions and Recommendations

The 1998 STD treatment guidelines divide urethritis into four mutually exclusive categories (figure 1).

1. **Asymptomatic.** This category includes presence of subjective symptoms, but objective evidence of inflammation is not obtained by the documenting of discharge, a positive LET, or a finding of $\geq 5$ WBCs/hpf on gram staining. Treatment is deferred until tests for gonorrhea and chlamydial infection are done. This approach will prevent unnecessary treatment but will identify cases of asymptomatic urethritis, especially if a nucleic acid amplification test is used. Among adolescents or in other groups where compliance or follow-up is especially problematic and prevalence of chlamydial/gonococcal infection is high, presumptive treatment should be considered.

2. **Urethritis with gram staining, which can be further differentiated into gonococcal urethritis and NGU.** If a gram stain identifies gram-negative diplococci, treatment for both gonorrhea and chlamydial infection is recommended. Partner referral is recommended. If a gram stain is negative for gonorrhea but still meets the criteria for urethritis, empirical treatment for NGU and testing for *N. gonorrhoeae* and *C. trachomatis* is recommended; partners should be referred if those tests are positive.

3. **Urethritis documented either by the presence of discharge or by a positive LET, with no gram staining result available.** Empirical treatment and diagnostic testing are recommended for both gonorrhea and chlamydial infection. Partners should be referred if these tests are positive. Again, partners need not be treated if neither *C. trachomatis* nor *N. gonorrhoeae* is
isolated, since the pathogenicity in the female partner is still unclear for organisms causing nonchlamydial NGU.

(4) Recurrent/persistent urethritis. Effective regimens have not been identified for treating patients who experience persistent symptoms or frequent recurrences following treatment. Common sense warrants that patients with persistent or recurrent urethritis who failed to comply with their original treatment regimen or are reexposed to an untreated partner should be retreated. Directly observed single-dose therapy and greater efforts toward partner management should also be considered. In addition, a wet-mount examination and culture of an intraurethral swab specimen for T. vaginalis should be performed, given the recent increased identification of this organism as a cause of urethritis. If the patient was compliant with the initial regimen and reexposure can be excluded, we recommend empirical treatment for trichomoniasis with 2 g of metronidazole, along with a 7-day course of erythromycin. If symptoms continue to persist, referral to a specialist may be warranted.

**Major Research Needs**

(1) Single-dose compared to multiple-dose regimens. Since the single-dosing regimen may be cost-prohibitive in many settings, especially in the public sector, we need to know the minimum effective dose of doxycycline. Doxycycline has been shown to be effective in the treatment of NGU at a dosage of 200 mg once daily, but clinicians need to know if shorter courses or lower doses are an option for effective treatment [41].

(2) Asymptomatic and gram stain-negative urethritis. The new nucleic acid amplification tests have raised several questions about defining the NGU syndrome. Does our classic criterion of the presence of PMNs on microscopy need to be changed if we are now isolating pathogens in asymptomatic patients who do not meet this criterion?

(3) Definition and etiology of persistent urethritis. We still do not have a good understanding of the etiology and optimal management of persistent urethritis. We need randomized controlled trials to give us some direction in our approach to these cases.

(4) Operational research. The term NGU is obsolete and represents several clinical entities. What are the appropriate diagnostic and treatment paradigms?

**References**