Nonchlamydial nongonococcal urethritis in men

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**A R T I C L E   I N F O**

Article history:
Received 15 March 2013
Received in revised form
12 April 2013
Accepted 5 June 2013
Available online 15 August 2013

Keywords:
onechlamydial urethritis
nongonococcal urethritis

**A B S T R A C T**

By definition, nonchlamydial urethritis (NGU) is an infectious condition involving urethral inflammation without Neisseria gonorrhoeae infection. According to recent studies, NGU accounts for 10–30% of initial visits to sexually transmitted infection (STI) clinics, and is one of the most common forms of STI in men. Chlamydia trachomatis is the most prevalent and well-established pathogen in NGU. However, nonchlamydial NGU is still a problematic disease in clinics because of its minimally symptomatic or asymptomatic manifestation. Various infection causes, including Mycoplasma, Trichomonas vaginalis, and herpes simplex virus, are possible pathogens in nonchlamydial NGU. In this brief review, we focus on the evaluation and management of nonchlamydial NGU.

1. Introduction

According to the National Health Insurance Database in Taiwan, the prevalence of sexually transmitted infection (STI) has been gradually rising in the past decades. Neisseria gonorrhoeae and Chlamydia urethritis are the most common pathogens of STIs in men. Nongonococcal urethritis (NGU), characterized by a urethral inflammation that is not caused by N. gonorrhoeae infection, is probably the most common form of STI in men. It accounts for 10–30% of new male cases in STI clinics. Many pathogens can be identified for NGU and Chlamydia trachomatis is the most prevalent and well-established. C. trachomatis infection accounts for 15–40% of cases of initial NGU, and some studies have reported up to 50% of new cases. However, nonchlamydial NGU is still a problematic disease for clinics. Various infectious pathogens, including Mycoplasma, viruses, and protozoan parasites, are possible causes of NGU and exhibit similar symptoms. However, pathogens still cannot be detected in most cases of nonchlamydial NGU. This makes it difficult for physicians to make an accurate diagnosis.

In this brief review, we focus on the common pathogens of nonchlamydial NGU: their prevalence, evaluation, and pathogenesis. The recommended regimens and prevention strategies for various causes of nonchlamydial NGU are also discussed in this article.

2. Urethritis

Urethritis, which is characterized by urethral inflammation, results from infectious, traumatic, and immune sources. In the infectious case, urethritis is usually acquired through an STI and shows similar symptoms and signs. In general, mucopurulent or purulent discharge from the urethral meatus and dysuria are the most common presentations. An itching or burning sensation in the urethra is also typical. It is diagnosed according to the mentioned findings or one of the following laboratory tests. The diagnosis is positive if a Gram stain of urethral discharge shows more >5 white blood cells (WBCs) per oil-immersion field. This recommended microscopic test is rapid, and features high sensitivity and specificity to identify a gonorrheal infection. The diagnosis is positive if a microscopic examination of first-void urine shows >10 WBCs per high-power field. The diagnosis is positive if a leukocyte esterase test of first-void urine shows positive results.

Using a urethral swab to collect secretions for cultures, hybridization tests, or nucleic acid amplification tests (NAATs) is a common diagnostic method to confirm a pathogen, whereas first-void urine specimens can only be tested using NAATs. Recently, NAATs have become gradually accepted and preferred for confirmation of the pathogen of infectious urethritis because of their high sensitivity and specificity. If diagnostic tests and microscopic tests are unavailable, the Center for Disease Control and Prevention (CDC) recommends that sexually active patients who present with urethritis upon examination be treated with drug regimens effective against both gonorrhea and chlamydia. Despite the availability of numerous testing methods, a pathogen still cannot be detected in many cases of urethritis, especially in nonchlamydial NGU. Numerous cases of nonchlamydial NGU go unnoticed because of

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** There are 3 CME questions based on this article.
most NGU patients. Recent data supporting *U. urealyticum* as a commensal or pathogenic bacterium are inconsistent. Further studies are required to improve our understanding of the role of *U. urealyticum* in NGU.

In a clinical manifestation of NGU, the urethral discharge is usually clear or mucoid, and has >5 WBCs per oil-immersion field. Although *M. genitalium* infection of NGU usually induces symptoms of urethral inflammation, asymptomatic infection is still common. The typical diagnostic methods used to detect *M. genitalium* urethritis are culture or direct microscopic smear. However, these two methods have relatively low sensitivity. A culture test requires swab specimens from the urethra. *M. genitalium* is more difficult to culture than other species of *Mycoplasma*, therefore, cultures have little benefit in clinical diagnosis. In recent clinical practice, *M. genitalium*-related NGU has been detected with NAATs by testing first-void urine or collecting urethral discharges. *Mycoplasma* spp. have no cell wall, thus, *M. genitalium* is resistant to all β-lactams or cephalosporins. The recommended antibiotics for *M. genitalium*-related NGU are macrolides (such as azithromycin) or tetracyclines (such as doxycycline). The dose regimens are the same as for chlamydial infection, and treatment should start after diagnosis. Some studies have reported that a single 1-g dose of azithromycin is more effective than doxycycline. However, treatment using these two antibiotics fails in some cases of chronic NGU caused by inadequate treatment and recurrent infection.

### 4. Trichomoniasis

Trichomoniasis is caused by *Trichomonas vaginalis* and is the most prevalent nonviral STI in sexually active populations, and affects an estimated 170 million people worldwide. *Trichomoniasis*, which is primarily observed in women, presents as an asymptomatic manifestation in up to one-third of infected women. Symptomatic manifestations involve inflammation, an itching sensation around the genital area, vulvar irritation and erythema, and is the most frequently reported pathogen in nonchlamydial NGU. Approximately 15–25% of cases of NGU are thought to be caused by *M. genitalium*. Previous studies have demonstrated a strong association between *M. genitalium* infection and NGU in men, especially among those with recurrent or persistent NGU. In contrast to the positive correlation of *M. genitalium* to NGU, *U. urealyticum* is relatively uncommon and weakly associated with

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**Fig. 1.** Nonchlamydial nongonococcal urethritis presents with mucopurulent discharges from the urethral meatus.

**Fig. 2.** Light microscopic picture of *Trichomonas vaginalis* smear.
purulent vaginal discharge, decreased vaginal pH level, and a typical erythematous cervix with punctate areas of exudation, also known as a strawberry cervix. However, the prevalence of the \( T. \text{vaginalis} \) infection in men is not well known because most infected men have minimal or no symptoms and transmit the pathogen unknowingly.\(^\text{15}\) In a recent study, 75% of infected men were asymptomatic.\(^\text{16}\) Other screenings of the community showed that the prevalence of trichomoniasis in men is approximately 10%\(^\text{17}\) in nonclinical cases and 12–17% in STI clinical cases.\(^\text{18–20}\) Other infected male patients may have symptoms similar to those of other NGUs. \( T. \text{vaginalis} \) has been recognized as a cause of non-chlamydial NGU in men, in whom it has the potential to induce balanoposthitis, epididymitis, urethral stricture, prostatitis, infertility, and even prostate cancer.\(^\text{21–25}\)

Various diagnostic methods are used to detect \( T. \text{vaginalis} \)-related NGU. Typically, diagnosis of trichomoniasis in men is confirmed by direct microscopic examination of secretions from all genitourinary sites, such as the urethra, epididymis, prostate, and semen (Fig. 2). However, this method has relatively low sensitivity, and is impractical in clinical and nonclinical settings.\(^\text{4}\) Culture testing of a urethral swab, first-void urine, or semen is another highly specific option. However, it is still not a sensitive diagnostic method. Urethral cultures are able to grow \( T. \text{vaginalis} \) in only 60% of cases.\(^\text{25}\) However, recent polymerase chain reactions and rapid antigen tests for the detection of \( T. \text{vaginalis} \) from first-void urine or urethral swabs have superior sensitivity for \( T. \text{vaginalis} \) diagnosis in men, and have become increasingly popular.\(^\text{18,26–28}\) A single 2-g dose of metronidazole or tinidazole, taken orally, is the regimen

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**Fig. 3.** The algorithm for the management of nonchlamydial nongonococcal urethritis in men. HSV = herpes simplex virus; IgG = immunoglobulin G; NAAT = nucleic acid amplification tests; PCR = polymerase chain reaction.
recommended by the CDC for *T. vaginalis* infection, or recurrent NGU, in men. The alternative regimen is 500 mg metronidazole taken orally twice a day for 7 days.\(^5\) Patients should avoid drinking alcohol during treatment, and for at least 24 hours after completion of metronidazole or 72 hours after completion of tinidazole, to prevent a disulfiram-like reaction.

This infection is typically acquired during sexual intercourse, and other circumstances of contamination are rare. Even without symptoms, an asymptomatic carrier continues to infect or reinfect a sexual partner until he or she has been treated. In a previous study, *T. vaginalis* was isolated from 67–100% of female partners of infected men and 14–60% of male partners of infected women.\(^{20}\) A more recent study also indicated that 73% of male sexual partners of women who had trichomoniasis were positive for *T. vaginalis* infection.\(^{16}\) Another community-based study showed that the prevalence of trichomoniasis was 10.7% in women and 6.3% in their male partners.\(^{10}\) Therefore, we suggest a concomitant survey and, if necessary, treatment of sexual partners of the infected person when the diagnosis of *T. vaginalis* infection is confirmed.

5. Herpes simplex virus

Herpes simplex virus (HSV) is an important pathogen in genital and oral isolates and is separated into two types. Both HSV-1 and HSV-2 have been recognized as causes of chronic, life-long genital infections. HSV-2 infection has been identified as the dominant cause of most recurrent genital ulcers. However, most people infected with HSV-2 are asymptomatic and have not been diagnosed with genital herpes. It is a major problem that many of these people tend to be unaware of their infection, and transmit the infection to their sexual partners.

However, in populations with a high frequency of orogenital exposure and anal intercourse, an increasing proportion of anogenital HSV-1 infection has been noted. Up to 50% of primary genital herpes is caused by HSV-1, but its recurrence and subclinical shedding are much less frequent than for genital HSV-2 infections.\(^{3,5,31}\) The typical clinical manifestation of a genital HSV infection is painful genital, anal, or perianal vesicles and ulcers, but many genital HSV infections are still subclinical. HSV is also a reported pathogen of NGU. Genital itching, dysuria, vaginal or urethral discharge, and tender inguinal lymphadenopathy are other predominant local symptoms of HSV infection. Urethral discharge and dysuria, which are similar to the classical symptoms of NGU, are noted in approximately one-third of men with a primary HSV infection.\(^3\) Bradshaw et al\(^{1}\) have indicated that HSV, usually HSV-1, accounts for 2–5% of cases of NGU. Consequently, sexually active patients and sexual partners with genital herpes or mucocutaneous lesions should be tested for HSV infection when NGU is diagnosed.

Virological tests, identification of HSV from first-void urine or urethral swab using a cell culture or NAAT, are more reliable than a physical examination, but are not widely available. Type-specific serological assays for immunoglobulin G antibodies of HSV, which determine the virus type, are more useful in clinical settings to survey latent-virus infection. Conversely, immunoglobulin M serological tests are not suggested as a diagnostic method because of long-term persistence in chronic herpes, the frequency of false results, and non-type-specific assays. Unlike recurrent genital HSV, which is usually self-limited, all primary genital herpes-related NGUs should be treated with recommended regimens of acyclovir, famciclovir, or valacyclovir, in addition to azithromycin or doxycycline.\(^1\)\(^,\)\(^4\) The regimens recommended by the CDC are: 400 mg acyclovir taken orally five times daily for 7–10 days; 250 mg famciclovir taken orally three times daily for 7–10 days, or 1 g valacyclovir taken orally twice daily for 7–10 days. Systemic antiviral drugs, which are capable of controlling the symptoms and reducing the duration of herpes episodes, offer clinical benefits to most symptomatic patients. However, these drugs cannot destroy latent viruses. To reduce recurrence of HSV, suppressive therapy for recurrent genital herpes has been established. Suppressive antiviral therapy has been reported to reduce the frequency of genital herpes recurrences by 70–80%.\(^{4,32}\) Topical therapies with antiviral drugs have minimal and limited benefits.

6. Conclusion

Asymptomatic infections are common and many patients are treated without diagnostic confirmation. Therefore, the prevalence of nonchlamydial NGU is likely to be much higher than reported. In clinical practice, it is a major problem that accurate diagnoses or adequate solutions are usually absent in most cases of nonchlamydial NGU. *M. genitalium* is the most common pathogen and causes 15–25% of nonchlamydial NGU. Recurrent and persistent nonchlamydial NGU should be evaluated for drug compliance and uncommon infection, such as *T. vaginalis*, *U. urealyticum*, or HSV infection. All persons with nonchlamydial NGU should remain abstinent from sexual activity for at least 7 days after complete treatment and symptomatic resolution. Comprehensive surveys of other STIs, especially HIV infection, syphilis, and gonorrhea, are recommended in the general treatment of nonchlamydial NGU because the infections are commonly combined. Finally, this paper describes clinical strategies in the management of nonchlamydial NGU in men (Fig. 3).

Conflicts of interest statement

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

Sources of funding

None.

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