Urethritis: Nongonococcal

100

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Key Points

- Nongonococcal urethritis (NGU) represents the commonest form of urethritis in developed countries.
- There is a wide range of responsible microorganisms, with *Chlamydia trachomatis* identified more frequently. However, in almost half of cases, no specific pathogen is detected.
- Patients with symptoms or objective signs should undergo testing with a Gram-stained urethral swab or first-pass urine specimen.
- Males with confirmed or suspected urethritis should be tested for *N. gonorrhoeae* and *C. trachomatis*.
- Patients with NGU should be offered a therapeutic regimen effective against *C. trachomatis*.
- Patient follow-up and proper management of sexual contacts are essential to ensure therapeutic success.

Definition and Epidemiology

It is a urethral inflammation not caused by *Neisseria gonorrhoeae*.

It is the commonest form of urethritis in Europe, the USA, Canada, and Australia. Although the related symptoms and signs are usually mild or absent and therapeutic regimens easy to follow, it has the potential of serious sequelae on the reproductive system of males and their female partners if the condition remains undiagnosed and untreated.

Basic Concepts of Pathogenesis

Urethritis may be due to infectious agents (bacterial, viral, fungal), noninfectious conditions (e.g., mechanical or chemical trauma, urethral strictures, and foreign bodies), or both. In infectious nongonococcal urethritis (NGU), the commonest pathogen is *Chlamydia trachomatis* accounting for 15–40 % of cases with a predilection for younger ages, followed by *Mycoplasma genitalium* (see Table 100.1). Other microorganisms including *Trichomonas vaginalis* (rates depending on its prevalence in the community, uncommon in men who have sex with men (MSM)), HSV, HPV, adenovirus, *Candida* sp., *N. meningitidis*, *Haemophilus* sp., *Moraxella catarrhalis*, *Streptococcus* sp., urinary tract infections, and enteric bacteria (in cases of insertive anal intercourse) are more uncommon, whereas in approximately 50 % of cases, no pathogen can be

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Table 100.1 Infectious agents in NGU

Pathogen	Detection rates (%)
Chlamydia trachomatis	15–40
Mycoplasma genitalium	10–25
Trichomonas vaginalis	1–20
HPV, *Candida* sp., *N. meningitidis*, *Haemophilus* sp., *Moraxella catarrhalis*, *Streptococcus* sp.	<10 %
Urinary tract infections	<10 %
HSV	<5 %
Adenovirus	<5 %
Enteric flora	<5 %
Ureaplasma urealyticum	Controversial

detected. *Ureaplasma urealyticum* colonizes the urethra in 30–40 % of healthy sexually active young males, but it has also been implicated in the pathogenesis of NGU.

It is speculated that the etiology of asymptomatic NGU may differ from symptomatic NGU, because detection rates of *C. trachomatis* and *M. genitalium* are lower in asymptomatic patients.

Clinical Presentation

NGU may be asymptomatic or cause mild to moderate urethral irritation, pruritus, dysuria, and minimal urethral discharge which is often noticed in the morning or after urethral massage.

Complications of NGU include epididymitis/orchitis which, if left untreated, can eventually lead to male infertility and Reiter's syndrome. In the case of chlamydial and probably *M. genitalium* NGU, female partners who are not referred for screening and therapy could potentially develop pelvic inflammatory disease (PID) with subsequent possible infertility or extrauterine pregnancy.

Physical Examination

The aim of physical examination is to check for the presence of urethral discharge, detect any observable concomitant sexually transmitted diseases (STDs), diagnose other conditions that could imitate NGU, and search for possible complications. Therefore, it should include:

- Inspection of the urethra for obvious discharge
- Inspection of the genitalia (including the perianal area) for any signs of other STDs (e.g., syphilis, condylomata acuminata, herpes simplex)
- Palpation of the urethra for possible strictures, abscesses, or foreign bodies
- Palpation of the testes and spermatic cord for signs suggestive of orchitis/epididymitis

Diagnosis

1. *Confirmation of urethritis*. Urethritis can be confirmed either with the sign of urethral discharge on physical examination or with the following laboratory tests revealing WBCs in the anterior urethra:
   (i) A Gram-stained urethral smear containing ≥5 WBCs per high-power microscopic field.
   (ii) A centrifuged and Gram-stained first-pass urine (FPU) specimen demonstrating ≥10 WBCs per high-power microscopic field.

   In the case of observable urethral discharge, urethral smear is preferable to FPU since it will assist to exclude gonococcal urethritis and probably demonstrate other pathogens (*T. vaginalis*, *Candida* sp.). Leukocyte esterase test on FPU and methylene blue-stained urethral smear have also been used but have lower sensitivity.

   All patients with confirmed or suspected urethritis should be tested for *N. gonorrhoeae* and *C. trachomatis*.
2. *Exclusion of gonococcal urethritis. N. gonorrhoeae* can be ruled out by the absence of polymorphonuclear leukocytes with intracellular Gram-negative diplococci in a Gram-stained urethral specimen and by diagnostic tests specific for gonococcal infection (culture of urethral smear, nucleic acid hybridization tests, or single nucleic acid amplification tests (NAATs)).

3. *Detection of causative microorganism*. Patients with NGU should be tested for *C. trachomatis*, since it is an STD reportable to health authorities; furthermore, its diagnosis could enforce compliance to treatment, partner notification, and proper management, as well as provide an opportunity for health education. Available tests for *C. trachomatis* in urethral swab specimens include NAATs, nucleic acid hybridization tests, enzyme-linked immunosorbent assay tests (ELISA), direct immunofluorescence, and cell culture, with NAATs having the higher sensitivity (90–95 %). In the case of overt urethral discharge, microscopic examination of a urethral specimen could detect *Candida* sp. (KOH preparation) and *T. vaginalis* (wet preparation). *M. genitalium* can be detected by NAAT, although in clinical practice this is not performed routinely.

Differential Diagnosis

NGU should be differentiated from the following conditions:

- By definition NGU has to be distinguished from gonococcal urethritis. Clinically, gonococcal urethritis is characterized by a more abrupt initiation of abundant purulent urethral discharge that causes considerable discomfort; diagnosis of *N. gonorrhoeae* is confirmed by Gram stain microscopy of urethral smear and specific testing as previously described.
- Chronic or acute prostatitis can manifest as pelvic pain, urethral discomfort, and premature ejaculation.
- Upper urinary tract infection is sometimes accompanied by minimal urethral discharge.
- Noninfectious causes of urethritis include mechanical or chemical trauma corresponding to individual sexual practices, urethral strictures and fissures, abscesses, or foreign bodies. Males with venereophobia often manipulate their penis to check for signs of disease, resulting in self-induced urethral irritation.

General Principles of Treatment

If laboratory-based diagnosis is not available, symptomatic patients should be treated for both gonorrhea and chlamydia. If NGU has been confirmed by Gram-stain microscopy, therapy should be initiated as soon as possible, even before the results of specific tests for *N. gonorrhoeae* and *C. trachomatis* are available.

According to 2009 European guideline on the management of male NGU and 2010 CDC STD treatment guidelines, recommended regimens include either azithromycin at a single dose of 1 g or doxycycline 100 mg orally twice a day for 7 days. Both drugs are highly effective against *C. trachomatis*. Azithromycin has the additional advantage of a single dose, with subsequent better compliance. In the case of urethritis caused by *M. genitalium*, azithromycin seems to be more beneficial compared to doxycycline, although treatment failures can be observed with both drugs. Azithromycin and doxycycline are generally effective against other NGU pathogens, with the exception of *T. vaginalis* that responds to metronidazole or tinidazole. Alternatively, patients can receive erythromycin, ofloxacin, or levofloxacin. Recommended and alternative therapeutic schemes are reviewed in Table 100.2.

All of the above therapeutic schemes appear to be efficacious. Randomized clinical studies comparing the cure rates of each regimen are difficult to perform, since the causal microorganism is often not identified.

Patients should refrain from sexual contacts for 1 week (7 days after treatment with azithromycin or during the 7 days of therapy with doxycycline), provided that by that time they are asymptomatic and their partners have also been treated.

Patients with NGU should be monitored for other STDs (including syphilis and HIV). As in all cases of STD counseling, patients should be informed about the 3 month "window" period that precedes serologic detection of these diseases in order to have a repeat test 3 months after the first screening.

Patients with concomitant HIV infection should be managed in the same way as HIV-negative patients. Pathogens causing urethritis facilitate the transmission of HIV.

Follow-Up

An initial follow-up contact with the patient to ensure that symptoms have subsided, and that the patient and his partners have completed therapy without having unprotected intercourse during the period defined by the provider, is advised 3 weeks after completing therapy. If all of the above conditions are fulfilled, a test of cure is not necessary; otherwise, the patient should be reassessed and re-treated. This follow-up visit is also useful in reviewing the results of the screening test and dealing with other STDs that may have been diagnosed. Earlier assessment is not suggested, because urethral discharge and associated symptoms can persist for sometime after NGU therapy, although the infectious cause has been eradicated.

For patients with documented chlamydial urethritis, a further follow-up visit after 3–6 months is advisable in order to repeat testing for *C. trachomatis*, since reinfection during the first 6 months following treatment is not unusual in this group.

Partner Referral

All sexual partners of males with NGU should be assessed and treated, even in the absence of specific diagnosis of a pathogen. The exact preceding period for defining partners at risk is not established, but it should involve at least 2 months prior to diagnosis, or even longer according to the individual history of sexual contacts. Patients and their partners should be informed that symptoms and signs may be absent or mild –especially in the cases of cervical, anal, or pharyngeal infection – and that failure to treat partners could result in reinfection of the person initially treated, as well as in possible complications for all involved sexual contacts. Management of partners should follow the same guidelines previously mentioned.

Pregnant partners of males with NGU cannot receive doxycycline, ofloxacin, or levofloxacin. However, azithromycin is considered safe and effective and can be administered at the standard single dose of 1 g orally. Alternatively, pregnant women can receive amoxicillin 500 mg orally three times a day for 7 days or erythromycin as described in Table 100.2, although gastrointestinal side effects related to erythromycin could result in noncompliance with the latter. A test of cure 3 weeks after completion of therapy is recommended for all pregnant women with documented chlamydial infection to ensure cure.

Persistent and Recurrent NGU

Approximately 10–20 % of patients continue to have symptoms or physical signs 1–3 months after completion of therapy for NGU. If compliance to initial therapy and proper partner management are ensured, these patients are considered to have persistent/recurrent NGU.

Etiology of persistent NGU is not clear but could be attributed to:

- Failure of the recommended schemes (especially doxycycline) to eradicate *M. genitalium*. Therapy with moxifloxacin 400 mg daily for 7 days has proved effective, but there have been reports of severe hepatotoxicity and Stevens–Johnson syndrome. Some authors propose more extended regimens with azithromycin to avoid resistance of *M. genitalium*.
- Resistance of *U. urealyticum* to doxycycline.
- Cases of NGU caused by *T. vaginalis* require therapy with metronidazole or tinidazole.

First- and second-line treatments for persistent/recurrent NGU are summarized in Table 100.3.

Treatment with metronidazole or tinidazole is only advised when *T. vaginalis* is suspected as the responsible organism (e.g., in areas with high prevalence of *T. vaginalis* or when detected by

Table 100.2 Treatment regimens for NGU

	Drug	Dosage	Frequency	Duration	Route of admission	Source of guidelines
Recommended therapies	Azithromycin	1 g	×1	Single dose	po	IUSTI/WHO 2009 European STD guidelines, CDC 2010 STD guidelines
	Doxycycline	100 mg	BID	7 days	po	IUSTI/WHO 2009 European STD guidelines, CDC 2010 STD guidelines
Alternative therapies	Erythromycin base	500 mg	BID	7 days	po	IUSTI/WHO 2009 European STD guidelines
	Erythromycin base	500 mg	QID	7 days	po	CDC 2010 STD guidelines
	Erythromycin ethylsuccinate	800 mg	QID	7 days	po	CDC 2010 STD guidelines
	Ofloxacin	200 mg	BID	7 days	po	IUSTI/WHO 2009 European STD guidelines
	Ofloxacin	400 mg	qd	7 days	po	IUSTI/WHO 2009 European STD guidelines
	Ofloxacin	300 mg	BID	7 days	po	CDC 2010 STD guidelines
	Levofloxacin	500 mg	qd	7 days	po	CDC 2010 STD guidelines

po orally, *BID* twice a day, *QID* four times a day, *qd* once daily

Table 100.3 Therapeutic regimens for persistent/recurrent NGU

	Drug	Therapeutic scheme	Source of guidelines
First-line treatments	Azithromycin	500 mg stat then 250 mg daily for the next 4 days	IUSTI/WHO 2009 European STD guidelines
	PLUS		
	Metronidazole[a]	400–500 mg BID for 5 days	
	Erythromycin	500 mg QID for 3 weeks	IUSTI/WHO 2009 European STD guidelines
	PLUS		
	Metronidazole[a]	400–500 mg BID for 5 days	
	Metronidazole	2 g stat in a single dose	CDC 2010 STD guidelines
	OR		
	Tinidazole	2 g stat in a single dose	
	PLUS		
	Azithromycin[b]	1 g stat in a single dose	
Second-line treatments	Moxifloxacin	400 mg once daily for 7–10 days	IUSTI/WHO 2009 European STD guidelines
	PLUS		
	Metronidazole[a]	400–500 mg BID for 5 days	

BID twice a day, *QID* four times a day
[a]In areas where *T. vaginalis* is prevalent
[b]If not used for initial episode

microscopy, culture, or an NAAT on urethral specimen or urine).

Re-treatment of sexual partners who had received appropriate therapy during the initial diagnosis is not needed. However, in cases of NGU attributable to *M. genitalium*, possible failure of initial therapy should be taken into account.

Further Reading

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