



Urethritis

Learning Objectives:

Upon completion of this content the learner will be able to:

1. List the etiologic agents of urethritis.
2. Describe the clinical manifestations and sequelae of urethritis.
3. State the clinical and laboratory criteria for the diagnosis of urethritis.
4. Summarize the clinical management of patients with urethritis and recurrent urethritis including recommended diagnostic tests, treatment, follow-up, patient counseling and partner management.

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Definition

Urethritis is a clinical syndrome affecting males that is characterized by urethral inflammation. It can result from infectious and non-infectious exposures and may be asymptomatic in up to half of cases. Symptoms of urethritis include urethral discharge, dysuria, or meatal pruritis. Urethritis is confirmed by the presence of a mucopurulent or purulent discharge, the laboratory finding of ≥ 5 WBC per oil immersion field on Gram-stained urethral smear or in the sediment of first-void urine which demonstrates ≥ 10 WBC per high power field. The majority of infectious cases are sexually transmitted.

I. Etiology and Natural History

- A. Gonococcal urethritis (GU): approximately 20 % of urethritis caused by *Neisseria gonorrhoeae*.
- B. Nongonococcal urethritis (NGU): approximately 80% of urethritis:

Etiologic Agent of NGU

<i>Chlamydia trachomatis</i>	15-40 %
<i>Ureaplasma urealyticum</i>	10-40 %
<i>Mycoplasma genitalium</i>	15-25 %
<i>Trichomonas vaginalis</i>	5-15 %
Herpes Simplex Virus	Unknown
<i>Candida albicans</i>	< 5 %
Other bacteria (enterics, anaerobes, <i>E. Coli</i> , <i>Haemophilus</i> species, gram positives)	< 5 %
Non-infectious (chemical, allergic or autoimmune)	?
Unknown	20-30 %

- 1. *Chlamydia trachomatis*:
 - a. Because of its well-defined role in the development of upper tract disease and infertility in females, chlamydia (CT) remains the most important pathogen causing NGU.

- b. In some areas of the U.S., the proportion of NGU caused by CT appears to be declining, possibly as a result of increased screening among asymptomatic persons at risk.
 - c. See also Chlamydia Curriculum Module.
- 2. *Ureaplasma urealyticum*: Although urethral colonization is not uncommon among men without urethritis, there is convincing evidence that *U urealyticum* is a urethral pathogen. In most studies, *U urealyticum* is significantly more common among men with NGU compared with men without urethritis.
- 3. *Mycoplasma genitalium*:
 - a) Detected in a significantly greater proportion of men with NGU as compared with men without urethritis.
 - b) Evidence for sexual transmission to female sex partners.
 - c) Evidence for etiologic role in cervicitis.
 - d) Limited evidence for invasive or upper genital tract disease in either men or women.
- 4. *Trichomonas vaginalis*: Proportion of NGU caused by trichomonas varies by geographic area and patient demographics. Rates over 10% have been documented in the southern U.S. Incidence of trichomonal NGU may be higher among men >30 years old.
- 5. Herpes simplex virus (HSV): Urethritis occurs in 15-30% of men with primary HSV infection though much less commonly with recurrent HSV. Many patients with HSV urethritis have visible penile HSV lesions.
- 6. Yeasts (Candida): Yeasts are rarely detected in urethritis etiology studies, but some men with candida balanitis have symptoms of urethritis.
- 7. Gram-negative bacilli:
 - a) Urethral Gram stain may demonstrate WBC and Gram-negative rods.
 - b) May be associated with cystitis, and occasionally with insertive anal sex.
 - c) Treatment should be directed toward Gram-negative rods.

C. Sexual transmission

- 1. Depending on the etiologic agent, rates of infection among sex partners vary from less than 50% to over 80%. GU has the highest rate of transmission followed by chlamydial NGU.

2. Routes of acquisition include vaginal, insertive oral, and insertive anal sex.
3. Despite non-STD and non-infectious etiologies, clinical evaluation and treatment of sex partners is critical for preventing complications and interrupting potential sexual transmission.

II. Epidemiology

- A. Urethritis affects an estimated 4 million American men each year.
- B. The peak age is similar for both NGU and GU: 20-24 years.
- C. NGU is more common than gonococcal urethritis (GU) in the U.S.
- D. In the U.S., NGU as a cause of urethritis is associated with higher socioeconomic status, higher education, fewer partners.

III. Clinical Manifestations

- A. The table below compares the general features of NGU and GU. However, considerable overlap exists between these presentations.

Clinical Features	NGU	GU
Incubation period	7-14 days	2-8 days
Onset	Gradual	Abrupt
Dysuria	Mild	Severe
Discharge Quality	Mucoid	Purulent
Discharge Quantity	Less	More

- B. Complications of urethritis:

1. Reiter's syndrome complicates 1-2% of chlamydial NGU. .

Disseminated gonococcal infection (DGI) is a complication of untreated infection with *N. gonorrhoea*, occurring in 0.5 to 3% of patients with untreated mucosal gonorrhoea. The most common clinical manifestations are joint pain and skin lesions.

2. Epididymitis is an infrequent (<3%) complication of chlamydial and gonococcal urethritis.
3. Conjunctivitis: uni- or bi-lateral ocular involvement as a result of self-inoculation. Prompt diagnosis and aggressive treatment are required to prevent corneal involvement and possible scarring or blindness.
 - a) Chlamydial: follicular conjunctivitis with onset 1-2 weeks following an exposure.
 - b) Gonococcal: mucopurulent with copious discharge and conjunctival swelling occurring 24-48 hours after exposure.
- C. Asymptomatic urethritis: up to half of men in STD clinic settings with urethritis are without signs or symptoms. Compared to GU, NGU is more often asymptomatic.

IV. Diagnosis

- A. Optimally, exam should be conducted two or more hours post-urination.
- B. Examine urethra for discharge: stripping/milking of the urethra may increase the yield of the examination.
- C. Gram stain of urethral swab specimen:
 1. Five or more WBC/oil-immersion field (1000x) confirms urethritis.
 2. Look for presence of Gram-negative intracellular diplococci (GNID), indicative of GU.
 3. The presence of numerous Gram-negative rods along with PMNs should raise the suspicion of urethritis caused by enteric bacteria (e.g., *E. coli*), especially in men reporting insertive anal sex.
- D. First-void urine (FVU):
 1. Ten or more WBC/high power field (400x) confirms urethritis on sediment of first 10-15 ml of urine.
 2. Leukocyte esterase test (LET) is less sensitive than microscopy of first-void urine sediment, but easier to perform.
- E. Tests for GC and CT:

1. Confirmatory tests for CT and GC performed at the time of empiric treatment are important for identifying a specific etiology which may improve compliance and facilitate partner management.
 2. GC culture of urethral exudate.
 - a. Special media and incubation conditions (low CO₂) are necessary.
 - b. Advantage of antimicrobial testing ability.
 3. For DNA probe hybridization and other non-urine-based CT tests: insert swab 2-3 cm for optimal results.
 4. For urine-based nucleic acid amplification tests (NAATs), collect the first 10-15 ml of urine. The urethral meatus should not be cleansed prior to urination.
 5. Most tests for GC do not vary greatly in sensitivity, however NAATS are significantly more sensitive for the detection of CT. For specific diagnostic test performance, see the GC and CT curriculum modules.
- F. Tests for mycoplasma and ureaplasma are not currently FDA-cleared for clinical diagnostic purposes. Because these organisms are common among men without urethritis and test results may not change clinical management, the usefulness of these tests is unproven.
- G. Routine tests for trichomonas, HSV, or other bacterial etiologies are not recommended in the initial evaluation of urethritis but may be useful in the evaluation of patients unresponsive to standard treatments for NGU.

V. Treatment

A. Presumptive treatment:

1. If diagnosis is equivocal (e.g., symptoms but no signs), the decision to empirically treat vs. treat based on test results is made on an individual basis (e.g., high-risk patients unlikely to return for follow-up, etc.).
2. Patients with symptoms but without documentation of urethritis should be treated empirically for gonorrhea and chlamydia if they are unlikely to return for follow-up evaluation.

- B. Gonococcal urethritis (treat for co-existent CT infection): Patients infected with *N. gonorrhoeae* often are co-infected with *C. trachomatis*, a finding which has led the CDC to recommend that patients treated for gonococcal infection also be treated routinely with a regimen effective against uncomplicated genital *C. trachomatis* unless chlamydia is ruled out by a nucleic acid amplification test (NAAT)

1. Recommended regimens to cover GC*:

Ceftriaxone:	125 mg intramuscularly in a single dose
Cefixime*	400 mg orally in a single dose

As of April 2007, flouroquinolones are no longer recommended for treatment of GC in the United States due to high rate of resistance. Cephalosporin allergic patients are advised to undergo desensitization before treatment, and if this is not possible, azithromycin 2g orally in a single dose may be used.

* The availability of cefixime has been unreliable, and it is available in suspension only.

3. Co-treat for CT infection.

Azithromycin	1 g orally in a single dose
Doxycycline	100 mg orally twice a day for 7 days

4. See Gonorrhea Curriculum Module for alternative treatment regimens including alternative oral cephalosporins.

C. NGU:

1. Recommended regimens*:

Azithromycin:	1 gm orally in a single dose
Doxycycline:	100 mg orally twice a day for 7 days

* The efficacy of doxycycline and azithromycin are comparable for the treatment of CT urethritis (95-100%) whereas *Mycoplasma genitalium* appears to respond better to azithromycin compared with doxycycline. Azithromycin, which is now available in generic form, offers the advantage of single dose regimen and the opportunity for directly observed therapy. Doxycycline remains less expensive, but requires a twice daily dosing for a full week.

2. Alternative regimens:

Erythromycin base:*	500 mg orally 4 times a day for 7 days
Erythromycin ethylsuccinate:*	800 mg orally 4 times a day for 7 days
Ofloxacin:	300 mg orally twice a day for 7 days

Levofloxacin: 500 mg orally once a day for 7 days

- * Erythromycin has lower efficacy and poorer tolerance than either azithromycin or doxycycline and thus should be avoided, if possible, as a first line therapy.

D. Other management considerations:

1. Directly observed therapy: single-dose regimens have the important advantage of improved compliance, especially if directly observed. To improve compliance, the medication should be provided in the clinic or provider's office whenever possible.
2. Patients should be advised to abstain from sex for 7 days, until therapy is completed, symptoms have resolved, and sex partners have been treated.
3. Follow-up: patients should be instructed to return for evaluation if symptoms persist or recur after completion of therapy. Symptoms alone, without documentation of signs or laboratory evidence of urethral inflammation, are not a sufficient basis for re-treatment, especially if patient denies sexual contact since time of initial treatment.
4. Partner management: Patients should refer all sexual partners of the past 60 days for evaluation and treatment. Because a specific diagnosis may facilitate partner management, testing for GC and CT is recommended. Sexual contacts to NGU should be offered evaluation and treatment.

VI. Recurrent or Persistent Urethritis

- A. Recurrent or persistent symptoms within six weeks following treatment affect 20-40% of NGU cases, up to 20% of men with chlamydial NGU, and up to 50% of men with non-chlamydial NGU.
- B. Possible etiologies of persistent urethritis:
 1. Re-infection; sex with untreated partner or new partner; sex within 7 days of initiating treatment.
 2. Non-compliance with pharmacotherapy.
 3. Persistent infection due to:
 - a) Inadequate drug tissue levels (e.g., prostatic involvement).

- b) Resistant pathogen c) HSV.
- d) Trichomonas.

- 4. Non-infectious etiologies:
 - a) Immunologic, allergic.
 - b) Intraurethral growth (e.g., condyloma).

C, Approach to the patient:

- 1. Question patient closely regarding re-exposure during or after treatment, compliance with oral regimen, and concurrent treatment of partner(s).
- 2. Re-examine and establish objective evidence of urethritis by exam, urethral Gram stain, leukocyte esterase test, or urine sediment microscopy.
- 3. If available, examine for trichomonas with saline wet mount microscopy of urethral discharge or urine sediment. Given the limited sensitivity of wet mount examination of urethral specimens for the detection of trichomonas, presumptive therapy may be warranted even in face of a normal wet mount. If the wet mount is negative or unavailable, spun urine or a urethral swab should be cultured for trichomonas.
- 4. Note any penile lesions suggesting HSV. Consider intraurethral culture for HSV or type-specific serology test.

D. Treatment for persistent/recurrent NGU – defined by persistent symptoms and signs:

- 1. Patients who failed to comply with the treatment regimen or were re-exposed to an untreated sex partner can be re-treated with the initial regimen*.
- 2. Recommended regimens for patients who have been compliant and not re-exposed include antimicrobials for trichomonas and tetracycline-resistant organisms:
 - a) Metronidazole 2 grams orally single dose or
Tinidazole 2 grams orally single dose
plus
Azithromycin 1 g orally single dose (if not used for initial episode).

* If doxycycline was used as the first-line regimen, azithromycin would be an appropriate treatment for recurrent NGU.

3. Patients with signs/symptoms of persistent urethritis following re-treatment, where re-infection is unlikely, should be referred to a urologic specialist for further evaluation and management.

VI. Prevention

- A. Partner management: patients should refer all sex partners within the preceding 60 days for evaluation and treatment. A specific diagnosis may facilitate partner referral; therefore, testing for GC and CT is encouraged.
- B. Patient counseling/education:
 1. Explain urethritis as a syndrome vs. an infection, specific disease etiology if known, routes of transmission and acquisition.
 2. Explain to patient why they are being treated, including possible sequelae to self and partners (e.g., increased HIV susceptibility, PID/infertility/ectopic pregnancy in female partners).
 3. Explain need for evaluation and treatment of sex partners to establish etiology and initiate treatment if indicated.

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