

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 to include recommended diagnostic tests, treatment, follow-up, patient counseling and partner management.

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Definition

Urethral inflammation most often manifested by urethral discharge, dysuria, or meatal pruritis; confirmed by the laboratory finding of increased number of polymorphonuclear leukocytes (PMNs) on Gram-stained urethral smear or in the sediment of a first-void urine.

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 Based on Culture

<i>Chlamydia trachomatis</i>	15-40 % *
<i>Ureaplasma urealyticum</i> **	10-40 %
<i>Mycoplasma genitalium</i> **	15-25 %
<i>Trichomonas vaginalis</i>	Up to 13 %
Herpes Simplex Virus	Rare
<i>Candida albicans</i>	< 1 %
Miscellaneous bacteria	< 1 %
Other (<i>E. Coli</i> , Haemophilus species, gram positives)	?
Unknown	20-30 %

*In some areas of the US. the proportion of NGU caused by *Chlamydia trachomatis* appears to be declining (possibly as a result of increased screening among asymptomatic persons at risk).

**Role in causing urethritis remains somewhat controversial.

1. *Chlamydia trachomatis* [See Chlamydia syllabus]
2. *Ureaplasma urealyticum*: despite evidence for *U. urealyticum* as a urethral pathogen, the role of this agent as a cause of clinical disease remains unclear. Urethral colonization is common among men without urethritis.

3. *Mycoplasma genitalium*:
 - a) Seen in a significantly greater proportion of men with NGU as compared with normal men, although casual association has yet to be proven.
 - b) Limited evidence for invasive or upper genital tract disease in either men or women.
4. *Trichomonas vaginalis*: recent data suggest that trichomonas is increasing as a cause of NGU (~10%). 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. Most, but not all, patients with HSV urethritis have visible penile HSV lesions.
6. Yeasts (*Candida*):
 - a) Yeast is not a well-documented cause of NGU.
 - b) 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.

II. Epidemiology

- A. Urethritis affects an estimated 4 million American men each year.
- B. NGU is more common than gonococcal urethritis (GU) in the U.S.
- C. In the U.S., NGU is more common than GU among men of higher socioeconomic status, higher education, fewer partners.
- D. In university health clinics, more than 85% of urethritis is nongonococcal.
- E. The peak age is similar for both NGU and GU: 20-24 years.
- F. Insertive oral and anal sex are risks for GU and have also been associated with NGU.

III. Clinical Manifestations

- A. The table below compares the general features of NGU and GU. However, a considerable overlap may exist 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 NGU (See Chlamydia syllabus).
 2. Disseminated gonococcal infection (DGI) occurs very rarely as a result of GU. In patients with DGI, gonococcal infection at the genital site most often remains asymptomatic.
 3. Epididymitis is an infrequent (<3%) complication.
 4. 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: ~1/3 of men in an STD clinic with NGU may be without signs or symptoms.

IV. Diagnosis

- A. Optimally, exam should occur two or more hours post-urination.
- B. Examine urethra for discharge: stripping/milking of the urethra may increase the yield of the examination.

C. Swab specimen/urethral Gram stain:

1. Five or more WBC/oil-immersion field (1000x) qualifies as urethritis.
2. Look for presence of Gram-negative intracellular diplococci (GNID), suggestive 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 with a history of anal insertive sex.

D. First-catch urine (FCU):

1. Ten or more WBC/high powered field (400x) qualifies as urethritis on sediment of first 10-15 ml of urine.
2. Leukocyte esterase test (LET) is less sensitive than first-catch urine testing, but easier to perform on fresh-spun urine.

E. Test for GC and chlamydia (CT) with culture or non-culture method:

1. GC: Okay to culture urethral exudate.
2. For non-urine based CT tests: insert swab 2-4 cm for optimal results.
3. For urine-based DNA amplification testing, collect the first 10-15 ml of urine. The urethral meatus should not be cleansed prior to urination.
4. For specific diagnostic test performance, see GC and CT syllabi.

F. Routine culture for ureaplasma is not recommended, as it may be present as often in men without urethritis as in those with urethritis.

G. 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 (i.e., high-risk patients unlikely to return for follow-up, etc.). Confirmatory testing for GC and chlamydia should be performed at the time of empiric treatment given the advantages of making a specific diagnosis, including improved compliance with treatment and partner notification.

V. Treatment

- A. Gonococcal urethritis (treat for co-existent chlamydial infection): Patients infected with *N. gonorrhoea* 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*. As testing for chlamydia has become quicker, more sensitive, and more widely available, some clinicians in geographic areas with low rates of co-infection might prefer to test for chlamydia rather than treat presumptively. However, presumptive treatment is indicated for patients who may not return for test results.

Recommended regimens to cover GC; for regimens to cover chlamydia, see below:

1. Cefixime: 400 mg po x 1
2. Ceftriaxone: 125 mg IM x 1
3. Ciprofloxacin: 500 mg po x 1
4. Ofloxacin:* 400 mg po x 1
5. Levofloxacin:* 250 mg po x 1

* Given the continued spread of quinolone-resistant *Neisseria gonorrhoea* worldwide, treatment using quinolones is inadvisable in many geographic areas. Quinolones should be avoided in any patient whose infection (or whose partner's infection) may have originated from an area where quinolone resistance is common (e.g., Asia, the Pacific Islands, Hawaii).

B. Chlamydial urethritis and NGU:

1. Recommended regimens:

- a) Azithromycin: ** 1 gm orally x 1
- b) Doxycycline: 100 mg b.i.d. x 7 days

** The efficacy of doxycycline and azithromycin are comparable for the treatment of CT urethritis (95-100%) and non-CT NGU (60-80%); azithromycin offers the advantage of single dose, directly observed therapy.

2. Alternative regimens:

- a) Erythromycin Base: *** 500 mg q.i.d. x 7 days
- b) Erythromycin ethylsuccinate: *** 800 mg q.i.d. x 7 days
- e) Ofloxacin: 300 mg b.i.d. x 7 days
- f) Levofloxacin 500mg po q.d. x 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. If used, a test-of-cure is indicated to ensure adequate therapy and cure.

C. Other management considerations:

1. Directly observed therapy: single-dose regimens have the important advantage of improved compliance, especially if provided as directly observed therapy. To improve compliance, the medication should be provided in the clinic or provider's office whenever possible.
2. 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. Patients should be routinely instructed to abstain from sexual intercourse for seven days regardless of therapy.
3. Partner referral: chlamydia can be isolated from 30-60% of female partners of men with either GU or NGU. Patients should refer all sexual partners of the past 60 days for evaluation and treatment. A specific diagnosis may facilitate partner referral. Therefore, testing for gonorrhea and chlamydia is encouraged.
4. Recurrent or persistent urethritis after standard first-line pharmacotherapy:
 - a) Possible etiologies of persistent urethritis:
 - 1) Re-infection.
 - 2) Non-compliance with pharmacotherapy.
 - 3) Persistent infection due to:
 - (a) Inadequate drug tissue levels (prostatic involvement?).
 - (b) Resistant pathogen (quinolone-resistant gonorrhea; tetracycline-resistant ureaplasma/mycoplasma).
 - (c) HSV.
 - (d) Trichomonas.
 - (e) Non-infectious etiologies.
 - (f) Intraurethral growth (e.g., condyloma).
 - b) 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 urethral Gram stain, urine sediment or LET.

- 3) If available, examine for trichomonas with saline wet mount, by obtaining urethral discharge or examining 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. Culture if wet mount negative on spun urine or urethral swab.
 - 4) Note any penile lesions suggesting HSV. Consider culturing for HSV.
- c) Treatment for persistent/recurrent urethritis:
- 1) Patients with persistent or recurrent urethritis should be re-treated with the initial regimen if they failed to comply with the treatment regimen or if they were re-exposed to an untreated sex partner.
 - 2) If patient has been compliant and not re-exposed, consider:
 - (a) Metronidazole 2 grams orally single dose **plus**
 - (b) Erythromycin base 500 mg orally 4 times a day for 7 days,
or
 - (c) Erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days.
 - 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 gonorrhea and chlamydia is encouraged.
- B. Patient counseling/education:

Nature of the infection:

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 referral/treatment of sex partners to establish etiology and possible treatment. A specific diagnosis of STD should prompt treatment of partners.

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