Much Ado About NGU

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Objectives

- **Epidemiology:** organisms associated with non-gonococcal urethritis (NGU)
- **Diagnosis:** tests for specific pathogens associated with NGU
- **Treatment:**
  - Clinical trial for NGU treatment
  - Potential for azithromycin and doxycycline treatment failures

Non-gonococcal Urethritis

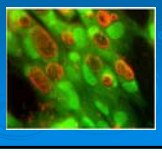
- Urethral inflammation that is not the result of infection due to *Neisseria gonorrhoeae.*
- Urethritis confirmed by one of the following:
  - Mucopurulent or purulent discharge on examination;
  - Gram stain of urethral secretions with ≥ 5 white blood cells per high power field (WBCs/HPF);
  - Positive leukocyte esterase on first-void urine, or microscopic examination of first-void urine sediment with ≥ 10 WBCs/HPF

Epidemiology

- Relative proportion of NGU: 19-78% in STD clinics, 85% on college campuses
- Reportable in North Carolina but not nationwide
  - Confirmed case = negative for gonorrhea, and an abnormal discharge or ≥ 5 WBCs/HPF on urethral gram stain or a positive leukocyte esterase test.

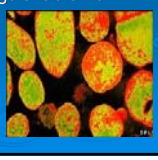
Chlamydia trachomatis

- Causes 15-44% of NGU
- Rates among US men - highest among 20–24 years of age (1,121 cases per 100,000 males in 2009).
- Symptoms 1-3 weeks after exposure with clear to white discharge, dysuria.
- Complications in men include epididymitis and infertility.



Mycoplasma genitalium

- Causes 15-40% of NGU
- Emerging STI, first implicated in 1981 in men with NGU
- Young age possible predictor for infection
- Causes relatively mild disease indistinguishable from chlamydial urethritis
- Unknown complications of persistent infection in men



Trichomonas vaginalis

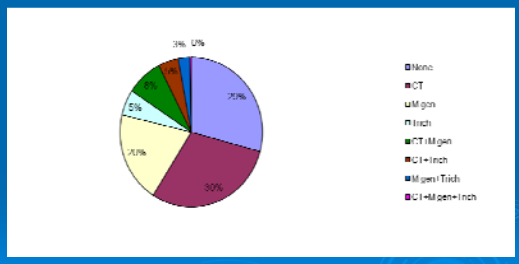
- Causes 10-20% of NGU
- Associated with the presence of other STIs (gonorrhea)
- Predictors in men include age ≥ 30 years
- Complications in men: epididymitis and prostatitis.

Other Causes

- *Ureaplasma urealyticum* 10-20%
- Herpes simplex virus 2-3%
  - Men who have sex with men (MSM), insertive oral sex
  - HSV-1 > HSV-2 when no lesions present
- Adenovirus 2-4%
  - MSM, insertive oral sex
- *Haemophilus* sp. (rare)
- Unknown 25-40%
  - Insertive oral sex, vaginal sex with a casual partner

Martin DH. *Cur Infect Dis Rep* 2008; 10: 128-132.
Bradshaw CS, et al. *J Infect Dis* 2006; 193: 336-45.

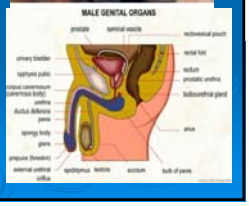
Co-infections and non-identifiable pathogens



Schwebke et al. *Clin Infect Dis* 2011; 52: 163- 170.

Examination

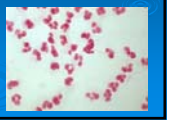
- Inspect for clear, purulent, or mucoid urethral discharge; inflammation in meatus
- "Milk" or strip the urethra beginning at the bulbous urethra behind the scrotum to meatus
- For symptomatic men without evidence of NGU, consider re-examination in the morning without voiding overnight.



Urethral Specimen Collection

Diagnosis of NGU

- Gram stain of urethral smear with ≥ 5 PMNs/HPF
  Terry PM, et al. *Int J Infect Dis* 1991: 150 men in GU clinic in England
  - For urethritis, sensitivity (94%) and specificity (91%)
  - For chlamydia, sensitivity (91%) and negative predictive value (96%), but specificity (68%) and positive predictive value (46%)
- First-void urine with leukocyte esterase
  Werner MJ et al. *J Ad Health* 1991; Schwebke J, et al. *J Clin Micro* 1991
  - For urethritis, sensitivity of 78%, specificity of 91%
  - For chlamydia, sensitivity of 88%



C. trachomatis: Diagnostic Tests

- Cell culture: "gold standard"
- Antigen detection: ELISA (EIA)
  - Detects bacterial antigens with an enzyme-labeled antibody
- Direct microscopy: direct fluorescence
  - Detects intact bacteria with a fluorescent antibody
- DNA hybridization: Non-amplification
  - Detects specific DNA or RNA sequences of *C. trachomatis*
- Nucleic acid amplification tests: PCR
  - Amplifies and detects organism-specific genomic or plasmid DNA or rRNA

C. trachomatis Diagnostic Tests

Test	Sensitivity	Specificity
Enzyme Immunoassay (EIA) – cervical, urethral	53-76%	95%
Direct Fluorescent Antibody (DFA) – cervical, urethral	80-85%	99%
Probe Hybridization – cervical, urethral	65-83%	88%
Polymerase chain reaction (PCR) – cervical, urethral, urine	90-96%	98-99%
Strand displacement assay (SDA)- cervical, urethral, urine	93-95%	94-98%
Transcription –mediated amplification (TMA) - cervical, urethral, urine	94-99%	98-100%

Detection of Other Pathogens

- *Mycoplasma genitalium* – culture is traditional gold standard
  Hardick J. et al. *J Clin Micro* 2006; 44: 1236-1240.
  - Multi-target polymerase chain reaction
    - Sensitivity 91.8% and specificity 99.5% in men
  - Transcription-mediated assay
    - Sensitivity 100% and specificity 97.9% in men
- *Trichomonas vaginalis* – culture is traditional gold standard
  Nye MB, et al. *Am J Obstet Gyne* 2009; 200: 187-188.
  - Polymerase chain reaction
    - Sensitivity 47% (urine) - 55% (urethral), specificity 100%
  - Transcription-mediated assay
    - Sensitivity 77% (urine) – 95% (urethral), specificity 96-98%

Treatment for NGU

CDC STD Treatment Guidelines 2010

- Recommended:
  - Azithromycin 1 g PO in single dose, OR
  - Doxycycline 100 mg PO twice a day for 7 days
- Alternative Regimens
  - Erythromycin base 500 mg PO four times per day for 7 days, OR
  - Erythromycin ethylsuccinate 800 mg PO four times a day for 7 days, OR
  - Levofloxacin 500 mg PO daily for 7 days, OR
  - Ofloxacin 300 mg PO twice a day for 7 days.

Recurrent and Persistent Urethritis

- Recurrent: new symptoms within 6 weeks after improvement
- Persistent: failure of significant improvement with 7 days
- If compliant with initial regimen and re-infection is excluded:

Metronidazole 2 gm PO in a single dose, OR
Tinidazole 2 gm PO in a single dose
PLUS
Azithromycin 1 gm PO in a single dose
(if not used in the initial treatment)

Clinical Trial of NGU Treatment

- Objectives:
  - To determine whether addition of tinidazole would result in higher cure rates
  - To compare the efficacy of azithromycin with doxycycline
- Methods:
  - Randomized, controlled, double-blind phase IIB trial of men aged 16-45 years with NGU
  - Tested for *C. trachomatis*, *M. genitalium*, *T. vaginalis* using nucleic acid amplification tests
  - Treatment arms: azithromycin +/- tinidazole; doxycycline +/- tinidazole
  - Followed at 1 and 3 weeks after treatment for clinical and microbiological cure

Schwebke et al. *Clin Infect Dis* 2011; 52: 163- 170.

Clinical Trial of NGU Treatment

- Results:
  - No differences in clinical cure rates between treatment regimens
  - Tinidazole eradicated 95% of *T. vaginalis* infections
  - *C. trachomatis* clearance rate was 95% with doxycycline, versus 77% with azithromycin (p =.011)
  - M. genitalium clearance rate was 31% with doxycycline, versus 67% with azithromycin (p =.002)
- Conclusions:
  - Addition of tinidazole to the initial NGU treatment regimen did not result in higher cure rates
  - Doxycycline had significantly better efficacy against *C. trachomatis*, and azithromycin was superior for treatment of *M. genitalium*

Treatment Failures

- *C. trachomatis*

  Horner P. *Sex Transm Infect* 2006; 82:340-343
  - Few reports of treatment failure with azithromycin in men or women
  - Doxycycline may be more efficacious in eradicating acute infection; azithromycin is more effective at eradicating persistent infection
- *M. genitalium*

  Wikstrom A. et al. *Sex Transm Infect* 2006; 82:276-279

  Bradshaw CS, et al. PLoS One 2006; 3: e3618
  - Other studies have shown cure rates of 36% after doxycycline
  - Persistence 16% after azithromycin, eradicated with moxifloxacin

Summary

- NGU caused by: chlamydia> mycoplasma> unknown pathogens> trichomononas >> HSV, adenovirus.
- Confirm urethritis via exam, urethral Gram stain, urine.
- Perform testing for specific pathogens if/when available
- Continue recommended treatment with azithromycin, but be aware of potential treatment failures for *C. trachomatis* and *M. genitalium*

NGU

"Is most tolerable, and not to be endured."
(Act 3 Scene 3)
William Shakespeare

"Medicine is a science of uncertainty and an art of probability."
William Osler