Urethral Discharge and Local STI Complications in Men

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Urethritis

SYMPTOMS
• Urethral discharge
• Dysuria
• Itching at end of urethra

SIGNS
• Urethral discharge

LABORATORY
• Increased number of PMNL on Gram stain of a urethral smear or in the sediment of the first-voided urine
Aetiology of urethritis

Gonococcal
• Neisseria gonorrhoeae

Non-gonococcal
• Chlamydia trachomatis (15-40%)
• Mycoplasma genitalium (15-25%)
• Trichomonas vaginalis (5-15%)
• Ureaplasma urealyticum (<15%)
• Herpes simplex (2-3%)
• Adenovirus (2-4%)
• Haemophilus spp. (rare)
• Unknown
**Neisseria gonorrhoeae**

- Gram negative diplococcus

- Asymptomatic and minimally symptomatic infections occur in the community – may be associated with AHU auxotrophs (US studies)

- Increasing antimicrobial resistance

- Concurrent *C. trachomatis* infection common
Chlamydia trachomatis

- Gram negative obligate intracellular bacterium
- Common cause of post-gonococcal urethritis
- Less common among MSM
- Isolated from urethras of:
  - 25-60% (usually 30-40%) NGU cases
  - 4-35% (usually 15-25%) GC cases
  - 0-7% of men without urethritis
Mycoplasma genitalium

- Intracellular bacterium without a cell wall

- Pooled data from 19 studies:
  NGU (21.1%) vs. normal men (6.7%); OR 3.8 (95% CI: 3.0 - 4.9)
  CT negative NGU (21.7%) vs. normal men (6.0%); OR 5.15 (95% CI: 3.6 – 7.4)

- Genotyping analyses of concurrently infected couples supports sexual transmission
Trichomonas vaginalis

- Flagellated protozoon

- Initial studies using microscopy +/- culture showed an association of *T. vaginalis* with NGU

- Organism frequently found in urethra of both symptomatic and asymptomatic men by NAAT – association of *T. vaginalis* with NGU vs. colonisation less clear

- *T. vaginalis* more important as a cause of NGU among African men as high prevalence of trichomoniasis
**Ureaplasma species**

- Higher isolation rates from men with *C. trachomatis* negative NGU than among *C. trachomatis* positive NGU/no urethritis cases

- Isolated more often from men with first episode NGU than those with a history of previous NGU episodes or men without urethritis

- Intraurethral inoculation of *Ureaplasma* sp. into non-human primates associated with increased numbers of PMNL in endourethral smears (some animals)

- Studies suggest *U. urealyticum*, rather than *U. parvum*, is associated with NGU
Other bacterial causes of NGU

- Most studies have not revealed differences in aerobic and anaerobic urethral flora between CT+/CT- NGU cases.

- *Haemophilus influenzae* and *Haemophilus parainfluenzae* are rare causes of NGU.

- *Neisseria meningitidis* may cause NGU – transmission by orogenital sex supported by PFGE in one case study.

- Association between NGU in males and BV in females – further research required to identify responsible bacteria.
Viral causes of NGU

- Urethritis occurs in 30% of men with primary HSV (less common in recurrent HSV)

- Recent PCR-based studies suggest HSV detected in 2-3% of cases

- In Australia, Bradshaw et al. (2006) demonstrated:
  - significantly more HSV detected in 329 NGU cases compared to 307 controls
  - HSV-1 was more commonly detected than HSV-2
  - unprotected oral sex was a risk factor

- Adenoviruses reported among men with urethritis in Australia and USA – seasonal, associated with receptive oral sex, may see co-existent conjunctivitis
Non-STI causes of NGU

- Urinary tract infection
- Bacterial prostatitis
- Urethral stricture (catheterisation/instrumentation)
- Phimosis
- Congenital abnormalities
- Chemical irritation
- Tumours
- Stevens Johnson syndrome
- Role of masturbation, “milking” urethra, frequency of sexual activity, coffee, alcohol, foods unclear
Epidemiology of urethritis

- Common STI syndrome among men – 60% among STI clinic attendees in South Africa

- NGU cases exceed gonococcal urethritis in USA/Europe – opposite situation in Africa

- For both GU and NGU, peak age range is 20-24 years, followed by 15-1 and then 25-29

- In Seattle study (1975), NGU associated with white ethnicity, better education, students, less likely to be unemployed, higher SE class, older at age of first intercourse, fewer total sex partners
Aetiology of urethral discharge in South Africa

MUS aetiology in Cape Town (n = 290) and Johannesburg (n = 217) determined by M-PCR (2007 data)

Source: STI Reference Centre (NICD)
Clinical examination

- Important to “milk” or “strip” the urethra if symptoms but no urethral discharge seen

- Patient should not have urinated for at least 4 hours – if no discharge seen, repeat examination early the following morning may be helpful (no urination overnight)

- Classify urethral discharge as “profuse”, “intermediate” or “scant”

- In practice, treatment given on symptomatic grounds by most clinicians – over-treatment of patients and issues in relation to partner treatment
Clinical presentation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gonorrhoea</th>
<th>NGU</th>
</tr>
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<tbody>
<tr>
<td>Discharge</td>
<td>Profuse and purulent</td>
<td>Scant and muco-purulent, may be absent</td>
</tr>
<tr>
<td>Dysuria</td>
<td>+++</td>
<td>+ (+++ with HSV/adenovirus)</td>
</tr>
<tr>
<td>Incubation period</td>
<td>2-6 days</td>
<td>1-5 weeks</td>
</tr>
<tr>
<td>Health seeking behaviour</td>
<td>early</td>
<td>late</td>
</tr>
<tr>
<td>Asymptomatic cases</td>
<td>+/-</td>
<td>++</td>
</tr>
</tbody>
</table>
Asymptomatic STIs - The hidden epidemic

Only 9% of men were symptomatic for STIs
Local complications of gonorrhoea

- Tender lymphadenopathy
- Foreskin oedema
- Peri-urethral abscess involving shaft
- Para-urethral gland abscess
- Tyson’s gland abscess
- Cowper’s gland abscess
- Epididymitis
- Prostatitis
- Conjunctivitis
Complications of chlamydial NGU

- Epididymitis
- Prostatitis
- Conjunctivitis (auto-inoculation)
- Reactive arthritis syndrome (formerly Reiter’s syndrome)
  - arthritis
  - conjunctivitis
  - keratoderma blenorrhagica
  - circinate balanitis
Diagnosis of urethritis

• Gram stain microscopy (GC, NGU) \[ \geq 5 \text{ PMNL/hpf x 5} \]
• Rapid tests (CT, TV – issues with current GC assays)
• Culture (GC CT, TV, Ureaplasmas, HSV, adenovirus)
• ELISA (CT)
• Monoclonal antibody tests (GC, CT)
• Nucleic acid amplification tests (GC, CT, TV, MG, HSV, Ureaplasma urealyticum)
  - PCR (Roche + others), SDA (Abbott) and TMA (GenProbe) commercial assays
  - in-house multiplex assays
Dual antibiotic therapy approach

- Since late 1980s, dual antibiotic treatment of men with gonorrhoea has been recommended in USA and UK settings for the syndromic management of urethritis
- 15-25% of men with gonorrhoea have *C. trachomatis*
- Eliminates most post-gonococcal urethritis cases
- Reduces number of chlamydial infected men
- Effect of this approach on reducing community chlamydial burden has not been tested – circumstantial evidence exists in USA
- Dual therapy may slow down development of antibiotic resistance by *N. gonorrhoeae* - theoretical
## Reliable treatment options (2009)

<table>
<thead>
<tr>
<th>Gonorrhoea</th>
<th>Chlamydial Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cefixime</strong> 400mg po stat</td>
<td><strong>Azithromycin</strong> 1g po stat.</td>
</tr>
<tr>
<td><strong>Cefpodoxime</strong> 200mg po stat</td>
<td><strong>Doxycycline</strong> 100mg 12 hourly po x 7 days</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong> 250mg imi</td>
<td><strong>Erythromycin</strong> 500mg 6-12 hourly po x 7 days</td>
</tr>
<tr>
<td><strong>Spectinomycin</strong> 2g imi stat</td>
<td><strong>Tetracycline</strong> 500mg 6 hourly po x 7 days</td>
</tr>
<tr>
<td><strong>Azithromycin</strong> 2g po stat</td>
<td></td>
</tr>
<tr>
<td><strong>Gentamicin</strong> 240mg imi stat</td>
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**Ciprofloxacin** 500mg po stat. should only be used where there is recent evidence of susceptibility (MIC ≤ 0.06 mg/l) from well-conducted antimicrobial resistance surveys (>95% isolates susceptible)
Syndromic management approach

- In Mwanza study (1995), syndromic management approach for all STI syndromes decreased HIV incidence by 38%.
- Works well for male urethral discharge syndrome.
- Avoids lab tests but regular microbiological surveillance is part of the syndromic approach.
- Treatment must cover gonorrhoea and chlamydial infection – now also important to consider *M. genitalium* and *T. vaginalis* infections.
- Some African countries, e.g. Namibia, have included metronidazole as part of first-line therapy for male urethral discharge – under discussion for SADC Region.
Syndromic management approach

- Educate, ensure compliance and counsel
- Promote abstinence during the course of treatment
- Promote and demonstrate condom use, provide condoms
- Stress importance of partner treatment and issue one notification slip for each sexual partner, follow up partner treatment during review visit
- Offer HIV counselling and testing, repeat HIV test after 3 months (HIV negative patients)
Recurrent & persistent urethritis

- First step is to review treatment compliance, sexual abstinence on treatment and partner notification outcomes – re-treat with first-line therapy as appropriate

- Most men with recurrent NGU are *C. trachomatis* negative

- *M. genitalium* may be resistant to doxycycline (up to 80% of cases) – role of macrolides (azithromycin preferred)

- Treat for trichomoniasis if not covered in first-line regimen

- If recurrent urethritis does not improve, refer to next level for specialist advice if available

- Investigations of recurrent urethritis cases unresponsive to GC/CT/MG/TV treatment are specialised – patients may require prolonged macrolide courses or NSAIDs
Treating urethritis effectively decreases HIV-1 RNA load in semen

Epididymo-orchitis

- Usually related to STIs or UTIs
- Acute unilateral scrotal pain and swelling
- Lack of recent epidemiological data in USA/UK - significant problem in USA/UK in 1960s-1980s
- Accounts for 2% of male STI presentations to PHCs in South Africa (2000-2006)

Gonococcal epididymo-orchitis
Aetiology of epididymo-orchitis

Infectious causes

- sexually-acquired urethritis (*C. trachomatis* and *N. gonorrhoeae*)
- urinary tract infections (*coliforms* and *Pseudomonas aeruginosa*)
- systemic bacterial, fungal, viral or parasitic infections

Non-infectious causes

- trauma
- amiodarone
- post-infectious aetiology
  (*Mycoplasma pneumoniae*, enteroviruses and adenoviruses implicated)
- systemic vasculitis
  (Henoch-Schönlein purpura, polyarteritis nodosa, Behçet’s syndrome)
Non-STD/UTI infectious causes of epididymo-orchitis

**Bacterial**
- Mycobacteria: *M. tuberculosis*, *M. chelonae*, *M. avium-intracellulare*, *M. kansasii*, *M. xenopei*, *M. bovis*, *M. leprae*
- Brucella spp.
- *Treponema pallidum*
- Nocardia spp.
- *Plesomonas shigelloides* and *Listeria monocytogenes* (immunosuppressed)

**Viral**
- mumps
- CMV (immunosuppressed)

**Fungal**
- histoplasmosis
- coccidioidomycosis
- blastomycosis
- cryptococcosis
- Candida spp.

**Protozoal**
- *T. vaginalis*

**Parasitic**
- schistosomiasis
- sparganosis
- filariasis
Epididymo-orchitis: predisposing factors

- Risk behaviour for STIs – recent untreated/inadequately treated urethral discharge
- Underlying genitourinary pathology in children (check for congenital anomalies)
- Underlying genitourinary pathology in older men:
  - history of prostatic calculi
  - recent genitourinary or prostate instrumentation
  - neurogenic bladder
  - prostatic hypertrophy
  - chronic bacterial prostatitis
- Immunosuppression (HIV/AIDS)
Differential diagnosis of epididymo-orchitis

- **Torsion of the testis** (pyuria and raised CRP suggest infection, ultrasound helpful, surgical emergency)
- **Testicular tumours** (25% present with scrotal pain)
- **Hydrocele** (transillumination, ultrasound)
- **Spermatocele** (transillumination, ultrasound)
- **Varicocele** (varicosities disappear in supine position)
- **Hernia** (may be reducible)
Diagnostic tests for epididymo-orchitis

- Gram stain of urethral smear
- Urinalysis of first pass urine for pyuria
- Microscopy and culture of mid-stream urine
- GC/CT screening tests (culture, NAAT etc.)
- Ultrasound and CRP if diagnosis uncertain
Management of epididymo-orchitis

**STI-related:**
- Ceftriaxone 250mg imi stat
- Doxycycline 100mg po 12 hourly x 14 days

**UTI-related:**
- Ciprofloxacin 500mg po 12 hourly x 10 days
  
  or

- Ofloxacin 400mg po 12 hourly x 10 days

Consider IV antibiotics if systemic illness

**No improvement or clinical progression:**
- Review lab tests and susceptibility data
- Assess for complications (ultrasound &/or surgery)
- Consider alternative diagnosis, e.g. TB

**Scrotal support enhances lymphatic and venous drainage**
Complications of epididymo-orchitis

• abscess formation
• infarction +/- gangrene
• hydrocele formation
• decreased fertility (bilateral epididymitis)