Update on Non-gonococcal Urethritis and Cervicitis

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Aims and Objectives

• Definition of non-gonococcal urethritis (NGU)
• Aetiologies NGU
  • Infectious versus non-infectious
• Diagnosis
  • How do we diagnose NGU
• Treatment
Non-gonococcal urethritis

- “Inflammation of the male urethra”
  - Presence of symptoms
    - Dysuria, discharge, urethral irritation
  - Positive findings on microscopy
    - $> 5$ PMNs/hpf in 5 or more fields
- Gonorrhoea negative

Infectious aetiologies of urethritis

- *Neisseria gonorrhoeae*  2-5%
- *Chlamydia trachomatis*  15-50%
- *Mycoplasma genitalium*  10-25%
- *Trichomonas vaginalis*  <1-5%
- *Ureaplasma urealyticum*  10-20%
  - Only causal in 20-60%
  - Not associated with PID in women
- 1-4% urinary tract infection (Leung 2001)
- 30-40% no cause identified
  - More common in asymptomatic NGU
**Chlamydia**

- **Common**
  - 4-9% young people (under 25) attending health care setting
  - 2-3% sexually active population < 25 yrs
  - Prevalence decreases after age 25 yrs
- **Diagnosis using nucleic acid amplification tests (NAATs)**
  - Revolutionised management
- **Less uncertainty about natural history**
  - Fast clearing within 1-2 weeks: Men = 25% Women = 33%
  - Slow clearing: Men = 2.75 years Women = 1.3 years

  Price M et al. HTA 2016 & Lewis J et al JID 2017;216

**Chlamydia Complications**

- **PID**
  - 17% (35% 16-24yr old)
- **Infertility**
  - Tubal factor infertility (TFI) accounts for 20-30% infertility
    - 30% TFI secondary to chlamydial infection
  - Male factor
    - ?Conflicting evidence
- **Ectopic pregnancy**
  - 5-10% caused by chlamydia
- **Neonatal complications**
  - Conjunctivitis; pneumonia
- **Sexually acquired reactive arthritis**

Price M et al. HTA report 2016 DOI:10.3310/hta20220
Gottlieb S JID 2010:201 S2:190
Chlamydia

Natural history

- Endocervical infection
  - Clearance without treatment 1.3yrs asymptomatic
  - 17%
- Pelvic inflammatory disease
  - 40%
- Salpingitis
  - 3%
  - 7%
- Ectopic pregnancy
- Infertility

Women with untreated infection have: 17% risk of PID; 7% risk of salpingitis; 0.5% risk of TFI; 0.2% risk of ectopic pregnancy.

- Risk of complications doubles with each recurrence of PID

Chlamydia

Diagnosis and management

- NAAT testing will detect majority of men
- Urethritis detection will shorten time to Rx
  - 60%
- Treatment
  - Doxycycline 100mg bd 7/7 >95% effective
  - Azithromycin 1g 92% effective
**Chlamydia-negative NGU**

- False-negative CT NAAT (5%)
- *M genitalium* - Index and/or partner
- *Trichomonas vaginalis*
  - Related to prevalence in population
- *Ureaplasma urealyticum*
  - Causes some cases
  - Not always pathogenic (20-60%)
  - Transmissible
  - Doesn’t cause disease in women
- Urinary tract infection
  - 1-4%
- HSV
  - Uncommon
- Adenovirus
  - Uncommon
- Unknown – 30%
  - ?Bacterial vaginosis associated bacteria
  - ?Other

**Mycoplasma genitalium**

- Affects 1-3% young people
  - 7% young people attending GUM
- Associated with NGU, cervicitis (PCB) and PID (mild), proctitis
  - 5-10% co-infection with chlamydia
- Associated with increased HIV transmission
- Increasing availability NAAT diagnosis
- Macrolide antimicrobial resistance
  - 40% in some centres
  - Associated with use of Azithromycin 1g stat

Taylor-Robinson Geniturin Med 1995
**Mycoplasma genitalium**

**Natural history**

- Most men (and women) probably resolve infection without developing disease.

**Mycoplasma genitalium**

**Treatment**

- Tetracyclines
  - Approx 40% effective

- Azithromycin (if macrolide sensitive)
  - 1g = 87% effective
    - 90% of treatment failures will develop macrolide resistance
  - 1.5g >95% effective
    - Associated lower risk macrolide resistance
  - 1g then 500mgs od for 2 days

- Quinolones
  - Moxifloxacin 400mg OD 10 days >95% effective
  - Ofloxacin 200mg BD 7 days ~ 50% failure
  - Resistance emerging

Ureaplasmas

- A lot of unknowns and poor information
  - Shepard 1974 associated with acute NGU - Did not control for chlamydia
  - Self inoculation studies - 2 doctors; Japanese scientist
  - Case-control studies NGU
    - Inconsistent association
    - High carriage rate in controls
    - Did not distinguish UU from U. parvum

- Associated chronic NGU

Ureaplasma urealyticum

- Ureaplasmas exist as two biovars
  - Ureaplasma parvum – biovar 1
  - Ureaplasma urealyticum – biovar 2

- Only U. urealyticum is pathogenic
  - Urethritis is associated with a high bacterial load
  - Asymptomatic carriage associated low load
  - More likely to cause urethritis on initial exposure
    - Associated NGU in men with fewer lifetime partners
    - Immune response important determinate disease

- Eradication standard therapy sub-optimal
  - Not associated persistent NGU
**Ureaplasma urealyticum**

**Diagnosis**
- NAAT diagnostic testing available
  - UK
- European countries
  - Culture is test of choice
    - Biovars not differentiated (UU vs UP)
    - No information on organism load
- Screening not recommended IUSTI

**Treatment**
- Difficult to eradicate *(Khosropour C 2015 & Horner P 2001)*
  - Doxycycline
    - 10% resistance
  - Macrolides
    - Resistance reported
    - Azithromycin 1g sub-optimal c.f. clarithromycin
      - Longer duration may be beneficial – extracellular infection
        - 1g then 500mgs od 2 days
  - Quinolones
    - Effective
    - Resistance reported
Why is urethritis important?
Urethritis and HIV

• Urethritis indicates infection with known pathogens with significant sequelae
• Urethritis = inflammation which promotes HIV transmission and acquisition
  o Men with a urethral discharge have an increased HIV viral load in semen
  o HIV positive men with urethritis (even asymptomatic) have a higher HIV load in semen than men without NGU
  o Treatment of urethritis may reduce HIV load in semen


Diagnosis of NGU
Genital tract inflammation & STIs

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M. genitalium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGU</td>
<td>4-5</td>
<td>15-30%</td>
</tr>
<tr>
<td>Asymptomatic NGU</td>
<td>2</td>
<td>5-10%</td>
</tr>
<tr>
<td><strong>Chlamydia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGU</td>
<td>5-10</td>
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</tr>
<tr>
<td>Asymptomatic NGU</td>
<td>2</td>
<td>10%</td>
</tr>
</tbody>
</table>

* hypothetical

Loge number of Leucocyte

Symptoms associated greater inflammation
### Male urethritis

<table>
<thead>
<tr>
<th>Leucocyte cell count (log10)</th>
<th>No of PMNLx10^6 PF</th>
<th>No of PMNLx10^6 PF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.4</td>
<td>57/3565 (1.6%)</td>
<td>397/1150 (34.5%)</td>
</tr>
<tr>
<td>0.4 - 4.9</td>
<td>76/3461 (5.4%)</td>
<td>558/2534 (17.4%)</td>
</tr>
<tr>
<td>5.0 - 9.9</td>
<td>45/3534 (17.4%)</td>
<td>397/1150 (34.5%)</td>
</tr>
<tr>
<td>≥ 10.0</td>
<td>5/9</td>
<td>38/1024 (3.3%)</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>13/1537 (0.8%)</td>
<td>10/1504 (0.7%)</td>
</tr>
</tbody>
</table>

**Chi-squared test results:**

- $\chi^2 = 12.31$, df = 6
- $p = 0.04$ (significant)

### Urethritis

<table>
<thead>
<tr>
<th>Discharge/Dysuria</th>
<th>No of Men</th>
<th>N =</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>37</td>
<td>2213</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>1537</td>
</tr>
</tbody>
</table>

**Discharge/Dysuria test results:**

- $p = 0.04$ (significant)

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Chlamydia  
Moi H et al STI 2009  
M. genitalium  
Wiggins R 2005 Int J STD & AIDS
Inflammation and symptoms

- Discharge and dysuria are surrogate markers for the strength of the inflammatory response

<table>
<thead>
<tr>
<th>M. genitalium</th>
<th>Negative controls</th>
<th>Asymptomatic NGU</th>
<th>Symptomatic NGU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Prevalence</td>
<td>2-5%</td>
<td>5-10%</td>
<td>10-25%</td>
</tr>
</tbody>
</table>

Inflammation and symptoms

- Asymptomatic screening for NGU
  - Poor predictor M. genitalium & Chlamydia
  - Extremely accurate testing methods now available
    - Use NAAT testing to screen for Chlamydia
Does lowering the cut-off increase STI detection?
Yes!
But…
• Increases risk of treating pathogen-negative NGU
• Urethral smear inaccurate especially at low levels of urethral inflammation

Can symptoms and signs predict infectious aetiology?
• Symptoms = higher degree of inflammation
• Asymptomatic urethral inflammation associated increased risk of pathogen-negative NGU
  • Reflects lower degree inflammation
Can urethral inflammation resolve without treatment?

• ~20% response in placebo controlled studies
• May be more likely with lower grades inflammation

22% asymptomatic polygamous men had urethritis
Swartz S et al JID 1979

• 29 asymptomatic men with ≥ 4 PMNs/hpf after 1 week
  • 15 (52%) had < 4 PMNs/hpf
  • 6/14 with ≥ 4 PMNs/hpf were chlamydia-positive

What causes low grade inflammation?

• Sexually transmitted infections
• Natural history of male urethra when exposed to female microbiome is unknown
  • BV associated bacteria
    • Complex - *U. urealyticum*
• Intra-prostatic reflux secondary to increased pelvic floor tone and urethral sphincter dysynergia
  • Proposed mechanism for CPPS (see next talk)
Symptomatic men < 5PMNs/hpf

- Early morning smear
  - **Good** negative predictive value
  - Reassured
  - Tested CT/NG
  - Asked to re-attend if symptoms do not settle

STIs and urethritis conclusion

- STI positivity increases
  - As degree of urethral inflammation increases
  - With presence of dysuria and discharge
    - Examination
- Current tests for urethritis
  - Poor
Diagnosis – The urethral smear

• Inaccurate
  • Specimen preparation
    • Time since last voided
    • Method
  • Client
    • Inter and intra – observer variation
  • Men with NGU esp 5-15 PMNL/hpf
  • Blunt curette (Scandinavia)
    • Not practical

Diagnosis – The urethral smear

• Painful
  • Loop least painful (50% cf swab)
  • Rayon swab worst
Treatment NGU

Azithromycin 1 g stat

- Chlamydia
  - $\geq 10\%$ failure rate
  - No antimicrobial resistance (AMR)
- M. genitalium
  - 13% failure rate
  - Antimicrobial resistance 12%
    - NAAT macrolide AMR testing limited availability
- Poor efficacy
  - Asymptomatic NGU
    - Generate antimicrobial resistance M genitalium
Doxycycline

- Chlamydia
  - <5% failure rate
  - No antimicrobial resistance

- M. genitalium
  - 60% failure rate
  - No antimicrobial resistance

- Poor efficacy M. genitalium
  - Poor option chlamydia –ve asymptomatic NGU

Management of NGU

- 1st line
  - Doxycycline 100mg bd 7/7

- Alternatives
  - Azithromycin 1g then 500 mgs od 2/7
  - Ofloxacin 400mg as single or divided doses 7/7

- Asymptomatic NGU
  - Risks outweigh benefits
    - Generates iatrogenic disease
Antibiotic therapy – chronic NGU

• Azithromycin >1g stat
  • Azithromycin 1 g then 500mgs od 2/7
    • Eradicate *M genitalium*
      • Probably >95% effective with prior doxycycline
    • Efficacy ureaplasmas?
• Metronidazole 400mg bd 5-7/7
  • Trichomonas
  • BV associated bacteria

Management - symptomatic

• Full history including sexual history
• Examination – discharge (use a chaperone)
• Urethral smear - loop
  • GC culture and Gram staining
• First pass urine specimen
  • Chlamydia and GC NAAT
  • *M genitalium* NAAT with AMR testing (if urethritis present)

If urethral smear negative and symptomatic
  • Reassure, await CT/NG result + EMS if symptoms persist
• Consider MSU
  • Urinalysis (nitrites + leucocyte esterase) +/- MC+S if symptoms UTI
• Early morning smear (EMS) if smear negative and symptoms persist
Management of NGU

• Discuss
  • Treatment
  • Implications of diagnosis

• Partner notification
  • Health adviser if clinically symptomatic
    • Greater risk Chlamydia/ M. genitalium
    • All at risk contacts past month

* M. genitalium antimicrobial resistance warning ~ 12%
Follow-up

- No need to reattend if:
  - Symptoms settled
  - Partner(s) treated
- If symptoms persist
  - Reassess urethritis consider EMS
  - Exclude:
    - Re-infection
    - Other causes of urethritis e.g. UTI

Urethritis and STIs

- No role for urethral smear in asymptomatic men
Patient’s perspective

- 25 yr old married man requests check-up following
  - Casual contact three weeks previously
  - Penile tip discomfort and occasional dysuria
  - Denies SI with his wife

Examination
- Urethral smear negative

Patient’s perspective

- An accurate diagnosis with effective treatment
  - STI excluded
  - Resolution of symptoms

- Discuss
  - Accuracy of diagnosis
  - Management options
Symptomatic men – Negative urethral smear

- Heart sink
- Early morning smear
  - Extra visit – wasted resources
- How can we improve diagnostic accuracy
  - Take a good urethral smear initially!

Diagnosing urethritis

- Urethral smear
  - At least five methodologies
  - Use a loop
- Spun deposit
  - Not possible health and safety
Urethritis and STI

• Symptomatic man and Gram stain negative
  • Take a good urethral smear initially
• Reassure
  • Await NAAT result
  • If symptoms do not settle
  • Early morning smear

Diagnosing urethritis when microscopy is not available

• Problems with sensitivity and specificity – not recommended
  • Urethral discharge
  • Leucocyte esterase test
  • Threads – Gram stained
**Urethral Discharge**

- Strong association urethritis
- Genitally unaware
  - 10-15% asymptomatic men with NGU will have a visible discharge
  - Mucopurulent (CDC)

**Leucocyte esterase test**

- Correlated urethritis
  - Not as sensitive as urethral smear
  - Less specific (false positives increased)
- Can be done on FPU specimen
- Recommended CDC
LE test

Threads in FVU

- Correlated urethritis
  - Poor sensitivity and specificity
- > 10 PMNLs/hpf
References

• European Guidelines NGU and *M genitalium*  
  http://www.iusti.org/regions/europe/euroguidelines.htm

• BASHH NGU guideline  
Cervicitis

Cervicitis – what is it?

- Inflammation of the cervix
  - Macroscopic appearance
  - Gram-stained cervical smear
Cervicitis - inflammation

- Macroscopic
  - Purulent/Mucopurulent discharge
  - Swab test
  - Easily induced and sustained endocervical bleeding on swabbing the endocervix

- Microscopic
  - $\geq 10$ PMNs per high power field
  - $\geq 30$ PMNs per high power field
Cervicitis

- All criteria associated with
  - Gonorrhoea
  - Chlamydia
  - *M. genitalium*: Post coital bleeding
  - BV
  - TV/HSV
- Association is strongest in high STI prevalent populations
Cervicitis - diagnosis

• Reproducibility
  • Improves with training and experience

What is the clinical importance of cervicitis?

• We just do not know!
• 2015 CDC Treatment guidelines
  • Treatment is determined by
  • Risk assessment CT/GC (immediate Rx)
  • Have they evidence of UGTI?
  • Await results of NAAT CT/GC
  • Role *M genitalium* NAAT unclear
    • Should consider testing
  • Role TV and possible role BV recognised
    • Treat if detected
What is the clinical importance of cervicitis?

• Is it the female equivalent of NGU in men?
• Should we be treating CT-negative cervicitis?
  • ?Partners
  • Which regimen – not azithromycin 1g
• Could treatment do more harm than good?