Chronic urethritis & the CPPS epididymo-orchitis and sexually required reactive arthritis

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Outline

• Define
  • Chronic urethritis
  • Chronic pelvic pain syndrome Syndrome (CPPS)
  • Overlap
• Aetiology and Treatment
  • Context clinical case
Chronic urethritis
Persistent vs recurrent urethritis

- Symptoms/signs
  - Discharge
  - Dysuria
  - Genital discomfort
- ≥ 5 PMNLs/hpf Gram stained urethral smear
  - ≥ 10 PMNLs/hpf Gram stained thread from FPU
- Persistent
  - Present for ≥ 30 days following treatment
- Recurrent
  - Recurrence within 90 days following treatment
- 10-20% men with acute NGU

Chronic pelvic pain syndrome (CPPS)
(non-bacterial Chronic Prostatitis)

- The presence of genitourinary pain in the absence of a defined uropathogen using standard culture techniques
- Inflammatory and non-inflammatory
- Three major domains
  - Pain
  - Urinary symptoms
  - Impact on quality of life
  - (sexual dysfunction)
- 2-9% men 25-50yrs old
Clinical Features

- Chronic NGU
  - Discharge
  - Dysuria
  - Penile irritation
  - Urethritis

- CPPS
  - Genital pain
  - Dysuria
  - Perineal
  - Penile tip
  - Testicular
  - Lower abdominal
  - Pain ejaculation
  - Urinary symptoms
  - Erectile dysfunction
  - Inflammation
  - Yes and no

Chronic NGU/CPPS

- Syndromes overlap
  - Extent unknown
- Aetiologies/pathogeneses poorly understood
- Diagnostic tools inadequate
- Treatments suboptimal
- Major morbidity psychological
Clinical scenario

• He’s back! – 4th time in 6 weeks
Clinical scenario

• He’s back! – 4th time in 6 weeks
• 30 yr old man diagnosed with acute NGU 6 wks ago
• SI CGF 2 weeks previously
  • RGF 2 years no SI since CGF
• Treated with doxycycline 100mg bd 7 days
• Returned 2wks later improved but still not right.
  • NGU –ve - reassured
• Returned again 2 weeks later with persistent symptoms
  • Had SI with RGF
  • urethritis on microscopy
  • Treated with azithromycin 1g then 500mgs od 2 dys and advised RGF needs treatment

Clinical scenario

• He’s distraught!
• His symptoms are still persisting despite treatment
  • No discharge
  • Penile tip and perineal pain
  • Dysuria and pain on ejaculation
  • Frequency of micturition
  • He has not been sexually active
• You were the doctor who reassured him on his 2nd visit!
Clinical scenario

- What are you feeling?
- What would you do?
- How would you explain to him
  - What is wrong with him
  - Aetiology (ies)
  - Diagnostic strategy
  - Treatment options
  - Prognosis

What is wrong with him?

Chronic NGU
vs
Chronic pelvic pain syndrome
Chronic NGU
Gram stained urethral smear

• Inaccurate
• Early morning smear

Aetiology – evidence base

• *C. trachomatis*
• *M. genitalium*
• *Ureaplasma urealyticum* (not *parvum*)
• *Trichomonas vaginalis*
• Unknown

N.B. STIs are not associated with asymptomatic chronic urethritis
Association of *M. genitalium* with urethritis – chronic NGU

- Detected in 20-40% of men with Chronic NGU
  - Greater inflammatory response
  - Usually have discharge

**Ureaplasma urealyticum**

- Association with Chronic NGU
  - Conflicting (Horner P 2001 & Khosropour C 2015*)
  - Subsequent UU detection not associated with symptoms
  - Minor role related to load
- Treatment failure
  - Antibiotic failure
- Partners?
  - Not associated with reproductive morbidity in women
  - Source re-infection
Trichomoniasis

- Uncommon cause urethritis in UK
  - Limited data: ? More common Afro-Carribean
  - Dependent on how common in local population

- Recurrent persistent urethritis
  - Birmingham 4% (1/27) (Ng A 2015)

Diagnosis

- *M. genitalium*
  - NAAT diagnostic tests now recommended

- *U. urealyticum*
  - No routine diagnostic test available – UK
  - Significance uncertain

- *Trichomonas vaginalis*
  - Culture and Wet mount poor sensitivity in men
  - NAATS now available and 40% more sensitive
## Which antibiotics? – in vitro data

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<th>Ofloxacine</th>
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<td>Trichomonas</td>
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</tr>
</tbody>
</table>

* 1 g then 500mgs od 2 days (BASHH guidelines)


## Antibiotic therapy – chronic NGU

- **Azithromycin 1grm stat then 500mgs od 2 days**
  - 500mg then 250mg 4/7
    - >95% effective *M genitalium*
      - Prior treatment doxycycline reduces risk macrolide AMR
    - Efficacy ureaplasmas?
  - Consider Rx partner with longer course
  - MG macrolide resistance UK 40-50%
- **Metronidazole 400mg bd 5-7/7**
  - Trichomona
  - BV associated bacteria

BASHH Mgen guideline
3rd line antibiotic therapy

- Moxifloxacin 400mgs od 10 dys
  - *M. genitalium*
  - ? Prior treatment doxycycline

4th line antibiotic therapy

- Clarithromycin 500mgs bd
  - Anti-inflammatory (Perletti G Mol Med Repo 2011)
  - Covers tetracycline resistant ureaplasmas
    - ?Greater efficacy than azithromycin
    - No effect if macrolide resistance
  - Duration
    - 3-4 weeks
      - Hooton 1990 and erythromycin
      - Standard treatment prostatitis
  - Not evaluated
- Doxycycline 100mgs bd 2-4 wks
  - Anti-inflammatory
  - Covers macrolide resistant ureaplasmas
Do you retreat Partners?

- Limited evidence base
- 60% partners *M. genitalium* infected
  - Efficacy antibiotics men = women
    - If recurrent NGU occurs in men following SI
      - Partner re-Rx
      - Use regimen effective in index case (in absence of diagnostic tests)
- MG NAAT testing plus macrolide AMR testing
- *U. urealyticum* may be difficult to eradicate (Horner 2001 & Khosropour C 2015))
  - ?significance - load

Suggested treatment pathway
Complications chronic NGU

- Pain
- Psychological
- Not associated reproductive morbidity
  - Male
  - Female
  - But data largely anecdotal and assumes partners treated (M. genitalium and sub-optimal treatment?)
- Not associated cancer
- Persistent urethral discharge (uncommon)
  - Long term antibiotics limited value

Chronic pelvic pain syndrome

- 8% prevalence men 25-50 yrs old
1978 classification
(1995)
(1978 classification classification) (Drach et al) (NIH)

- Acute bacterial prostatitis
- Chronic bacterial prostatitis
- Chronic nonbacterial prostatitis
- Prostatodynia

I. Acute bacterial prostatitis
II. Chronic bacterial prostatitis
IIIa. Chronic pelvic pain syndrome, inflammatory
IIIb. Chronic pelvic pain syndrome, non-inflammatory
IV. Asymptomatic inflammatory prostatitis

**Aetiology and Pathogenesis**

- Infection
- Intraprostatic reflux
- Increased Pelvic Floor Muscle Tone
- Sensitisation
- Psychosomatic Factors
- Autoimmunity
- Perception and Interpretation
- Emotions and Coping Strategies
CPPS: Aetiology and pathogenesis

- Increased pelvic floor muscle tone
- Intraprostatic reflux
  - Mechanical or functional obstruction
  - Reflux and influx of sterile urine, micro-organisms, antigens
- Perception and interpretation
  - Hypogastric nerve plexus
  - Obsessive persona
  - Feedback loop
- Pain cycle and sensitisation
Hypogastric plexus and referred pain

CPPS pain reinforcement feedback loop

CP/CPPS reinforcement feedback loop

Susceptible person
  e.g. anxious or obsessive
  personality trait

Stress ↑

Anxiety ↑

Pelvic floor
  muscle tone ↑

Pain ↑

Other/hernia

Inflammation

Infection

Unknown

Muscle spasm

Intraprostatic
  urinary reflux
Pain Sensitization

Experiencing pain makes us hypersensitive to more pain.

Diagram:
- Hyperalgesia
- Allodynia
- Normal pain response

Noxious stimuli can sensitize the nervous system response to subsequent stimuli. The normal pain response as a function of stimulus intensity is depicted by the curve at the right, where even weak stimuli are not experienced as pain. However, a traumatic injury can shift the curve to the left. Then, noxious stimuli become more painful (hyperalgesia) and typically painless stimuli are experienced as pain (allodynia).

http://www.chronicprostatitis.com/chronic-prostatitis-is-a-psychoneuromuscular-condition/

**CPPS pain reinforcement feedback loop**

**CPPS: Treatment**
- Strong placebo effect - the good doctor
- Evidence to support:
  - Alpha-blockers
    - Anti-muscarinics
  - Antibiotics
    - Quinolones 4+weeks
    - Tetracyclines/Clarithromycin
  - Combination more effective
  - Pelvic floor re-education
    - Bio-feedback
    - Trigger points - physiotherapy
  - Acupuncture
  - NSAID (cox 2)

Rees J BJU Int 2015; 116: 509–525
Anothaisintawee T JAMA 2011;305:78.
**CPPS: Treatment**

- Other
  - Low dose amitriptyline?
  - Pregabalin
  - Sertralline
- Alternative medicines
  - Quercetin
  - Pollen extract

Rees J BJU Int 2015; 116: 509–525
Anothaisintawee T JAMA 2011;305:78.

**CPPS: Diagnosis**

- Clinical – history
CPPS: Diagnosis

- Clinical – history
  - Explore symptom pattern
  - Explore anxieties
  - Explore persona

- Introduce concept of CPPS and increased pelvic floor tone using diagrams and how this can cause referred pain.

- Get them to identify pelvic floor muscles

- Exam
  - exclude other causes
  - Pelvic floor examination
**CPPS: Diagnosis**

- Exclude Infection
  - *M genitalium* – NAAT & urethritis
  - UTI – chronic bacterial prostatitis (uncommon)
- Non-inflammatory vs inflammatory
  - ? urethral smear
    - Antibiotics – clarithromycin if STI –ve and has urethritis

**CPPS: Treatment**

- Establish diagnosis
  - Excluded other causes
  - Symptoms and signs consistent
  - Persona consistent
- In depth discussion CPPS feedback loop
- Advice pelvic floor relaxation
  - Pelvic floor drop exercises
- Alpha-blockers
  - Anti-muscarinics
- Antibiotics
  - Clarithromycin 3 weeks
 CPPS: Treatment

- In men who do not respond to therapy consider
  - Pelvic floor physiotherapy
  - Referral Urology - Urodynamics – if symptoms bladder outflow obstruction do not improve
  - Pain clinic

 CPPS: Treatment

- Biopsychosocial approach
  - Explain aetiology/pathogenesis
  - Social support
  - Coping strategies
  - Cognitive behavioural interventions
- Multidisciplinary team
**CPPS: Prognosis**

- 30% improved 2 years
  - 2/3rds improved Bristol (80 patients)

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**Clinical scenario**

- He’s back! – 4th time in 6 weeks
- 30 yr old man Rx acute NGU 6 wks ago
- SI CGF 2 weeks previously
- Sub-optimal response NGU –ve – reassured
- Returned 2 wks later with persistent symptoms
  - Had SI with RGF
  - urethritis on microscopy
  - Treated with azithromycin 1.5grm and metronidazole
    - RGF treated azithromycin 1grm
- Returns 2wks later symptoms persisting
Clinical scenario

- He’s distraught!
- His symptoms are still persisting despite treatment
  - No discharge
  - Penile tip and perineal pain
  - Dysuria and pain on ejaculation
  - Frequency of micturition
  - He has not been sexually active
- What would you do?

What should you have done?

![Management of NGU Flow Diagram](image-url)
What are you going to do?

• Listen
• Listen
  • Empathic
  • Use NIH-Chronic Prostatitis Symptom Index
• Address his concerns

What are you going to do?

• Establish a positive therapeutic relationship using active listening skills and empathy
• Discuss causes of CPPS and possible role of anxiety perpetuating symptoms due to increased pelvic muscle tone with referred pain.
• Obsessive traits should be discussed in a positive light i.e. a problem-solver who thinks things through
• Provide CPPS patient leaflet and go through “Pelvic floor drop exercises”
• Address anxieties around infection, cancer and infertility
• Discuss support and coping strategies
• Ensure UTI has been excluded
• Consider PSA if clinically indicated
Referral to CPPS clinic

All patients should:
• Have a CPPS-directed history and examination undertaken including PR for prostate and pelvic tone assessment
• Complete NIH CPSI score

1. Has NGU guideline been followed?
   Consider:
   • Re-infection - efficacy of partner notification and sex during treatment.
   • Adherence to treatment given.
   • M. genitalium testing.
   Rx. Moxifloxacin 400mg OD 14 days +/- Alpha blocker e.g. Tamsulosin 400 mcg OD.

2. STI a concern
   • Has an early morning smear been undertaken?
   • Consider risk of re-infection (see 1.)
   • M. genitalium testing.
   Rx. Clarithromycin 500mg BD 3 weeks +/- Alpha blocker (Moxifloxacin should not be used 1st line unless urethritis persists - M. genitalium testing first).

   If symptoms persist:
   • Repeat urethral smear
     o Negative: reassure - if symptoms continue see Rx for Category 4).
     o Positive: Moxifloxacin 400mg BD 14 days.

3. STI not a concern
   • Alpha blocker to be used if symptoms suggestive of increased pelvic tone
   • M. genitalium testing.
   Rx. Clarithromycin 500mg BD 3 weeks +/- Alpha blocker.

   If symptoms persist:
   • Repeat urethral smear
     o Negative: reassure - if symptoms continue see Rx for Category 4).
     o Positive: Moxifloxacin 400mg BD 14 days.

4. Consider:
   • Early morning smear if STI is a concern.
   • Alpha blocker to be used if symptoms suggestive of increased pelvic tone
   • M. genitalium testing.
   Rx. Clarithromycin 500mg BD 3 weeks +/- Alpha blocker.

   If symptoms improve but not resolved: Continue Clarithromycin for further 1-2 weeks or switch to Doxycycline 100mg BD 4 weeks or Ofloxacin 200mg BD 4 weeks.

   If symptoms unchanged: Switch to alternative therapies (below).

Symptoms continue to persist

• Further treatment should be based on response to initial therapy – use NIH CPSI to monitor.
• Poor response is often linked to undertaking the pelvic floor drop exercises incorrectly and/or not understanding how increased pelvic floor tone can cause their symptoms
• Prolonged therapy may be required.
  • Consider additional agents e.g. NSAIDs, Tricyclics
• If symptoms resolve, and then recur after sexual intercourse consider infection but also the anxiety feedback loop.
  • Have you excluded an STI?
  • Remember to consider the effect of symptoms upon relationship with partner
• If urinary symptoms persist consider referral to Urology
Patient outcomes

- 2010 27 patients mean visits 6.5
- 2012 24 patients mean number visits 3.5

<table>
<thead>
<tr>
<th>Domain</th>
<th>NIH CPSI score (Score 0-43)</th>
<th>First attendance</th>
<th>Last attendance</th>
<th>p-value</th>
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<td>Pain</td>
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<td>7.4</td>
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<tr>
<td>Urinary symptoms</td>
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<td>0.2</td>
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<td>Quality of life</td>
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<td><strong>Total</strong></td>
<td><strong>22.1</strong></td>
<td><strong>14.7</strong></td>
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</tr>
</tbody>
</table>

Chronic urethritis – when microbiology doesn’t help

- A structured empathic approach to management
- Clinically very rewarding
  - Brief intervention
- Consider pelvic floor physiotherapy if refractory
References

• BASHH NGU and Mgen guidelines
• Ramsden et al. Chronic pelvic pain in men. Medicine 2018

Epididymo-orchitis

• Aetiology
• Clinical presentation
• Management
Epididymo-orchitis

- Aetiology
  - <35 – STI
  - >35 – Gram-negative enteric organism

Epididymo-orchitis
Clinical

- Usually unilateral
- +/- symptoms urethritis or UTI
- Consider torsion
  - Onset sudden
  - Pain severe
  - Initial tests no evidence of urethritis or UTI
  - <20
❖ Epididymo-orchitis

Clinical

• Tender on palpation
• Swelling epididymis +/- testis
• +/-
  • Discharge
  • Pyrexia
  • hydrocoele

❖ Epididymo-orchitis management

• STI screen as for NGU
• MSU
  • Urinalysis leucocyte esterase and nitrites
• If torsion a possibility – refer
  • 6 hours (some recovery up to 24 hours)
  • Sudden onset (within hours)
  • <20yrs as torsion until proven otherwise
  • Pain is severe
    • Prescribe antibiotics in addition to surgical referral if cannot exclude cinfection
Epididymo-orchitis management

- Scrotal support +/- bed rest
- Antibiotics empirical
  - Ceftriaxone 1 g (+/-) + doxycycline 100mg bd 14/7
  - Second line: Ofloxacin 200mgs bd 14/7
  - Enteric – Ofloxacin 200mg bd 14/7; cipro 500mg bd 10/7
- Partner notification
- Review
  - 2-3 days if no improvement
  - 2 weeks – response to treatment and PN
  - Ensure no persistent testicular abnormality
    - Occult presentation testicular cancer

Sexually acquired reactive arthritis

- SARA
- *Sterile inflammation of the synovial membranes, tendons and fascia triggered by an infection at a distant site, usually gastrointestinal or genital*
  - Includes Reiter’s syndrome
Sexually acquired reactive arthritis

- Aetiology
- Clinical presentation
- Management

SARA - aetiology

- Male > female
- Associated HLA-B27
- Micro-organisms
  - C. trachomatis 35-69%
  - N gonorrhoeae <16%
  - Ureaplasmas
- Family history
SARA - clinical

- New sexual partner within 3 months
- 80% men symptoms urethritis
- Arthritis within 30 days SI
- Arthritis develops ~2 weeks after onset GU sym

SARA - clinical

- Pain +/- swelling in one or more joints
  - Knees or feet
- Enthesopathy 20% – esp heels
- Tenosynovitis 30%
- Dactylitis 16%
- Low back pain 10%
- Irritation eyes 20-50%
  - Iritis <10%
- Systemic symptom ~10%
- Dermatological
  - Psoriasiform rash – 12%
SARA - clinical

- Self limiting
  - Duration 4-6 mths
  - Severe ~ 20%
- Recurrent
  - 50%

SARA management

- Full STI screen
  - Evidence urethritis/cervicitis
- Acute phase proteins
- FBC
- Urinalysis
- Blood culture
- Synovial fluid examination
  - MC+S, culture, crystals
- Ultrasound/MRI
- Exclusion other arthritides
  - autoantibodies, Rheumatoid factor, urate, sarcoid
SARA management

- Refer/ liaison with appropriate specialist
  - Rheumatology
  - Dermatology
  - Opthalmology – slit lamp
- Rest +/- physio to prevent muscle wasting
- NSAID
  - - COX2 or NSAID + PPI if at risk Upper GI probs
- Antibiotic therapy as for STI diagnosis
  - Conflicting evidence prolonged therapy may be of benefit (Carter 2005)
- Steroids
  - Local injection
  - Systemic +/- disease modifying agents

IUSTI Guidelines

- Epididymo-orchitis
- SARA
- [https://iusti.org/regions/europe/euroguidelines.htm](https://iusti.org/regions/europe/euroguidelines.htm)