The 2024 European guideline on the management of epipidymo-orchitis

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Overview:

Epididymo-orchitis is an inflammatory process of the epididymis +/- testes(1). This clinical syndrome typically presents with acute onset of pain and swelling. It is usually caused by either sexually transmitted pathogens ascending from the urethra or non-sexually transmitted enteric bacteria introduced via the urinary tract.

Principle changes in the 2024 guidelines

For treatment of patients with a history suggestive of sexually transmitted pathogen - Ceftriaxone dose increased to 1g intramuscularly (IM) single dose alongside doxycycline 100mg OD for 14 days.

The use of dual therapy with azithromycin is no longer recommended, unless Cefixime is being given as an alternative to ceftriaxone.

For treatment of patients with a history suggestive of both sexually transmitted and enteric pathogen Ceftriaxone IM single dose AND Levofloxacin 500mg orally once daily for 10-14 days / Ofloxacin 200mg orally twice daily for 10-14 days.

Aetiology and transmission:

**Sexually transmitted infections (STIs):**

*Chlamydia trachomatis*: the most common STI identified in epididymo-orchitis. More often seen in younger patients but may be present in any sexually active individual.

*Neisseria gonorrhoeae*: less common than Chlamydia, again more frequently identified in younger patients. Significant mucopurulent urethral discharge is often reported.

*Mycoplasma genitalium*: an under-recognised cause in sexually active individuals, in part due to variable availability of suitable diagnostics.

Enteric organisms (usually Enterobacteriaceae): in men engaging in insertive anal intercourse(2).

**Non-sexually transmitted infections:**

Enteric organisms (usually Enterobacteriaceae): risk factors include recent or recurrent urinary tract infection, obstructions within the urinary tract or recent surgery and/or instrumentation of the urinary tract (3).

Mumps (causing orchitis without epididymitis): uncommon in individuals who received childhood mumps vaccination (part of MMR)(4).

**Rare causes to consider:**

Tuberculosis (TB): Often associated with renal or multisystem TB but may be an isolated finding. More often seen in patients born in high-risk countries or regions for TB (5).

Brucella: Rare across most of Europe but should be considered in patients with history of residency or travel from Brucella endemic areas. Brucella serology should be tested in patients with relevant travel history, in particular the Middle East and parts of north Africa (6, 7).

Ureaplasma urealyticum: Limited data demonstrating causation with this organism and would typically be treated regardless by empiric anti-chlamydial therapy. Not typically classified as an STI but can be contracted through sexual contact (8).

Syphilis: A rare cause with 11 confirmed cases in the past 59 years (9).

Melioidosis: Only in patients with travel history from *Burkholderia* *pseudomallei* endemic areas (South-East Asia and northern Australasia). Associated with prostatic abscess.

Enteroviruses: Potential rare cause of self-limiting epididymitis in children and young men, although evidence proving causation is lacking (10).

Candida: Unusual complication of candida infections of urinary tract, which tend to develop in the context of surgery or instrumentation (11).

Beçhet’s disease: Occurs in 12-19% of men with this condition, most often in those with severe disease (12).

Amiodarone induced: Symptoms anticipated to resolve on cessation of drug (13).

Clinical features:

Acute onset scrotal pain (typically unilateral) with or without swelling (14).

Tenderness on palpitation.

Urethral discharge or dysuria(15-17)

Pyrexia

Hydrocoele may be present

Disease-specific symptoms and signs

Mumps: headache and fever followed by unilateral/ bilateral parotid swelling. This is followed 7–10 days later by unilateral testicular swelling. Atypically, those affected can present with bilateral testicular swelling, epididymitis alone or without systemic symptoms(18, 19).

TB: subacute/more chronic onset of painless/painful scrotal swelling systemic symptoms, scrotal sinus, thickened scrotal skin(5, 20).

Brucellosis: fever, sweats, headache, back pain and weakness in acute infection(21).

Complications

These tend to be more frequently seen with uropathogen-associated infection(2, 22).

* Hydrocele;
* Abscess
* Infarction of the testicle;
* Infertility – there is a poorly understood relationship between epididymo-orchitis and infertility

Diagnosis

Epididymo-orchitis is a clinical diagnosis based on symptoms and signs. The history, eliciting genitourinary symptoms and the risk of STIs (including anal intercourse), alongside examination findings and preliminary investigations will suggest the most likely aetiology and guide empiric antibiotics.

Historically, STIs have been attributed as the predominant cause for epididymitis in the < 35 age group and enteric pathogens in the > 35 age group. Evidence to support this approach is limited, and age and sexual history taking are not sufficient for guiding antibiotic therapy alone(10).

Differential diagnosis

Testicular torsion is the main differential diagnosis. This is a surgical emergency. If a young man or adolescent presents with a painful swollen testicle of sudden onset then the diagnosis is testicular torsion until proven otherwise.(23). The patient should be promptly referred to urologist. Testicular salvage is required within 6 h and the likelihood of a good outcome decreases with time(24, 25). Empiric antibiotics should also be issued in these circumstances.

Torsion is more likely if:

* The patient is under 20 years (but can occur at any age)
* The pain is sudden (within hours)
* The pain is severe
* Preliminary tests do not show urethritis or likely urinary tract infection(24, 25).

Although colour Doppler has high sensitivity for diagnosing torsion, it cannot be used to exclude the condition(26, 27). If there is suspicion of testicular torsion, arranging an ultrasound should not delay surgical exploration.

Preliminary investigations

* Diagnosis of urethritis with microscopy of a Gram-stained/methylene blue-stained (28, 29) urethral smear showing > 5 polymorphonuclear leucocytes (PMNLs) per high power field (HPF) x 1000 OR a spun down sample from first pass urine (FPU) Gram stained showing > 10 PMNLs per HFP (1000x);
* Urine dipstick – useful only as an adjunct to midstream urine culture (MSU)(30). A negative dipstick test in men should not exclude the diagnosis of urinary tract infection UTI(31, 32). The presence of nitrite and leukocyte esterase suggests UTI in men with urinary symptoms(31, 32).

Laboratory investigations

* Urethral swab for *N. gonorrhoeae* culture;
* FPU/urethral swab for nucleic acid amplification test (NAAT) for *N. gonorrhoeae, C. trachomatis and M. genitalium*;
* MSU for microscopy and culture;
* C-reactive protein and erythrocyte sedimentation rate can support the diagnosis of epididymitis if raised, but surgical referral or antibiotic treatment should not be delayed on the basis of these tests(33, 34).

All patients with sexually transmitted epididymo-orchitis should be screened for other STIs including blood borne viruses (see International Union against Sexually Transmitted Infection Guideline on the organisation of a consultation for STIs)(35).

Men who have sex with men (MSM) should be tested for *N. gonorrhoeae and C. trachomatis* fromall potentially exposed sites(36).

Management:

An assessment should be made of the likelihood of the causative pathogen being sexually transmitted or an enteric organism to determine an appropriate empiric antibiotic regimen. Relevant factors include history of sexual exposures (insertive anal intercourse also being a risk for enteric uropathogens), patient age, previous microbiological results, history of surgery or recent catheterisation and any anatomical risk factors present. Determining therapy by using the patient’s age in isolation is no longer considered a suitable surrogate for the risk of sexually transmitted infections.

Treatment with levofloxacin or ofloxacin alone is recommended only in scenarios where there is strong confidence that a sexually transmitted infection is not implicated. Whilst these quinolone antibiotics penetrate well into epididymal tissue and provide suitable cover for most enteric organisms and chlamydia isolates, increasing rates of quinolone resistance seen in *N*. *gonorrhoeae* make them an unreliable treatment for gonorrhoea (37).

Risks for both sexually transmitted and enteric pathogens

History suggestive of enteric pathogen

History suggestive of sexually transmitted pathogen

Levofloxacin 500mg orally once daily for 10-14 days / Ofloxacin 200mg orally twice daily for 10-14 days

Ceftriaxone 1g intramuscularly single dose

 +

Doxycycline 100mg orally twice daily for 14 days

Ceftriaxone 1g intramuscularly single dose

 +

Levofloxacin 500mg orally once daily for 10-14 days / Ofloxacin 200mg orally twice daily for 10-14 days

-Investigations should be sent as previously detailed regardless of the empiric antimicrobial decision. In all cases, microbiological results should be reviewed promptly, and treatment adapted as appropriate.

-Where *M. genitalium* testing has been performed and the organism identified, treatment should be adapted to include an appropriate antibiotic, typically Moxifloxacin 400mg orally once daily for 14 days(38).

-Where Ceftriaxone is not available or delivery of intramuscular medication challenging, a single dose of Cefixime 800mg administered orally is a reasonable alternative to Ceftriaxone, although may be inferior for treating pharyngeal gonorrhoea infections (39), and should be given with Azithromycin 2g orally.

-When prescribing quinolone antibiotics, Levofloxacin or Ofloxacin are preferred to Ciprofloxacin due to their anti-chlamydial activity(40).

-Where available, local antimicrobial susceptibility data for Enterobacteriaceae and *N. gonorrhoeae* should be accounted for and may take precedence over the recommendations in this guideline.

Additional principles of management:

Information, explanation and advice should be given to the patient: an explanation of the causes of epididymo-orchitis (both sexually transmitted and non-sexually transmitted), the short-term course of the infection and the long-term implications for themselves and their partner, including partner notification if a sexually transmitted cause is identified or suspected;

General advice to patient should include; analgesia, rest and scrotal support;

Points to note and consider

1. Where gonorrhoea is considered unlikely, urethral/ FPU microscopy negative for Gram-negative intra-cellular diplococci, no risk factors for gonorrhoea identified (absence of all of the following – a purulent urethral discharge, known contact of a gonorrhoeal infection, men who have sex with men, black ethnicity)(41) and in countries/populations where there is known very low gonorrhoea prevalence, omitting ceftriaxone or using ofloxacin could be considered.(42) Ofloxacin treats *N. gonorrhoeae, C. trachomatis* and most uropathogens with good penetration into the prostate. However, it is not first line treatment for *N. gonorrhoeae* due to increasing bacterial resistance to quinolones.(39)

Partner notification

For patients with confirmed or suspected sexually transmitted epididymo-orchitis (*N. gonorrhoeae, C. trachomatis* or *M. genitalium*) all partners potentially at risk should be notified and evaluated. They should be tested for all STIs(35) and given treatment with antibiotics to cover *C. trachomatis* (and *N. gonorrhoeae* or *M. genitalium* if confirmed in the index patient). The duration of look-back for contact tracing would be six months for confirmed *C. trachomatis* epididymo-orchitis, 60 days for confirmed *N. gonorrhoeae* epididymo-orchitis and three months for confirmed *M. genitalium* epididymo-orchitis. In other cases thought to be STIs other than those specified above, the duration of look-back is arbitrary, although 60 days is suggested.(43, 44)

Follow-up

At three days if there is no improvement in symptoms, the patient should be seen for clinical review and the diagnosis should be reassessed. For gonococcal epididymo-orchitis, a test of cure using culture can be done three days following completion of treatment.

At two weeks to assess for treatment compliance, assessment of symptoms and partner notification. This could be done by telephone but if the patient has persisting symptoms, arrangements should be made for clinical review. For gonococcal epididymo-orchitis, a test of cure using NAAT should be done two weeks following completion of treatment. At four weeks after completing therapy, a test of cure is required if epididymo-orchitis is confirmed to be secondary to *C. trachomatis* or *M. genitalium*.

Further investigations

All patients with suspected/confirmed sexually transmitted epididymo-orchitis should be screened for all other STIs including blood borne viruses.(35) All patients with uropathogen-confirmed epididymo-orchitis should be referred to a urology specialist for further investigations looking for structural abnormalities/urinary tract obstruction.(45)

In patients where there has not been significant improvement in symptoms/signs after completion of therapy, or there is diagnostic doubt, a scrotal ultrasound should be ordered. Differential diagnoses to consider in these circumstances include progression to abscess,(46) testicular ischaemia/infarct,(47) testicular/epididymal tumour.(14) Further referral to urology should also be considered.

Prevention/health promotion

Patients should be advised that consistent condom use will reduce the risk of acquiring sexually transmitted epididymo-orchitis.(47)

Clinical Scenarios

**Patient 1**

78M presented with left testicular pain and swelling for past 1 week. Past medical history (PMHx) includes benign prostatic hyperplasia (BPH), hypertension, Type 2 diabetes. Drug history includes, ramipril, amlodipine, metformin and tamsulosin. He has no known allergies.

Sexual history reveals no sexual intercourse for >1 year.

Previous microbiology results include a fully sensitive *E.coli* urine.

Examination revealed a left sided tender swollen testicle, which did not transilluminate. Observations were stable.

**Treatment**: This history and presentation is suggestive of Epididymo-orchitis caused by an enteric pathogen. This patient should be treated with Levofloxacin 500mg orally once daily for (or Ofloxacin 200mg orally twice daily) for 10-14 days

This patient should be followed up at 2 weeks to ensure resolution of symptoms. They should be referred to urology for further investigation.

**Patient 2**

45M presented with right testicular pain and swelling and dysuria. Symptom onset was acute staring with the dysuria and have persisted for 3 days. He has no PMHx and takes no regular medications. He has no known drug allergies.

On detailed sexual history taking the patient is MSM and practices insertive anal sex. He has had 3 sexual partners in the past 3 months. He has not has a recent sexual health screen.

Examination revealed a right sided tender swollen testicle, which did not transilluminate. Observations were stable. There was no clinical suspicion of testicular torsion.

**Investigations**: This patient should have triple site testing, along with urine dip +/- microscopy. He should also be tested for blood born viruses, syphilis and *M. genitalium*.

**Treatment**: This history reveals the patient is at risk for both sexually transmitted and enteric pathogens. The patient should be treated with a single dose of Ceftriaxone 1g intramuscularly and either Levofloxacin 500mg orally once daily for 10-14 days or Ofloxacin 200mg orally twice daily for 10-14 days.

This patient should be followed up at 2 weeks to ensure resolution of symptoms +/- test of cure if gonorrhoea is found to be the causative pathogen. Should the pathogen be sexually transmitted previous sexual partners should be notified.

He should be given advice on abstinence and use of condoms following successful treatment.

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