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GUIDELINES

The 2024 European guideline on the management of epididymo-orchitis

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Abstract

The European guideline on the management of epididymo-orchitis has been updated in 2024. This guideline offers advice on the diagnosis, investigation, treatment and follow-up for the management of epididymo-orchitis. For treatment of patients with a history suggestive of sexually transmitted pathogens—ceftriaxone dose increased to 1 g intramuscularly (IM) single dose alongside doxycycline. 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 including risks for both sexually transmitted and enteric pathogens—ceftriaxone IM single dose and either ofloxacin or levofloxacin is recommended. Where enteric pathogens are suspected as the likely cause, either ofloxacin or levofloxacin is recommended as monotherapy. This guideline covers a range of clinical scenarios, including rarer and non-sexually transmitted causative agents.

KEYWORDS

antibiotic, epididymis, epidiymo-orchitis, Europe, orchitis, treatment

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.

PRINCIPAL CHANGES IN THE 2024 GUIDELINES

For treatment of patients with a history suggestive of sexually transmitted pathogens—ceftriaxone dose increased to 1 g intramuscularly (IM) single dose alongside doxycycline 100 mg 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 including risks for both sexually transmitted and enteric pathogens—ceftriaxone IM single dose and ofloxacin 200 mg orally twice daily for 10–14 days/levofloxacin 500 mg orally once daily for 10–14 days.

AETIOLOGY AND TRANSMISSION

Sexually transmitted infections

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

See Appendix S1 for search strategy.

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

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

Enteric organisms (usually Enterobacteriaceae): in patients 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 a history of residency or travel from Brucella endemic areas. Brucella serology should be tested in patients with a relevant travel history, in particular the Middle East, South Asia and parts of north Africa.[6,7]

Ureaplasma urealyticum: Limited data demonstrate 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 literature over the past 59 years.[9]

Melioidosis: Consider in patients with a 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 tends 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]

SARS-CoV-2: Paediatric patients with SARS-CoV2 may be at higher risk.[14]

Why was the study undertaken?

- This study was undertaken to update the European clinical guidelines previously produced in 2016 to reflect the latest evidence.

What does this study add?

- This study adds the latest recommendations for treatment of epididymo-orchitis, based on the latest evidence. Changes include updated antimicrobial guidelines and clinical scenarios.

What are the implications of this study for disease understanding and/or clinical care?

- The implications of this study include improved outcomes for patients with epididymo-orchitis and ensuring European guidelines to reflect the latest evidence.

CLINICAL FEATURES

Acute onset scrotal pain (typically unilateral) with or without swelling.[15]

Tenderness on palpation.

Urethral discharge or dysuria.[16–18]

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.[19,20]

TB: subacute/more chronic onset of painless or painful scrotal swelling, often along with systemic symptoms, scrotal sinus or thickened scrotal skin.[5,21]

Brucellosis: fever, sweats, headache, back pain and weakness in acute infection.[22]

COMPLICATIONS

These tend to be more frequently seen with uropathogen-associated infection.[2,23]

- 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.[24] The patient should be promptly referred to a urologist. Testicular salvage is required within 6 h and the likelihood of a good outcome decreases with time.[25,26]

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 support urethritis or a likely urinary tract infection.[25,26]

Although colour Doppler has high sensitivity for diagnosing torsion, it cannot be used to exclude the condition.[27,28] 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[29,30] urethral smear showing >5 polymorphonuclear leukocytes (PMNLs) per high power ×1000 field (HPF) OR a spun down sample from first pass urine (FPU) Gram-stained showing >10 PMNLs per HPF ×1000;
- Urine dipstick—useful only as an adjunct to midstream urine culture (MSU).[31] A negative dipstick test should not exclude the diagnosis of urinary tract infection UTI.[32,33] The presence of nitrite and leukocyte esterase suggests UTI in men with urinary symptoms.[32,33]

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 (CRP) and erythrocyte sedimentation rate (ESR) can support the diagnosis of epididymitis if raised, but surgical referral or antibiotic treatment should not be delayed on the basis of these tests.[34,35]

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 organization of a consultation for STIs).[36]

Men who have sex with men (MSM) should be tested for *N. gonorrhoeae and C. trachomatis* from all potentially exposed sites.[37]

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. See Figure 1.[38–40] 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. While 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.[41] Epididymo-orchitis is considered a strong enough indication for the use of quinolones; however, the patient should be counselled regarding the risks and benefits of their use.[42]

- 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 400 mg orally once daily for 14 days[43] **(1C)**.
- Where ceftriaxone is not available or delivery of intramuscular medication is challenging, a single dose of cefixime 800 mg administered orally is a reasonable alternative

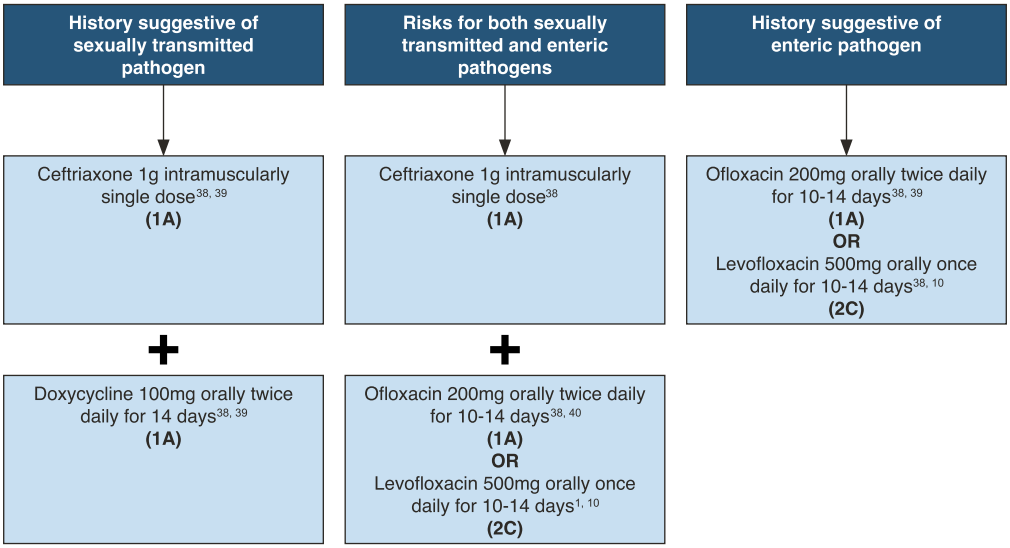

FIGURE 1 Management of epididymo-orchitis.

to ceftriaxone, although it may be inferior for treating pharyngeal gonorrhoea infections[44] and should be given along with azithromycin 2 g orally.
- When prescribing quinolone antibiotics, levofloxacin or ofloxacin is preferred to ciprofloxacin due to their anti-chlamydial activity.[45]
- 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

Where gonorrhoea is considered unlikely, urethral/ FPU microscopy is negative for Gram-negative intracellular diplococci, no risk factors for gonorrhoea are identified (absence of all of the following: purulent urethral discharge, known contact of a gonorrhoeal infection, men who have sex with men[46] and in countries/populations where there is known very low gonorrhoea prevalence, omitting ceftriaxone or using ofloxacin could be considered).[47] 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.[44]

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[36] 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 and 60 days for confirmed *N. gonorrhoeae* epididymo-orchitis. For confirmed *M. genitalium* epididymo-orchitis, current partner(s) (i.e. partners with whom the index patient has recently had unprotected sex and with whom the patient will continue to have sex) should be tested and treated with the same antimicrobial as the index patient.[43] In other cases thought to be STIs other than those specified above, the duration of look-back is arbitrary, although 60 days is suggested.[43,48]

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. See Figure 2. For gonococcal epididymo-orchitis, a test of cure using culture can be done 3 days following completion of treatment.

At 2 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,

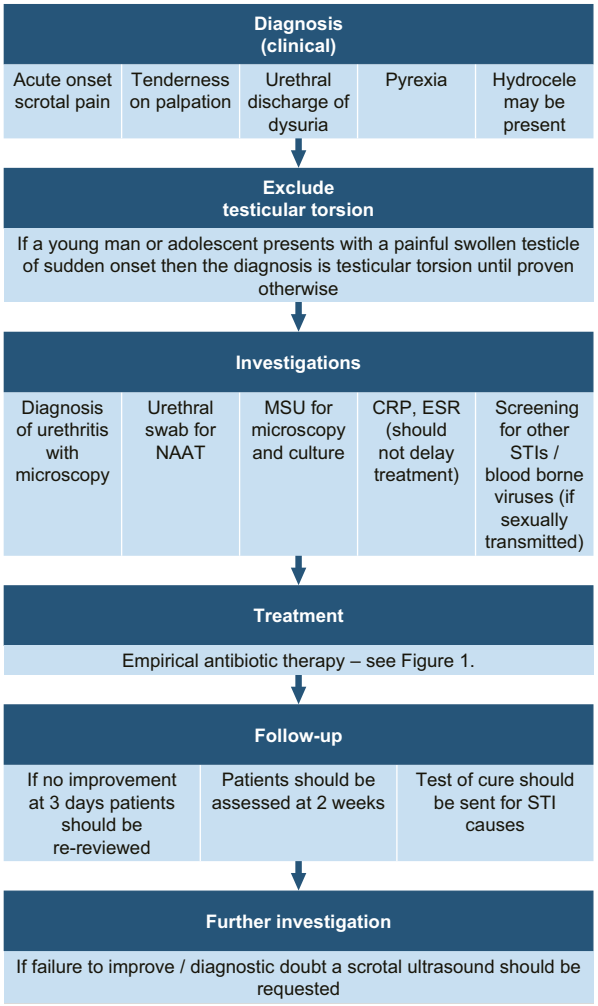

FIGURE 2 Clinical care pathway for management of epididymo-orchitis.

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 4 weeks after completing therapy, a test of cure is required if epididymo-orchitis is confirmed to be secondary to *C. trachomatis* or *M. genitalium*. If a sexually transmitted pathogen is confirmed, patients should be given advice to abstain from sexual contact until the test of cure confirms successful treatment. If patients are unable to abstain, they should be advised on condom use.

FURTHER INVESTIGATIONS

All patients with suspected/confirmed sexually transmitted epididymo-orchitis should be screened for all other STIs including blood-borne viruses.[36] All patients with uropathogen-confirmed epididymo-orchitis should be referred to a urology specialist for further investigations looking for structural abnormalities/urinary tract obstruction.[49]

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,[50] testicular ischaemia/infarct,[51] testicular/epididymal tumour.[15] Further referral to urology should also be considered.

See Table 1 for grading of recommendation and the quality of evidence.

TABLE 1 Grading of recommendation and the quality of evidence.

Grade	Recommendation
1	A strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach
2	A weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values
	Quality of evidence
A	High-quality evidence that comes from consistent results from well-performed randomized controlled trials (RCTs), or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect
B	Moderate-quality evidence from randomized trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias or some combination of these limitations or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias
C	Low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion of most potential sources of bias
D	Evidence based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate

PREVENTION/HEALTH PROMOTION

Patients should be advised that consistent condom use will reduce the risk of acquiring sexually transmitted epididymo-orchitis.[51]

CLINICAL SCENARIOS

Patient 1

78 (M) presented with left testicular pain and swelling for the past 1 week. Past medical history (PMHx) includes benign prostatic hyperplasia (BPH), hypertension and 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 urinary culture results include isolates of *E. coli* susceptible to quinolone antibiotics.

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 ofloxacin 200 mg orally twice daily (or levofloxacin 500 mg orally once 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

45 (M) presented with right testicular pain along with swelling and dysuria. Symptom onset was acute, starting with dysuria and has 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 reports having condomless insertive anal sex. He has had three sexual partners in the past 3 months. He has not had 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 for chlamydia and gonorrhoea, along with urine dip +/− microscopy. He should also be tested for blood-borne viruses, syphilis and *M. genitalium*.

Treatment

The patient is at risk for both sexually transmitted and enteric pathogens. He should be treated with a single dose of ceftriaxone 1 g intramuscularly and either ofloxacin 200 mg orally twice daily for 10–14 days or levofloxacin 500 mg orally once 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.

As a sexually transmitted pathogen is suspected, he should be given advice on abstinence until cured and education given on safe sex following successful treatment.

Proposed date for review: 2029.

Composition of editorial board

Please refer to document at http://www.iusti.org/regions/Europe/pdf/2014/Editorial_Board2014.pdf.

List of contributing organizations

Please refer to text at https://iusti.org/treatment-guidelines/.

For author contributions please see Appendix S1.

AUTHOR CONTRIBUTIONS

Conceptualization: E.J, J.F, R.P; Methodology: E.J, J.F, R.P.; Formal analysis: E.J, J.F, J.D.C.R, Z.K, M.S., R.P; Resources: Writing (original draft): E.J, J.F; Writing (review and editing): J.D.C.R, Z.K, M.S., R.P; Visualization: J.F; Supervision: R.P; Project administration: J.F, R.P.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

No ethical approval was required for this study.

ETHICS STATEMENT

All patient data used have been fully anonymized.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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