EAU Guidelines on

Urological Infections

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European Association of Urology

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Urological Infections Guidelines Panel has compiled these clinical guidelines to provide medical professionals with evidence-based information and recommendations for the prevention and treatment of urological infections. These guidelines also aim to address the important public health aspects of infection control and antibiotic stewardship. Separate EAU guidelines documents are available addressing paediatric urological infections [1] and infections in patients with neurological urinary tract dysfunction [2].

It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

1.2 Panel composition

The EAU Urological Infections Guidelines Panel consists of an international group of urologists with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/urological-infections/

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions, which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/urological-infections/

1.4 Publication history

The Urological Infections Guidelines were first published in 2001. *This 2016 document consists of the first completed sections of an entirely new Urological Infections Guideline formulated following new EAU guideline production methodology. Subsequent sections will be added over the next three years to cover the key clinical questions*. In the interim, the previous 2015 guidelines will be available through the EAU website Uroweb for sections not yet contained in the new guideline, http://uroweb.org/guideline/urological-infections/.

2. METHODS

2.1 Introduction

For the 2016 Urological Infections Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. All chapters were written based on systematic reviews of topics or questions prioritised by the Guideline Panel. These reviews were performed using standard Cochrane systematic review methodology, http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

Systematic review results for the following evidence questions are included in the 2016 Urological Infections Guidelines:

1. What is the diagnostic accuracy of alternative urinary investigations compared with urine culture for the diagnosis of bacteriuria in adult patients prior to urological interventions [3]?
2. In men with acute epididymitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?
3. Which technical or procedural strategies are effective for reducing infectious complications of prostate biopsy [4]?

References used in this text are graded according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

This document was subject to independent peer review prior to publication.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2017 update of the Urological Infections Guidelines.

Topics are:

1. What is the most effective management for people with asymptomatic bacteriuria?
2. In women with recurrent symptomatic lower urinary tract infection what interventions reduce the rate of recurrence?
3. What interventions reduce the rates of symptomatic urinary tract infection, bacteriuria and bacteremia in patients with urinary catheters?
4. What is the best antimicrobial prophylaxis strategy to reduce risk of infectious complication of prostate biopsy?
5. In men with symptoms of urethritis or men being screened for sexually transmitted infection what is the best method of detecting the causative pathogen?
6. In men with symptoms of urethritis what are the best treatment strategies for clinical or microbiological cure?
7. In urological patients with urosepsis what interventions improve outcomes?

3. ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship programmes aim to optimise the outcome of prevention and treatment of infection whilst curbing overuse and misuse of antimicrobial agents [6-10]. Measures of success include regulating antibiotic prescribing, and reduction in both the rate of healthcare associated infections such as *Clostridium difficile* and the emergence of resistant organisms [10]. In urology, antimicrobial stewardship programmes should include a series of measures to ensure rational, evidence based use of antibiotics in the prevention and treatment of infections of the urinary tract and male accessory glands, as well as non-antibiotic strategies. Programmes require a stewardship team approach comprising urologists, infectious diseases physicians, microbiologists and clinical pharmacologists or pharmacists [7-10].

The most important components of antimicrobial stewardship programmes are [8]:

- Regular training of staff in best use of antimicrobial agents.
- Adherence to local, national or international guidelines.
- Regular ward visits and consultation with infectious diseases physicians, with audit.
- Treatment outcome evaluation.
- Monitoring and regular feedback to prescribers of their antimicrobial prescribing performance and local pathogen resistance profiles.

Several studies in hospital settings have shown that regular ward visits and audit of practice by infectious disease physicians markedly reduce overall use of antimicrobial agents by promoting shorter duration of therapy, earlier step-down to oral medication and avoidance of antibiotic use when patient outcome is unlikely to be compromised [10, 11]. Studies specific to the urology setting are lacking but a case-control study showed reduction in antibiotic usage and bacterial resistance in hospitalised urology patients when EAU Guidelines on peri-operative prophylaxis were adhered to, without change in the rate of infectious complications [12].

4. DETECTION OF BACTERIURIA PRIOR TO UROLOGICAL PROCEDURES

4.1 Evidence question

What is the diagnostic accuracy of alternative urinary investigations compared with urine culture for the diagnosis of bacteriuria in adult patients prior to urological interventions?

4.2 Background

Identifying bacteriuria prior to diagnostic and therapeutic procedures aims to reduce the risk of infectious complications by controlling any pre-operative detected bacteriuria and to optimize antimicrobial coverage in conjunction with the procedure. However, the absence of bacteriuria by itself is not an assurance against infectious complications and antimicrobial prophylaxis according to the Urological Infections Guidelines 2015 is recommended [13].

The standard method, laboratory culture of an appropriate urine sample, is time consuming and logistically difficult. Alternative rapid near-patient methods such as reagent strip (dipstick) urinalysis, automated microscopy, flow cytometry, and dipslide culture have been developed but their diagnostic accuracy is uncertain.

4.3 Evidence summary

A systematic search of the literature to February 2015 identified 3,033 titles of which 210 were selected for full text review and 18 studies investigating diagnostic accuracy of different index tests with urine culture as the reference standard were included [14-31]. None of the studies focused on a urology patient population.

*4.3.1 **Reagents strip (dipstick) urinalysis***

Sixteen studies assessed dipstick urine analysis using a variety of criteria for a positive test [14-22, 25-27]. The criterion that resulted in the best overall diagnostic accuracy was when a positive test was defined as at least one of nitrite and leucocyte esterase being detected however, low sensitivity (0.8) limits clinical usefulness, in the setting of assessment of bacteriuria, prior to urological surgery [LE 2].

*4.3.2 **Automated microscopy***

Two studies used automated microscopy of urine sediment following centrifugation [23, 27]. Although sensitivity was high (0.98), specificity was too low for effective use in this setting (0.59) and optimum diagnostic thresholds were not determined [LE 2].

*4.3.3 **Dipslide culture***

We found two studies on dipslide technology using different culture media [24, 31]. In one study diagnostic accuracy was high (0.98) although contaminated samples were excluded [31]. The other study showed lower accuracy below the level required in this setting [24]. Overall, dipslide technology is currently unsuited to routine use in this setting with further studies required to determine the best combination of culture media [LE 2].

*4.3.4 **Flow cytometry***

We found no studies on this technology that met our inclusion criteria. The poor quality of available studies was confirmed in a recent meta-analysis [32].

In summary, laboratory urine culture remains the standard investigation to detect both the presence and absence of clinically relevant concentrations of bacteria in urine [LE 3].

4.4 Recommendation for the detection of bacteriuria prior to urological procedures

Recommendation	LE	GR
Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients prior to undergoing urological interventions.	3	B

5. ACUTE INFECTIVE EPIDIDYMITIS

5.1 Evidence question

In men with acute epididymitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?

5.2 Epidemiology, Aetiology and Pathophysiology

Epididymitis is a common condition with incidence ranging from 25 to 65 cases per 10,000 adult males per year and can be acute, chronic or recurrent [33]. Acute epididymitis is clinically characterised by pain, swelling and increased temperature of the epididymis, which may involve the testis and scrotal skin. It is generally caused by migration of pathogens from the urethra or bladder. Torsion of the spermatic cord (testicular torsion) is the most important differential diagnosis in boys and young men.

The predominant pathogens isolated are *Chlamydia trachomatis*, Enterobacteriaceae (typically *Escherichia coli*) and *Neisseria gonorrhoeae* [34]. Men who have anal intercourse and those with abnormalities of the urinary tract resulting in bacteriuria are at higher risk of epididymitis caused by Enterobacteriaceae. The mumps virus should be considered if there are viral prodromal symptoms and salivary gland enlargement. Tuberculous epididymitis may occur in high risk groups such as men with immunodeficiency and those from high prevalence countries, it frequently results in a discharging scrotal sinus. *Brucella* or *Candida* species are rare possible pathogens.

5.3 Diagnostic Evaluation

Culture of mid-stream specimen of urine should be performed and any previous urine culture results should be checked. Sexually transmitted infection (STI) with *Chlamydia trachomatis* or *Neisseria gonorrhoeae* should be detected by nucleic acid amplification test (NAAT) on first voided urine. A urethral swab or smear should be performed for Gram staining and culture if *Neisseria gonorrhoeae* is likely. Detection of these pathogens should be reported according to local arrangements. All patients with probable STI should be advised to attend an appropriate clinic to be screened for other sexually transmitted infections. Men with Enterobacteriaceae may require investigation for lower urinary tract abnormalities. If tuberculous epididymitis is suspected, three sequential early morning urine samples should be cultured for acid-fast bacilli (AFB) and sent for screening by NAAT for *Mycobactrium tuberculosis* DNA [35]. Prostate secretion, ejaculate, discharge from a draining scrotal fistula, as well as fine needle aspiration and biopsy specimens should be investigated using microscopy, AFB culture and NAAT, respectively.

5.4 Disease Management

Men with suspected STI should be informed of the risks to others and advised not to have sex until free of infection. Empirical antimicrobial therapy has to be chosen by consideration of the most probable pathogen and degree of penetration into the inflamed epididymis and may need to be varied according to local pathogen sensitivities and guidance. Generally, both *Chlamydia trachomatis* and Enterobacteriaceae should be covered initially and the regimen modified according to pathogen identification. Doxycycline and some specific fluoroquinolones have good clinical and microbiological cure rates in patients with suspected *Chlamydia trachomatis* and both achieve adequate levels in inflamed male genital tissues with oral dosing. Macrolide antibiotics such as azithromycin are effective against *Chlamydia trachomatis* but not tested in epididymitis. Fluoroquinolones remain effective for oral treatment of Enterobacteriaceae although resistance is increasing and local advice should be sought. Fluoroquinolones should not be considered for gonorrhoea. Single high parenteral dose of a third generation cephalosporin is effective against *Neisseria gonorrhoeae*; current resistance patterns and local public health recommendations should guide choice of agent.

Clinical response to antibiotics in men with severe epididymitis should be assessed after about 3 days and men with likely or proven STI should be assessed at 14 days to check cure and ensure tracing and treatment of contacts according to local public health recommendations.

5.5 Evidence Summary

We found three guidelines based on systematic reviews [36-38] with search dates of December 2009, March 2012 and April 2013 respectively. Our structured search of the literature from January 2010 to March 2015 identified 553 titles of which 45 were selected for full text review and five were included [39-43].
Data from a large comparative case series [LE 3] suggested that young age and history of sexual activity are not sufficiently predictive of a sexually transmitted pathogen to guide antibiotic treatment in acute epididymitis [43].

Empiric antibiotic regimens [LE 3] from existing guidelines [36-38] and panel consensus:

1. For men with acute epididymitis at low risk of gonorrhoea (e.g. no discharge) a single agent or combination of two agents of sufficient dose and duration to eradicate *Chlamydia trachomatis* and Enterobacteriaceae should be used. Appropriate options are:
   A. A fluoroquinolone active against *Chlamydia trachomatis* by mouth once daily for 10 to 14 days*

   OR

   B. Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for 10 to 14 days* ***plus*** an antibiotic active against Enterobacteriaceae** for 10 to 14 days*

2. For men with likely gonorrhoeal acute epididymitis a combination regimen active against Gonococcus and *Chlamydia trachomatis* must be used such as:
   A. Ceftriaxone 500 mg intramuscularly single dose ***plus***
   Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for 10 -14 days*

3. For non-sexually active men with acute epididymitis a single agent of sufficient dose and duration to eradicate Enterobacteriaceae should be used. Appropriate option is a fluoroquinolone by mouth once daily for 10 to 14 days*

**Depending upon pathogen identification and clinical response*
*** A parenteral option will be required for men with severe infection requiring hospitalisation*

Surgical exploration may be required to drain abscesses or debride tissue. A comparative cohort study [LE 3] found that lack of separation of epididymis and testis on palpation and the presence of abscess on ultrasound (US) may predict requirement for surgery following initial antibiotic treatment [39].

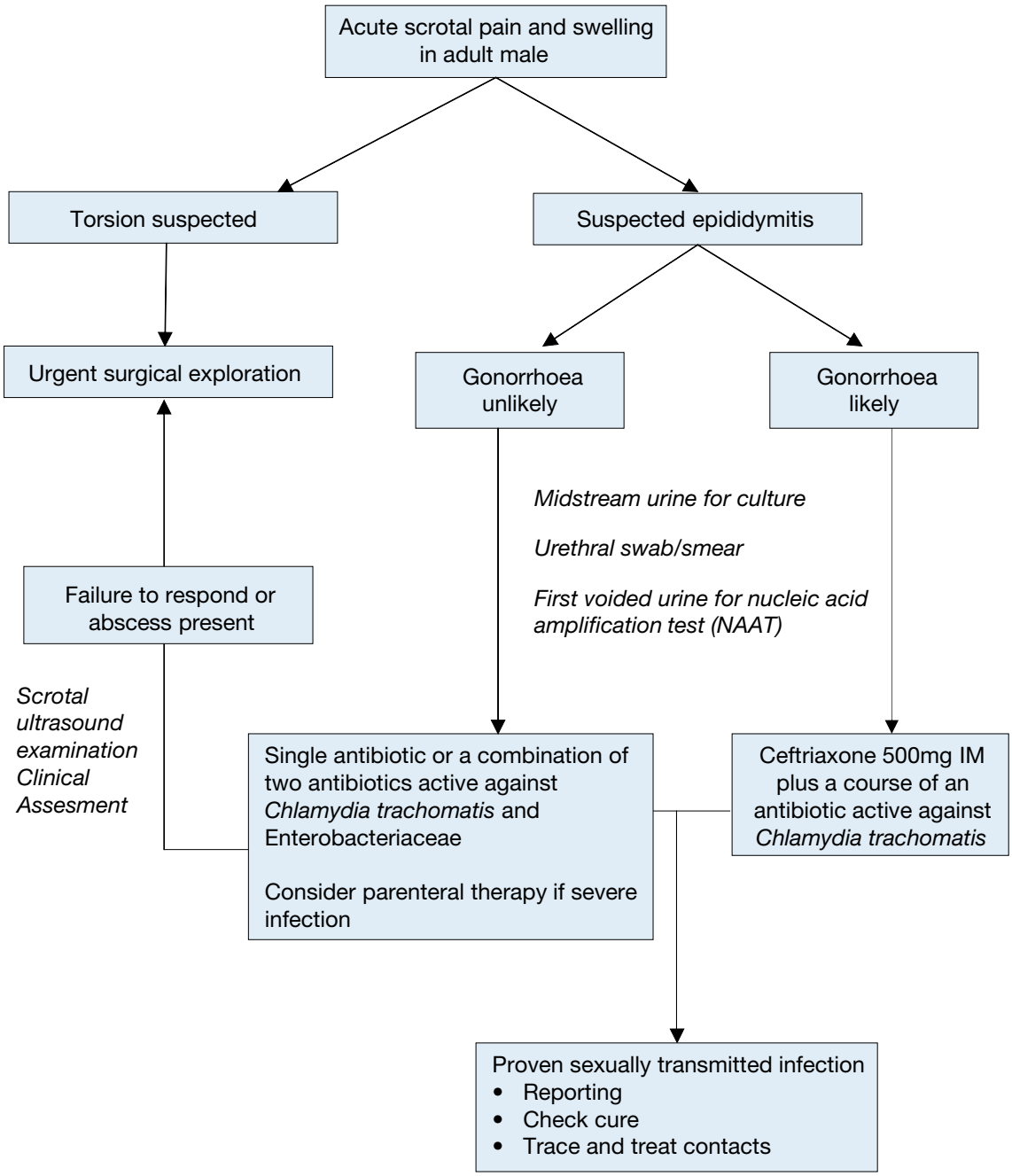
A cohort study [LE 4] found semen parameters may be impaired during epididymitis but recovered following successful treatment [42]. Comparative clinician cohort studies suggest adherence to guidelines for assessment and treatment of epididymitis is low, particularly by urologists compared to sexual health specialists [40] and by primary care physicians [41].

5.6 Recommendations for the treatment of acute infective epididymitis

Recommendations	LE	GR
Obtain a mid-stream urine and a first voided urine for pathogen identification.	3	A*
Initially prescribe a single antibiotic or a combination of two antibiotics active against *Chlamydia trachomatis* and Enterobacteriaceae in young sexually active men; in older men without sexual risk factors only Enterobacteriaceae have to be considered.	3	A*
If Gonorrhoeal infection is likely give single dose ceftriaxone 500 mg intramuscularly in addition to a course of an antibiotic active against *Chlamydia trachomatis*.	3	A*
Adjust antibiotic agent when pathogen has been identified and adjust duration according to clinical response.	3	A*
Follow national policies on reporting and tracing/treatment of contacts for STI.	3	A*

** Upgraded based on Panel consensus*

Figure 1: Diagnostic and treatment algorithm for adult men with acute epididymitis.



IM = Intramuscularly

6. PROSTATE BIOPSY INFECTION: NON-ANTIBIOTIC PREVENTION

6.1 Evidence question

Which non-antibiotic strategies are effective for reducing the risk of infective complications in men undergoing prostate biopsy?

6.2 Epidemiology, Aetiology and Pathophysiology

Histological examination of needle biopsies of the prostate is the principle method for prostate cancer diagnosis. Prostate biopsy is a common procedure in high-resource countries with, for example, about 32,000

procedures performed in England during 2013 [44] giving a rate of 2.6/1,000 men at risk per year. Transrectal ultrasound-guided biopsy (TRUS) is the current standard technique although the transperineal route is also used [45]. Infection is the most clinically significant harm experienced by men following prostate biopsy and includes urinary tract infection, prostatitis, and urosepsis. There is some evidence that the risk is increasing [46]. Infection generally occurs by implantation of rectal commensal organisms into the prostate, urethra or bloodstream during needle insertion. Severity of infection will depend on bacterial inoculum, virulence and status of host defence.

6.3 Diagnostic Evaluation

Urine culture prior to prostate biopsy has an uncertain predictive value [47].

6.4 Disease Management

The focus is on prevention of infectious complications. Possible strategies include antibiotic prophylaxis [48] for which the 2015 guideline should be consulted [13] and non-antibiotic strategies the effectiveness of which will be described in this section. Established infection is treated according to standard pathways [44].

6.5 Evidence summary

A systematic search of the literature to March 2015 identified 1,550 titles of which 133 were selected for full text review and 50 randomised-controlled trials (RCT) were included [49-99]. Infectious complications were generally measured as a secondary outcome.

*6.5.1 **Number of biopsy cores***

Meta-analysis of seven trials involving 1,162 men found no evidence that extended biopsy (> 6-24 cores) templates resulted in more infectious complications than standard templates (6-12 cores) (LE 1a) [49-55].

*6.5.2 **Periprostatic injection of local anaesthetic***

Meta-analysis of 23 RCTs with 3,397 participants found no evidence that use of peri-prostatic injection of local anaesthesia resulted in a higher rate of infectious complications compared to no injection [LE 1a] [56-78]. Five other RCTs investigated differing injection techniques with no difference found in infective complications [95-97, 99-100]. A pooled analysis could not be performed because of heterogeneous study designs.

*6.5.3 **Route of biopsy***

Three RCTs involving 446 men compared transrectal and transperineal routes of biopsy [79-81]. Overall two men (0.4%) suffered infectious complications after transperineal biopsy, compared to five (1.1%) after transrectal biopsy [RR (95% CIs) = 0.45 (0.10 – 1.97)]. The studies were heterogeneous in design, did not state how infectious outcomes were assessed and used differing antimicrobial prophylaxis between arms [LE 1b].

*6.5.4 **Rectal preparation***

Meta-analysis of six trials including 1,446 men showed that use of a rectal povidone-iodine preparation before biopsy in addition to antibiotic prophylaxis resulted in a lower rate of infectious complications [RR (95% CIs) =0.53 (0.41 to 0.70)] [LE 1a] [82-87]. This was in agreement with a previous meta-analysis which included four of these trials [101]. Single RCTs showed no evidence of benefit for perineal skin disinfection [88] or use of phosphate or glycine rectal enema [89, 90].

*6.5.5 **Other interventions***

Combining data from two RCTs with 253 participants showed that single biopsy use of biopsy needles resulted in nine infectious complications compared to 22 with single patient use of the biopsy needle. The difference was not significant [RR (95% CIs) = 0.51 (0.24 to 1.08)] [92, 93]. A single RCT found no evidence that disinfection of a single patient use needle between cores resulted in fewer infectious complications [94].

6.6 Recommendation on non-antibiotic strategies for reducing the risk of infective complications in men undergoing prostate biopsy

Recommendation	LE	GR
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy in addition to antibiotic prophylaxis if local risk of infectious complication is high.	1a	B*

**Downgraded as highest quality trial in meta-analysis showed no difference [81]*

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8. CONFLICT OF INTEREST

All members of the EAU Urological Infections Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: http://www.uroweb.org/guidelines/. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.