

2009 European (IUSTI/WHO) Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults

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AETIOLOGY AND TRANSMISSION

- Gonorrhoea (meaning 'flow of seed') and its related clinical manifestations are caused by infection with the bacterium *Neisseria gonorrhoeae*;
- Infection predominantly involves the columnar epithelium of the urethra, endocervix, rectum, pharynx and conjunctivae. Although it usually remains localized to the initial sites of infection, it can ascend the genital tract to cause pelvic inflammatory disease (PID) and epididymo-orchitis or disseminate as bacteraemia;
- Transmission is by genital-genital, genital-anorectal, oro-genital or oro-anal contact or by mother-to-child transmission at birth;
- The highest incidence of gonorrhoea is in young adults (15–29 years) and there is a disproportionate burden of disease in ethnic minority groups and men who have sex with men (MSM).^{1,2}

CLINICAL FEATURES

Symptoms and signs of gonorrhoea commonly reflect localized inflammation of infected mucosal surfaces in the genital tract.^{3–6}

Symptoms

- In men, the predominant presentation is of acute urethritis with symptoms of urethral discharge and dysuria;
- In women, symptoms relate to endocervical and urethral infection and include increased or altered vaginal discharge, intermenstrual bleeding, dysuria and menorrhagia;
- Asymptomatic genital tract infection occurs in women (up to 50%) and men (up to 10%). Rectal and pharyngeal infections are usually asymptomatic.⁷

Physical signs

- In men, the most common finding on examination is a mucopurulent urethral discharge, which may be accompanied by erythema of the urethral meatus;
- In women examination may be normal or a mucopurulent discharge may be evident from the cervix, sometimes accompanied with hyperaemia and contact bleeding of the endocervix.

Complications

PID in women and epididymo-orchitis in men are the most notable complications from local spread of gonococcal infection.

Gonococcal bacteraemia is uncommon (less than 1% of infections) and is usually manifest by skin lesions, fever, arthralgia, acute arthritis and tenosynovitis.

DIAGNOSIS

- The diagnosis of gonorrhoea is established by identification of *N. gonorrhoeae* in genital, rectal, pharyngeal or ocular secretions;
- Microscopy using Gram or methylene blue staining offers good sensitivity ($\geq 95\%$) and specificity as a rapid diagnostic test in symptomatic men with urethral discharge.⁴ Microscopy has poor sensitivity ($\leq 55\%$) in asymptomatic men and in identifying endocervical ($\leq 55\%$) or rectal infection ($\leq 40\%$) and cannot be recommended as a test of exclusion in these situations.^{4,6}
- Culture offers a specific and cheap diagnostic test that readily allows confirmatory identification and antimicrobial susceptibility testing. Selective culture media containing antimicrobials are recommended⁸ (level of evidence III; grade B recommendation). Culture is appropriate for endocervical, urethral, rectal and pharyngeal specimens. The sensitivity of culture is high for genital samples providing that specimen collection, transport and isolation procedures are good. An appropriate quality control is needed for the gonorrhoea culture system since commercial media vary in their selectivity and sensitivity. Culture should be performed if symptoms persist following treatment;

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- Nucleic acid amplification tests (NAATs) are generally more sensitive ($\geq 90\%$) than culture.^{9,10} They can be used on urine samples, self-taken vaginal swabs and swabs from the endocervix and urethra. Female urine samples offer a lower sensitivity than swabs from the genital tract and are not recommended. Samples giving a positive NAAT result should be subjected to confirmatory testing,^{11–13} i.e. repeated with a NAAT targeting another sequence (level of evidence III; recommendation level B). The positive predictive value of unconfirmed positive NAAT results in low prevalence populations is suboptimal;
- NAATs are significantly more sensitive than culture from pharyngeal and rectal swabs.¹⁴ Commercially available NAATs are not licensed for use on specimens from these sites. If they are used after laboratory evaluation, confirmatory testing is mandatory^{14b} (level of evidence IIb; grade B recommendation);
- Women may have genital tract infection localized to the endocervix or urethra. A single endocervical or vaginal sample tested by a NAAT offers sufficient sensitivity (90%) for screening purposes;^{15,16}
- A minority of MSM with gonorrhoea (20–30%) have infection at multiple sites.⁷ Tests should be taken from the urethra/urine, rectum and pharynx as directed by sexual practices.

Indications for testing (level of evidence IV; grade C recommendation)

- Symptoms or signs of urethral discharge in men;
- Vaginal discharge with risk factor for STI (age <30 years, new sexual partner);
- Mucopurulent cervicitis;
- Sexually partner of a person with sexually transmitted infection (STI) or PID;
- Acute epididymo-orchitis in male aged <40 years;
- Acute PID;
- Screening of young adults for STI;
- Screening individuals with new or multiple recent sexual partners;
- Purulent conjunctivitis in a neonate.

MANAGEMENT

Information, explanation and advice for the patient

- Patients should be advised to avoid sexual intercourse until they and their partners have completed treatment and they are asymptomatic (level of evidence IV; grade C recommendation);
- Patients should be given a detailed explanation of their infection together with clear written information (level of evidence IV; grade C recommendation).

Therapy

- Antimicrobial resistance is a major determinant of treatment efficacy and has severely limited treatment options.^{17–20} Therapy recommended in this guideline adheres to the standard of $\geq 95\%$ microbiological cure rate at genital sites in summed clinical trials;^{20,21}
- Resistance of *N. gonorrhoeae* to antimicrobials continues to evolve across Europe and *in vitro* resistance to penicillin,

tetracyclines and quinolones exceeds 10% of isolates tested in many countries.^{1,17} Resistance to azithromycin is increasing with high-level resistance recently reported in the UK.^{22–24} There remains significant geographical variation in resistance and local alternative treatments based on local surveillance data of resistance may be reasonable.

Indications for therapy (level of evidence IV; grade C recommendation)

- Identification of intracellular Gram-negative diplococci at a genital site by microscopy;
- Positive culture or confirmed NAAT from any site for *N. gonorrhoeae* (unconfirmed NAAT from urogenital specimens from high-risk patients);
- On epidemiological grounds, if a recent partner has confirmed gonococcal infection;
- On demonstration of a purulent urethral discharge in men or mucopurulent cervicitis in women when rapid diagnostic tests are not available and after specimen collection for laboratory testing. In this circumstance, combined treatment for gonococcal and chlamydial infection should be given.

Recommended regimens

For infections of the urethra, cervix and rectum in adults and adolescents:^{20,25–27}

- Ceftriaxone 250 mg intramuscular (IM) as a single dose (level of evidence Ib; grade A recommendation). If ceftriaxone 250 mg for IM injection is not available, the IM suspension can be mixed as follows: 3.5 mL of 10 mg/mL lidocaine without adrenalin is suspended into a 1 g vial of ceftriaxone and mixed. One millilitre of the mixture is drawn and injected IM;

or

- Cefixime 400 mg oral as a single dose (level of evidence Ib; grade A recommendation);

or

- Spectinomycin 2 g IM as a single dose (level of evidence Ib; grade A recommendation).

Co-infection with *Chlamydia trachomatis* is common in young (<30 years) heterosexual patients with gonorrhoea.¹ Treatment for gonorrhoea should routinely be followed with effective treatment for chlamydial infection unless a sensitive test has excluded co-infection^{26,27} (level of evidence IV; grade C recommendation).

Alternative regimens

- Other single-dose cephalosporin regimens.

Alternative injectable or oral cephalosporins offer no advantage in terms of efficacy and pharmacokinetics over ceftriaxone or cefixime. Where these specific antimicrobials are not available, a variety of other cephalosporins have proven efficacy in the treatment of urogenital and anorectal gonorrhoea. Possible alternatives include cefotaxime (500 mg or 1 g IM) and cefodizime (500 mg IM).²⁵

Oral alternatives to cefixime cannot yet be recommended. Clinical trial data on cefpodoxime (400 mg oral) are very

limited²⁸ and the pharmacokinetics of cefuroxime axetil (1 g oral) are suboptimal as a single-dose treatment.²⁹

- Single-dose quinolone regimens.

Quinolones cannot generally be recommended for the treatment of gonorrhoea because of the widespread and rising prevalence of quinolone resistance.^{1,19,20} When an infection is known before treatment to be quinolone sensitive, ciprofloxacin 500 mg oral as a single dose or ofloxacin 400 mg oral as a single dose has proven efficacy (level of evidence Ib; grade A recommendation).^{25,30}

- Azithromycin.

Clinical trials have demonstrated that azithromycin has high efficacy (>98%) as a single oral 2 g dose.³¹ It is not recommended as treatment for gonorrhoea because of the increasing prevalence of resistance in Europe^{1,17,22–24} and gastro-intestinal intolerance.

Therapy for gonococcal infection of the pharynx

Many antimicrobials have demonstrated lower efficacy ($\leq 90\%$) in eradicating *N. gonorrhoeae* from the pharynx than in eradicating genital infection.^{25,32} This correlates with the pharmacokinetic properties of the individual antimicrobials. Single-dose treatments with penicillin or spectinomycin have poor efficacy at eradicating pharyngeal gonorrhoea.

- Recommended treatments for pharyngeal infection: Ceftriaxone 250 mg IM as a single dose (level of evidence Ib; grade A recommendation);²⁰
- Alternative treatments for pharyngeal infection when quinolone or azithromycin resistance excluded or highly unlikely: ciprofloxacin 500 mg as a single oral dose or azithromycin 2 g as a single oral dose.

Therapy in pregnancy or when breast-feeding

- Recommended treatments (level of evidence Ib; grade A recommendation):³³

Ceftriaxone 250 mg IM as a single dose;

Or

Cefixime 400 mg as a single oral dose;

Or

Spectinomycin 2 g IM as a single dose;

Pregnant and breast-feeding women should not be treated with quinolone or tetracycline antimicrobials.

Therapy in patients with β -lactam allergy

- Recommended treatment: Spectinomycin 2 g IM as a single dose;
- Alternative treatments in patients with known β -lactam allergy when quinolone or azithromycin resistance excluded or highly unlikely: ciprofloxacin 500 mg as a single oral dose or azithromycin 2 g as a single oral dose.

Therapy for gonococcal epididymo-orchitis

- According to the European Guideline on epididymo-orchitis recommended treatment:

Doxycycline 100 mg twice daily for 14 days;

+

Either ceftriaxone 250 mg IM or ciprofloxacin 500 mg stat according to local knowledge of antibiotic sensitivities.

Therapy for disseminated gonococcal infection

- Recommended treatment (level of evidence IV; grade C recommendation):³⁴

Initial therapy:

Ceftriaxone 1 g IM or IV every 24 hours; or

Cefotaxime 1 g IV every 8 hours; or

Spectinomycin 2 g IM every 12 hours.

Therapy should continue for seven days, but may be switched 24–48 hours after symptoms improve to one of the following oral regimens:

Cefixime 400 mg twice daily

or if quinolone resistance is excluded:

Ciprofloxacin 500 mg twice daily.

Therapy for ophthalmia neonatorum

- Recommended treatments:²⁷

Ceftriaxone 25–50 mg/kg IV or IM as a single dose not to exceed 125 mg; or

Cefotaxime 100 mg/kg IM as a single dose;

Frequent conjunctival irrigation with saline.

PARTNER NOTIFICATION

- Sex partners should be contacted and offered testing and treatment for gonorrhoea and chlamydial infection (level of evidence IV; grade C recommendation);
- For cases of gonorrhoea, all sex partners within the preceding 60 days of diagnosis should be evaluated and treated²⁰ (level of evidence IV; grade C recommendation). If a patient's last intercourse was more than 60 days prior to their diagnosis, their last sexual partner should be evaluated.

FOLLOW-UP AND TEST OF CURE

- Assessment after treatment is recommended to confirm compliance with therapy, resolution of symptoms and signs, and partner notification (level of evidence IV; grade C recommendation);
- A test of cure is not routinely necessary for anogenital infection if a recommended treatment has been given. Indications for test of cure include (level of evidence IV; grade C recommendation):

○ Persistence of symptoms;

○ Re-exposure to infection;

○ When there is possible antimicrobial resistance to the therapy given;

○ When stipulated by national or local practice;

○ Pharyngeal infection.

NOTIFICATION

Infections with *N. gonorrhoeae* should be notified to local, regional and national authorities as required by statute.

QUALIFYING STATEMENT

Decisions to follow these recommendations must be based on professional clinical judgement, consideration of individual patient circumstances and available resources. All possible care has been undertaken to ensure publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing clinician to ensure the accuracy and appropriateness of the medication they prescribe.

SEARCH STRATEGY

A Medline search was conducted in January 2008 using PubMed for articles published since the development of the first European guideline on the management of gonorrhoea in adults. Search headings were kept broad (gonorrhoea and *N. gonorrhoeae*) to include epidemiology, diagnosis, antimicrobial resistance, drug therapy, clinical trials and prevention and control. Only publications and abstracts in the English language were considered. The Cochrane library was searched for all entries related to gonorrhoea. Sexually transmitted diseases guidelines produced by the US Centers for Disease Control (www.cdc.gov/std/) and the British Association for Sexual Health and HIV (www.bashh.org) were also reviewed.

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APPENDIX 1

LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS

Levels of Evidence

- Ia Evidence obtained from meta-analysis of randomized controlled trials.
- Ib Evidence obtained from at least one randomized controlled trial.
- IIa Evidence obtained from at least one well-designed study without randomization.
- IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.
- III Evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies and case-control studies.

- IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of Recommendations

A (Evidence levels Ia, Ib)

Requires at least one randomized control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence levels IIa, IIb, III)

Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation.

C (Evidence IV)

Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates the absence of directly applicable studies of good quality.