UK national guideline for the management of gonorrhoea in adults, 2011

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Summary: The British Association for Sexual Health and HIV (BASHH) UK gonorrhoea guideline has been updated in 2011. It offers advice on diagnosis, treatment and health promotion for anogenital and pharyngeal gonorrhoea. Nucleic acid amplification tests (NAATs) are now being used more for diagnosis and are increasing detection rates in the pharynx and rectum. First line treatment using ceftriaxone with azithromycin is now advised, along with routine test of cure (TOC). The aim is to slow the spread of resistant gonorrhoea now that fewer antibiotics remain effective. A patient information leaflet has been developed.

Keywords: guideline, gonorrhoea, disease management, treatment, anti-bacterial agents, antibiotics, UK

CHANGES SINCE 2005 GUIDELINE

- Nucleic acid amplification tests (NAATs) can be used for both anogenital and pharyngeal specimens. Supplementary testing is required for reactive tests from low prevalence populations and for specimens from the rectum or pharynx;
- First-line treatment is now ceftriaxone 500 mg intramuscularly immediately plus azithromycin 1 g orally immediately;
- Test of cure is recommended for all cases;
- A patient information leaflet is available (see website);
- There is a link for reporting cephalosporin treatment failures to the HPA.

INTRODUCTION

The main purpose of this guideline is to offer recommendations on the diagnosis, treatment and health promotion principles for the effective management of anogenital and pharyngeal gonorrhoea. It is aimed primarily at people aged 16 years and older presenting to services offering level 3 care in sexually transmitted infection (STI) management within the UK. However, the principles of the recommendations could be adopted at all levels.

Editorial independence

This guideline was commissioned and edited by the Clinical Effectiveness Group (CEG) of the British Association for Sexual Health and HIV (BASHH). No external funding was sought or obtained.

Rigour of development

This guideline was produced according to specifications set out in the CEG's 2010 document 'Framework for guideline development and assessment'[1] outlined at http://bashh.org/guidelines. This guideline has been updated by reviewing the previous gonorrhoea guideline (2005) and medical literature since its publication. A MEDLINE search of published articles in any language for the years 2005–09 was done using the subject headings 'gonorrhoea' and *'Neisseria gonorrhoeae'*. All entries in the English language or with abstracts in English were viewed because of the paucity of 'clinical trials' or 'reviews'. The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness and Cochrane Controlled Trials Register were reviewed using the textword 'gonorrhoea' and all entries were considered. Abstracts from meetings in the relevant period were hand-searched and considered. The draft guideline was appraised with the AGREE instrument, posted on the BASHH website for a consultation period of three months and piloted in a sample of clinics. In response to the consultation a number of changes were made, which are supported by more recent references.

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AETIOLOGY

Gonorrhoea is the condition of being infected with the Gram-negative diplococcus *Neisseria gonorrhoeae.* The primary sites of infection are the mucous membranes of the urethra, endocervix, rectum, pharynx and conjunctiva. Transmission is by direct inoculation of infected secretions from one mucous membrane to another.

Clinical features

Symptoms[2–4]

Men:

- Urethral infection commonly causes urethral discharge (>80%) and/or dysuria (>50%), starting within 2–5 days of exposure;

- Urethral infection can be asymptomatic (<10%);
- Rectal infection is usually asymptomatic but may cause anal discharge (12%) or perianal/anal pain or discomfort (7%);
- Pharyngeal infection is usually asymptomatic (>90%).

Women:

- Infection at the endocervix is frequently asymptomatic (up to 50%);
- Increased or altered vaginal discharge is the most common symptom (up to 50%);
- Lower abdominal pain may be present (up to 25%);
- Urethral infection may cause dysuria (12%) but not frequency;
- Gonorrhoea is a rare cause of intermenstrual bleeding or menorrhagia;
- Rectal infection more frequently develops by transmucosal spread of infected genital secretions than from anal intercourse and is usually asymptomatic;
- Pharyngeal infection is usually asymptomatic (>90%).

N. gonorrhoeae may coexist with other genital mucosal pathogens, notably *Chlamydia trachomatis, Trichomonas vaginalis* and *Candida albicans*. If symptoms are present, they may be attributable to the co-infecting pathogen.

Signs[2,3]

Men:

- A mucopurulent or purulent urethral discharge is commonly evident;
- Rarely, epididymal tenderness/swelling or balanitis may be present.

Women:

- Mucopurulent endocervical discharge and easily induced endocervical bleeding (<50%) (note: mucopurulent endocervical discharge is not a sensitive predictor of cervical infection [<50%]);
- Pelvic/lower abdominal tenderness (<5%);
- Commonly, no abnormal findings are present on examination.

Complications

Transluminal spread of *N. gonorrhoeae* from the urethra or endocervix may occur to cause epididymo-orchitis or prostatitis in men and pelvic inflammatory disease (PID) in women. Haematogenous dissemination may also occur from infected mucous membranes to cause skin lesions, arthralgia, arthritis and tenosynovitis (disseminated gonococcal infection). There are no recent studies quantifying the risks of developing complicated gonococcal infections but reporting from genitourinary (GU) medicine clinics in the UK indicates that these conditions are uncommon.[5]

DIAGNOSIS

- This guideline should be read in conjunction with the Health Protection Agency 'Guidance for gonorrhoea testing in England and Wales' (2010) and BASHH guidelines on testing for STIs/gonorrhoea;[6,7]
- The diagnosis of gonorrhoea is established by the detection of *N. gonorrhoeae* at an infected site;
- The approach and method used to test for gonorrhoea will be influenced by the clinical setting, storage and transport system to the laboratory, local prevalence of infection and the range of tests available in the laboratory;
- No test for gonorrhoea offers 100% sensitivity and specificity;[6,8–10]
- Microscopy (×1000) of Gram-stained genital specimens allows direct visualization of *N. gonorrhoeae* as monomorphic Gram-negative diplococci within polymorphonuclear leukocytes. It offers good sensitivity (90–95%) in men with urethral discharge and is recommended to facilitate immediate diagnosis in symptomatic men (level of evidence III; grade C recommendation). Microscopy of urethral smears in asymptomatic men is less sensitive (50–75%).[2] Microscopy should be done on men with rectal symptoms. In women, microscopy has poor sensitivity for the identification of gonococcal infection: 37–50% for endocervical smears and 20% for urethral smears.[3] Microscopy is not recommended for urethral smears in women or for detecting asymptomatic rectal infection because of low sensitivity (level of evidence III; grade C recommendation). Microscopy is not appropriate for diagnosing gonorrhoea in pharyngeal specimens;
- Detection of *N. gonorrhoeae* can be achieved by NAATs or culture. NAATs are generally more sensitive than culture and offer testing on a wider range of specimen types.[6,9–13] NAATs show high sensitivity (>96%) in both symptomatic and asymptomatic infection.[11,13] They show equivalent sensitivity in urine and urethral swab specimens from men[14] and in vaginal and endocervical swabs from women.[15] The test sensitivity in female urine is significantly lower and urine is not the optimal specimen in women[6,13,16] (level of evidence II; grade B recommendation);
- Persons undergoing testing for genital tract gonorrhoea are usually also tested for infection with *C. trachomatis*. NAATs are the standard test methodology for *C. trachomatis* testing and commercial tests offer dual capability to also test for *N. gonorrhoeae* on the same sample. When testing for genital tract infection, a dual NAAT for both pathogens maximizes sensitivity and operational ease of specimen collection, transport and processing;
- NAATs are significantly more sensitive than culture for detecting *N. gonorrhoeae* in the rectum and pharynx although are not yet licensed for use at these sites.[17–21] Commercially available NAATs differ in their cross-reactivity to commensal *Neisseria* species which may be present at significant levels at these sites, particularly in the pharynx.[22] At present it is recommended that reactive specimens from the rectum and pharynx are confirmed by supplementary testing, i.e. using a different molecular target (level of evidence III; grade C recommendation);[6,8,23]
- Culture continues to offer a specific, sensitive and cheap diagnostic test at genital sites. It allows confirmatory identification and antimicrobial susceptibility testing, which is of increasing importance as antimicrobial resistance to *N. gonorrhoeae* continues to evolve. Selective culture media containing antimicrobials are recommended to reduce contamination[24] (level of evidence II; grade B recommendation);
- Whatever the testing approach adopted, positive test results should give a positive predictive value of >90%. In areas of

low gonorrhoea prevalence the use of NAATs may require supplementary testing to confirm the diagnosis.[6,8,23] Clinicians need to be familiar with the test performance of NAATs and be able to interpret results in their clinical setting.[25,26]

SPECIMEN COLLECTION

Men

A first pass urine is the preferred sample for NAAT testing.[8,11,14,16] Microscopy and culture require a urethral/meatal swab specimen. The collection and testing of rectal and pharyngeal swab specimens should be directed by sexual history, symptoms at these sites and also considered in men who receive oral–anal or digital–anal contact.[27]

Women

Vaginal or endocervical swab specimens are equally sensitive for detecting *N. gonorrhoeae* by NAAT testing.[15] Culture requires an endocervical and urethral swab specimen for maximum sensitivity. Urine is a suboptimal sample for the detection of *N. gonorrhoeae* in women.[6,8,10,13,16] The collection and testing of rectal and pharyngeal swab specimens should be directed by sexual history, symptoms at these sites and also considered in women who are sexual contacts of gonorrhoea.

- For culture, direct plating of genital samples and use of transport media with prompt laboratory plating both give acceptable results[23] (evidence level IV);
- Data are lacking on the sensitivity of a single set of tests to identify infection with *N. gonorrhoeae*. The use of a single endocervical or vulvovaginal NAAT sample will identify 90–95% of women with gonococcal infection.[3,28] Women infected with *N. gonorrhoeae* often have infection at multiple sites.[29] A minority of men who have sex with men with gonorrhoea have infection at multiple sites, thus all exposed sites need sampling;[19]
- To confidently exclude infection in patients who attend within three days of sexual contact, a second set of tests should be considered if epidemiological treatment with effective antimicrobial therapy is not given[30] (evidence level IV, recommendation level C). Conventionally this would be 14 days after contact.

MANAGEMENT

General advice

- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced with clear and accurate written information (level of evidence IV; grade C recommendation);
- Patients should be advised to abstain from sexual intercourse until they and their partner(s) have completed treatment (level of evidence IV; grade C recommendation); if azithromycin is used, this will be 7 days after treatment was given.

Further investigation

- A culture should be taken in all cases of gonorrhoea diagnosed by NAATs prior to antibiotics being given, if possible,[6] so that susceptibility testing can be performed and resistant strains identified;
- Screening for coincident STIs should routinely be performed in patients with or at risk of gonorrhoea (evidence level III, recommendation level C).

TREATMENT

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

- Identification of intracellular Gram-negative diplococci on microscopy of a smear from the genital tract;
- A positive culture for *N. gonorrhoeae* from any site;
- A positive NAAT for *N. gonorrhoeae* from any site. Supplementary testing is recommended if the positive predictive value of the test is $<90\%$;[6,8,22]
- Recent sexual partner(s) of confirmed cases of gonococcal infection;
- Consider offering on epidemiological grounds following sexual assault.

Recommended treatment[31–39]

Uncomplicated anogenital infection in adults:

- Ceftriaxone 500 mg intramuscularly as a single dose with azithromycin 1 g oral as a single dose (level of evidence IV; grade C recommendation) (Box 1);
- *N. gonorrhoeae* has progressively exhibited reduced sensitivity and resistance to many classes of antimicrobials. Published trials of gonorrhoea treatment reflect clinical efficacy in past eras of antimicrobial sensitivity. Surveillance data in England and Wales show significant levels of *N. gonorrhoeae* resistance to penicillin (22% in 2009), tetracyclines (68% in 2009) and ciprofloxacin (35.3% in 2009).[40–42] High-level azithromycin resistance (MIC >256 mg/L) was observed in 2007 in the UK.[43] In 2009, decreased susceptibility to cefixime (MIC $\geq$ 0.25 mg/L) was observed at 1.2% and four isolates (0.3%) with decreased susceptibility to ceftriaxone (MIC $\geq$ 0.125 mg/L) were also identified.[40] Three UK cases of clinical cefixime failure were reported in 2011.[44,45] Most resistant infections are acquired in the UK;

Box 1 Administration of ceftriaxone 500 mg

Ceftriaxone is supplied as a powder which needs to be reconstituted with lidocaine solution. In the UK, it is currently available as vials of 250 mg or 1 g, the 1 g size generally being considerably more economical.

To reconstitute, mix the contents of the 1 g vial with 3.5 mL of 1% lidocaine injection BP: half (2.1 mL) of the resulting solution provides 500 mg ceftriaxone.

It should be given by deep intramuscular injection.

The remaining solution can be used for up to 24 hours later, where permitted by local regulations, if it is kept in the dark at 2–80°C (i.e. in refrigerator).

- The increasing recognition of multidrug resistant *N. gonorrhoeae* has been the driving force for the recommendation of extended spectrum cephalosporins as the preferred treatment of gonorrhoea.[46] Concerns about the upward drift of resistance to cephalosporins[47] justify the increased dose of ceftriaxone now recommended;
- Azithromycin is recommended as co-treatment irrespective of the results of chlamydia testing (level of evidence IV, grade C recommendation), to delay the onset of widespread cephalosporin resistance.[47] There is some *in vitro* evidence of synergy between azithromycin and cephalosporins,[48] and improved eradication of pharyngeal gonorrhoea has been reported when azithromycin was combined with cephalosporin therapy.[49]

ALTERNATIVE REGIMENS

Clinicians using alternative regimens for the treatment of gonorrhoea are recommended to regularly review local and national trends in gonococcal antimicrobial resistance. All the agents below should be accompanied by azithromycin 1 g oral as a single dose.

- Cefixime 400 mg oral as a single dose (level of evidence 1b; grade A recommendation). Only advisable if an intramuscular injection is contraindicated or refused by the patient. Observations in Asia have raised serious concerns over the adequacy of the 400 mg cefixime dose for the treatment of genital tract gonorrhoea. Repeated treatment failures have been reported with cefixime and other oral extended spectrum cephalosporins;[46,50]
- Spectinomycin 2 g intramuscularly as a single dose (level of evidence 1b; grade A recommendation). Spectinomycin was not being manufactured in 2010 so may be difficult to obtain. See BASHH website (www.bashh.org.uk) for further details;
- Other single dose cephalosporin regimens, notably cefotaxime 500 mg intramuscularly as a single dose (level of evidence Ib; grade A recommendation) or cefoxitin 2 g intramuscularly as a single dose plus probenecid 1 g oral. Alternative injectable or oral cephalosporins offer no advantage in terms of efficacy and pharmacokinetics over ceftriaxone or cefixime;[34]
- Cefpodoxime is an alternative oral third generation cephalosporin that as a single dose of 200 mg orally is licensed for the treatment of uncomplicated gonorrhoea.[51] Published trial data are limited, but in view of its less favourable pharmacokinetics than cefixime and suboptimal efficacy against pharyngeal infection, it should be used with caution at a dose of 400 mg (level of evidence II; grade C recommendation);
- Quinolones cannot generally be recommended for the treatment of gonorrhoea because of the high prevalence of quinolone resistance worldwide.[41,42,52] When an infection is known before treatment to be quinolone sensitive, ciprofloxacin 500 mg orally as a single dose or ofloxacin 400 mg orally as a single dose have proven efficacy (level of evidence Ib; grade A recommendation);[38,53]
- High-dose azithromycin (2.0 g as a single dose) has shown acceptable efficacy in clinical trials, but was associated with high gastrointestinal intolerance.[54] The clinical efficacy of azithromycin does not always correlate with *in vitro* sensitivity testing[55,56] and high-level azithromycin resistance has been observed in the UK.[43] A single dose of azithromycin 1.0 g alone is not recommended as treatment for gonorrhoea (level of evidence II; grade C recommendation);
- The alternative treatment regimens listed do not comprise all effective treatment regimens, but reflect clinical practice in the UK.

TREATMENT OF COMPLICATED INFECTIONS

Gonococcal PID

Ceftriaxone 500 mg intramuscularly immediately followed by oral doxycycline 100 mg twice daily plus metronidazole 400 mg twice daily for 14 days (see PID guidelines www.bashh.org.uk)

Gonococcal epididymo-orchitis

Ceftriaxone 500 mg intramuscularly plus doxycycline 100 mg twice daily for 10–14 days (see epididymo-orchitis guideline www.bashh.org.uk)

Gonococcal conjunctivitis

A three-day systemic regimen is recommended as the cornea may be involved and is relatively avascular (level of evidence IV, grade C recommendation). The eye should be irrigated with saline/water:

- Ceftriaxone 500 mg intramuscularly daily for three days;
- For non-anaphylaxis allergy: ceftriaxone as above;
- If history of penicillin anaphylaxis or established cephalosporin allergy: spectinomycin 2 g intramuscularly immediately daily for three days *or* azithromycin 2 g oral immediately plus doxycycline 100 mg twice daily for one week plus ciprofloxacin 250 mg daily for three days (grade C recommendation, level of evidence IV).

Disseminated gonococcal infection (grade C recommendation)

- Ceftriaxone 1 g intramuscularly or intravenous every 24 hours or cefotaxime 1 g intravenous every eight hours or ciprofloxacin 500 mg intravenous every 12 hours (if the infection is known to be sensitive) or spectinomycin 2 g intramuscularly 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, ciprofloxacin 500 mg twice daily or ofloxacin 400 mg twice daily.

ALLERGY

Third-generation cephalosporins such as cefixime and ceftriaxone show negligible cross-allergy with penicillins.[57] Contraindications to the administration of ceftriaxone are hypersensitivity to any cephalosporin or previous immediate and/or severe hypersensitivity reaction to a penicillin or other beta-lactam drug.[58]

Recommended treatments for patients giving a history of such hypersensitivity:

- Spectinomycin 2 g intramuscularly as a single dose (level of evidence Ib; grade A recommendation) with azithromycin 1 g oral as a single dose *or*
- Azithromycin 2.0 g oral as a single dose (level of evidence Ib; grade B recommendation) *or*
- Ciprofloxacin 500 mg orally as a single dose when the infection is known or anticipated to be quinolone sensitive.

PREGNANCY AND BREASTFEEDING

Pregnant and breastfeeding women should not be treated with quinolone or tetracycline antimicrobials. Azithromycin: manufacturer advises use only if adequate alternatives are not available. Pregnancy does not diminish treatment efficacy.

Recommended regimens:[59–61]

- Ceftriaxone 500 mg intramuscularly as a single dose with azithromycin 1 g oral as a single dose (level of evidence IV; grade C recommendation) *or*
- Spectinomycin 2 g intramuscularly as a single dose. (level of evidence Ib; grade A recommendation) with azithromycin 1 g oral as a single dose

PHARYNGEAL INFECTION

Single-dose antimicrobials treatments have in general demonstrated lower efficacy ($\leq$90%) in eradicating *N. gonorrhoeae* from the pharynx than in eradicating genital infection.[32,62] Failure has even been reported with ceftriaxone.[63]

Recommended treatments:[32,62]

- Ceftriaxone 500 mg intramuscularly as a single dose with azithromycin 1 g as a single dose (level of evidence IV; grade C recommendation) *or*
- Ciprofloxacin 500 mg orally as a single dose if *N. gonorrhoeae* known to be quinolone sensitive (level of evidence Ib; grade B recommendation) *or*
- Ofloxacin 400 mg orally as a single dose if *N. gonorrhoeae* known to be quinolone sensitive (level of evidence Ib; grade B recommendation). Single dose treatment with spectinomycin has poor efficacy in eradicating gonococcal infection of the pharynx.[32]

HIV INFECTION

Treatment for gonorrhoea in HIV-infected individuals is the same as in those who are HIV-negative.

CO-INFECTION WITH *C. TRACHOMATIS*

Genital infection with *C. trachomatis* commonly accompanies genital gonococcal infection (35% of heterosexual men and 41% of women with gonorrhoea, GRASP 2008). Testing for *C. trachomatis* should routinely be performed on all adults with gonorrhoea or treatment given to eradicate possible co-infection[30,39] (level of evidence IV; grade C recommendation).

SEXUAL PARTNERS

Partner notification should be pursued in all patients identified with gonococcal infection, preferably by a trained health adviser in GU medicine. Action and outcomes should be documented.[64] Partner notification should follow national recommendations:[65]

- Male patients with symptomatic urethral infection should notify all partners with whom they had sexual contact within the preceding two weeks or their last partner if longer ago;
- Patients with infection at other sites or asymptomatic infection should notify all partners within the preceding three months. Sexual partners should be offered testing and treated epidemiologically for gonorrhoea (level of evidence IV; recommendation level C).

FOLLOW-UP AND TEST OF CURE

Assessment after treatment may be helpful (level of evidence IV; grade C recommendation):

- To confirm compliance with treatment;
- To ensure resolution of symptoms;
- To enquire about adverse reactions;
- To take a sexual history to explore the possibility of reinfection;
- To pursue partner notification and health promotion.

A test of cure (TOC) is now recommended in all cases (evidence level IV, grade C recommendation). This is (a) to identify emerging resistance, which on past experience is likely to occur in due course[47] and (b) because the susceptibility results that indicate potential failure to ceftriaxone and cefixime are not yet defined.

Where resource or practical considerations require TOC to be selective rather than universal, then the following patients should be prioritized:

- Persisting symptoms or signs;
- Pharyngeal infection (all treatments are less effective at eradicating pharyngeal infection[62]);
- Treatment with anything other than the first-line recommendations.

Method and timing of TOC

The current evidence is very scanty and the following is based on expert opinion and pragmatic considerations:

- Persisting symptoms or signs – test with culture, performed at least 72 hours after completion of therapy;[24]
- If asymptomatic – test with NAATs where available, followed by culture if NAAT-positive. Test two weeks after completion of antibiotic therapy.[66]

Note that infection identified after treatment may well be due to reinfection.[4,67]

CEPHALOSPORIN CLINICAL FAILURE FOLLOWING TREATMENT FOR GONORRHOEA

Cases of failure of cephalosporin therapy should be reported to the Health Protection Agency using on-line forms, at the HIV and STI web portal: https://www.hpawebservices.org.uk/HIV_STI_WebPortal/Login.aspx.

Only authorized users are permitted to access this secure website – all GU clinics have been issued with usernames and passwords. Otherwise, they can be obtained from http://www.gumcad@hpa.org.uk.

AUDITABLE OUTCOME MEASURES

- All patients treated for gonorrhoea should be recommended to have a TOC;
- All patients with gonorrhoea should be screened for genital infection with *C. trachomatis* or receive presumptive treatment for this infection;
- All patients identified with gonorrhoea should have partner notification carried out according to the published standards of the BASHH Clinical Standards Unit;[68,69]
- All patients identified with gonorrhoea should be offered written information about STIs and their prevention;
- All patients with gonorrhoea should receive first-line treatment or the reasons for not doing so documented.

ORGANIZATIONAL AND FINANCIAL CONSIDERATIONS

While the treatments recommended differ in price, they are not expensive and the importance of achieving a cure is so great that cost should not be a factor in choosing the most effective agent. Clinics managing gonorrhoea should have staffing and facilities allowing the use of injectable antibiotics. Re-introducing routine TOCs will increase cost but should identify emerging resistant strains, which have the potential to cause much greater health costs.

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 specification 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.

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