# 2012 European Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults

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## AETIOLOGY AND TRANSMISSION

- Gonorrhoea (meaning 'flow of seed' in old greek) and its related clinical manifestations are caused by infection with the Gram-negative bacterium *Neisseria gonorrhoeae*;
- Infection predominantly involves the columnar epithelium of the urethra, endocervix, rectum, pharynx and conjunctivae. Although it usually remains localised to the initial sites of infection, it can ascend to the upper genital tract to cause pelvic inflammatory disease and epididymo-orchitis or disseminate as bacteraemia;
- Transmission is by direct inoculation of infected secretion from one mucosa to another, i.e., genital-genital, genital-anorectal, oro-genital or oro-anal contact or by mother-to-child transmission at birth;
- In 2008, the World Health Organization (WHO) estimated 106 million cases of gonorrhoea among adults globally, a similar global incidence to genital chlamydial infections.[1] In Europe, gonorrhoea is the second most common bacterial sexually transmitted infection (STI), i.e. after chlamydial infections.[2] However, the incidence in several countries is underestimated because of suboptimal diagnostics, case reporting and surveillance. There is considerable geographic variation in the distribution of gonorrhoea and infection is reported three times more frequently in men than women,[2] reflecting the significantly higher proportion of symptoms in men and the burden of infection in men who have sex with men (MSM). The highest incidence of gonorrhoea is in young adults (15 to 29 years) and, in many countries, there is a disproportionate burden of disease in ethnic minority groups and MSM.[1-4]

## CLINICAL FEATURES

Symptoms and physical signs of gonorrhoea commonly reflect localised inflammation of infected mucosal surfaces in the genital tract.[5-8]

### Symptoms

- In men, the predominant presentation is of acute urethritis with symptoms of urethral discharge (>80%) and dysuria (>50%), usually starting within 2-8 days of exposure. Asymptomatic urethral infection is uncommon in men (less than 10% of urethral infections);

- In women, genital tract symptoms relate to endocervical and urethral infection and include increased or altered vaginal discharge (≤50%), lower abdominal pain (≤25%), dysuria (10-15%) and rarely intermenstrual bleeding or menorrhagia. Endocervical infection is commonly asymptomatic (≥50%);
- Rectal and pharyngeal infections are usually asymptomatic.[9,10]

**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**

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

Gonococcal bacteraemia rarely occurs (less than 1% of infections) and is usually manifested by skin lesions, fever, arthralgia, acute arthritis and tenosynovitis (disseminated gonococcal infection (DGI)).[5,11,12]

**DIAGNOSIS**

- The diagnosis of uncomplicated gonorrhoea is established by identification of *N. gonorrhoeae* in genital, rectal, pharyngeal or ocular secretions;
- *N. gonorrhoeae* can be detected by nucleic acid amplification tests (NAATs) or culture. The bacterium can also be visualized on microscopy of stained genital tract smear to facilitate rapid diagnosis in symptomatic patients. No test offers 100% sensitivity and specificity;
- Microscopy (×1000) using Gram or methylene blue staining for identification of diplococci within polymorphonuclear leukocytes offers good sensitivity (≥95%) and specificity as a rapid diagnostic test in symptomatic men with urethral discharge [level of evidence III; grade C recommendation].[5,6,13] Microscopy has poor sensitivity (≤55%) in

asymptomatic men and in identifying endocervical (≤55%) or rectal infection (≤40%) and cannot be recommended as a test of exclusion in these situations [III; C].[6,8] Microscopy is not recommended for identification of pharyngeal infection due to poor specificity as well as low sensitivity;

- Culture offers a specific and cheap diagnostic test that readily allows confirmatory identification. It is the only diagnostic test that enables antimicrobial susceptibility testing and capacity to perform culture remains essential to detect and monitor evolving antimicrobial resistance. Selective culture media containing antimicrobials are recommended [III; B].[14] Non-selective media can beneficially be used in addition to the selective media for urogenital and conjunctival samples if affordable. Culture is appropriate for endocervical, urethral, rectal, pharyngeal and conjunctival specimens but not for urine. The sensitivity of culture is high for genital samples providing that specimen collection, transport, storage and isolation procedures are optimized. An appropriate quality assurance is needed for the gonorrhoea culture system since commercial media and culture procedures vary in their selectivity and sensitivity. Culture (ideally supplemented with a NAAT for optimal diagnostic sensitivity) should be performed for antimicrobial sensitivity testing in patients with persisting infection or symptoms following treatment or if treatment failure is suspected;[15,16]
- NAATs are more sensitive than culture, offer testing on a wider range of specimen types and are less demanding in specimen quality, transportation and storage.[17-25] They show high sensitivity (>96%) in both symptomatic and asymptomatic infection, show equivalent sensitivity in urine and urethral swab specimens from men[23] and equivalent sensitivity in clinician-taken or self-taken vulvo-vaginal and endocervical swabs from women.[24] NAATs significantly outperform transported samples for culture and are the sample of choice for testing individuals who are asymptomatic.[17,18] In women, urine samples offer a lower sensitivity than swabs from the genital tract and are not the optimal sample for testing [II; B].[17,20,21,25] The performance characteristics of different commercially available or in house gonococcal NAATs differ substantially, particularly in regard to specificity;
- When using NAATs to detect *N. gonorrhoeae*, the positive predictive value (PPV) of the testing protocol used should exceed 90%. The principal factors influencing the PPV are

the prevalence of gonorrhoea in the population tested and variation in the specificity of available NAATs, particularly at non-genital sites. If the used diagnostic NAAT does not display a PPV exceeding 90%, positive samples are recommended to be subjected to confirmatory testing, i.e. repeated with a NAAT targeting another sequence [III; B];[26-28]

- NAATs are significantly more sensitive than culture for detecting pharyngeal and rectal infection[29-35] and are the test of choice for screening for rectal and pharyngeal gonococcal infection. However, commercially available NAATs are not licensed for testing specimens from these sites and they differ significantly in their specificity,[36,37] particularly at the pharynx due to the frequent presence of non-gonococcal *Neisseria* species. It is recommended that strict local evaluation is performed before introducing a NAAT to test rectal and pharyngeal samples. When used after evaluation, confirmatory testing is recommended, i.e. repeated with a NAAT targeting another sequence [IIb; B];[18,27,28]
- Women may have genital tract infection localized to the endocervix or urethra. In the current era of NAAT testing, asymptomatic women are commonly offered screening for gonorrhoea and chlamydial infection by a single vulvo-vaginal or endocervical test.[38] This pragmatic approach is endorsed although there remains a lack of evidence to confirm its effectiveness in excluding gonorrhoea [IV, C]. The additional contribution of routinely testing rectal and pharyngeal sites when screening women for gonorrhoea is poorly defined in Europe, although sampling these sites should be considered when there is a history of direct exposure [IV; C].[10] Evidence on the minimum incubation period necessary before testing can be recommended is lacking, although clinical experience suggests that positive NAAT results may be observed within 1-2 days of infection.
- A minority of MSM with gonorrhoea (20-30%) have infection at multiple sites.[9,39] Tests should be taken from the urethra/urine, rectum and pharynx as directed by sexual practices.

**Indications for testing [IV; C]**

- Symptoms or signs of urethral discharge in men;
- Vaginal discharge with risk factor for STI (age <30 years, new sexual partner);
- Mucopurulent cervicitis;

- Persons diagnosed with any other STI;
- Sexual partner of persons with an STI or PID;
- Acute epididymo-orchitis in a male aged <40 years;
- Acute pelvic inflammatory disease;
- When screening young adults (<25 years of age) for sexually transmitted infection;
- When screening individuals with new or multiple recent sexual partners;
- Purulent conjunctivitis in a neonate or adult;
- Mother of a newborn with ophthalmia neonatorum.

## MANAGEMENT OF PATIENT

### Information, explanation and advice for the patient

- Patients should be advised to abstain from sexual contact for seven days after they and their partners have completed treatment and their symptoms have resolved [IV; C];
- Patients (and their sex partners) should be given information about their infection, including details about transmission, prevention and complications. It is recommended that both verbal and written information be provided [IV; C];
- A patient information leaflet is available on the IUSTI – Europe website for guidelines (http://www.iusti.org/regions/Europe/euroguidelines.htm).

### Therapy

*Neisseria gonorrhoeae* has shown a remarkable capacity to develop resistance to multiple classes of antibiotics including penicillins, tetracyclines, macrolides and fluoroquinolones.[40,41] After a steady rise in minimum inhibitory concentrations (MICs) in recent years, resistance and even clinical failures to extended-spectrum cephalosporins (ceftriaxone and cefixime) have now been confirmed.[15,40-49] In this emergent situation including the fear that gonorrhoea may become untreatable, the WHO has published the 'Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in *Neisseria gonorrhoeae*'.[50] The European Centre for Disease Prevention and Control (ECDC) has published the 'Response Plan to Control and Manage the Threat of Multidrug-Resistant Gonorrhoea in Europe'[51] and the Centers for Disease Control and Prevention (CDC) has also launched a public health response plan for the United States (U.S.).[52] Ceftriaxone and cefixime have a strong evidence-base for efficacy in the treatment of gonorrhoea

and were the principal recommended treatments in the 2009 guideline. As a consequence of the emergence of clinically important resistance to extended-spectrum cephalosporins and the absence of robust alternative antimicrobials that can be administered as a single dose, these guidelines have adopted combination antimicrobial therapy as a strategy to delay and combat the widespread development of multi-drug resistance rather than only recommending administration of an increased dose of the extended-spectrum cephalosporin. According to limited data, combination antimicrobial therapy with extended-spectrum cephalosporins and azithromycin seems to show synergy in-vitro and in-vivo,[53-55] and also eradicates concomitant *Chlamydia trachomatis* infection, which is relatively common in many settings. Published clinical trials on the treatment of gonorrhoea do not address the rapidly evolving situation of resistance to extended-spectrum cephalosporins and provide very limited data on the treatment of multidrug resistant gonorrhoea. Treatment regimens recommended in this guideline are based on early clinical efficacy trials, pharmacokinetic/pharmacodynamic considerations,[42] in vitro antimicrobial susceptibility surveillance data,[40,41] case reports of antimicrobial resistance,[15,43-49] and anticipated trends in antimicrobial resistance. Nevertheless, there remains significant geographical variation in resistance and local alternative treatments based on comprehensive, quality assured local surveillance data of resistance may be reasonable.[40]

***Indications for therapy [IV; C]***

- Identification of intracellular diplococci at a genital site by Gram-stain or Methylene blue-stain microscopy;
- Positive culture or confirmed NAAT from any site for *N. gonorrhoeae* (or unconfirmed NAAT from urogenital specimens in settings where PPV>90%);
- On epidemiological grounds, if a recent partner has confirmed gonococcal infection;
- On epidemiological grounds, mother of neonate with confirmed gonococcal infection;
- On epidemiological grounds, treatment can be considered following sexual assault;
- 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 always be given.

***Recommended treatments for uncomplicated N. gonorrhoeae infections of the urethra, cervix and rectum in adults and adolescents when the antimicrobial sensitivity of the infection is unknown.***[56-60]

Ceftriaxone 500 mg intramuscularly (IM) as a single dose **together with** azithromycin 2 g as single oral dose [IV; C].

***NOTE: Azithromycin tablets may be taken with or without food but gastrointestinal side effects can be less if taken after food.***

If ceftriaxone 500 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 gram vial of ceftriaxone and mixed. 2 ml of the mixture is drawn and injected IM.

***Alternative regimens***

1. Cefixime 400 mg oral as a single dose [Ib; A] **together with** azithromycin 2 g as a single oral dose [IV; C]. This regimen is only an alternative option if ceftriaxone is not available or administration of injectable antimicrobials is not possible or refused by the patient.
2. Ceftriaxone 500 mg IM as a single dose [IV; C]. This regimen is only an alternative option if azithromycin is not available or patient is unable to take oral medication.
3. Spectinomycin 2 g IM as a single dose [Ib; A] **together with** azithromycin 2 g as a single oral dose [IV; C]. This regimen can be used if resistance to extended-spectrum cephalosporins is identified or suspected, or patient has history of penicillin anaphylaxis or cephalosporin allergy.

Co-infection with *C. trachomatis* is common in young (<30 years) heterosexual patients and MSM with gonorrhoea.[3] If treatment for gonorrhoea does not include azithromycin, treatment with azithromycin 1 g oral as a single dose or doxycycline 100 mg oral dose twice daily for 7 days should be given for possible chlamydial co-infection unless co-infection has been excluded with NAAT testing [GPP – good practice point].[57,58]

- Other single dose cephalosporin regimens

Cefixime 400 mg has been widely used as an oral single dose treatment for gonorrhoea. Multiple recent reports of treatment failures and pharmacodynamic investigations have raised serious concerns over the adequacy of 400 mg of cefixime as single dose treatment.[42,44-47,49] Cefixime is only an alternative option if administration of an intramuscular injection is not possible or refused by the patient. However, caution should be taken using cefixime 400 mg only, particularly for treatment of pharyngeal infection, and ideally, if used, it should always be given together with azithromycin 2 g as a single oral dose (see alternative regimen 1 above).

Alternative injectable or oral cephalosporins offer no advantage in terms of efficacy and pharmokinetics/pharmacodynamics over ceftriaxone or cefixime, and treatment efficacy for pharyngeal infection is less certain. Accordingly, alternative cephalosporins cannot be recommended.[56-61]

- Single dose fluoroquinolone regimens

Fluoroquinolones cannot generally be recommended for the treatment of gonorrhoea because of the worldwide high prevalence of quinolone resistance.[3,40,41,50] When an infection is known before treatment to be fluoroquinolone sensitive, based on appropriate laboratory susceptibility testing and there are indications against using ceftriaxone, ciprofloxacin 500 mg oral as a single dose or ofloxacin 400 mg oral as a single dose have proven high efficacy [Ib; A].[56,62]

- Azithromycin

Clinical trials have demonstrated that azithromycin has high efficacy (>98 %) as a single oral 2 g dose.[63,64] However, it is not recommended for the treatment of gonorrhoea unless there is a history of penicillin anaphylaxis or cephalosporin allergy and, ideally, infection is proven before treatment to be azithromycin sensitive. High level azithromycin resistance and treatment failure have been observed in Europe[41,65-69] and clinical outcome does not always correlate with in-vitro sensitivity.[70]

***Therapy for uncomplicated gonococcal infection of the pharynx***

Many antimicrobials have demonstrated lower efficacy (≤90%) in eradicating *N. gonorrhoeae* from the pharynx than in eradicating genital and anorectal infection.[56-60,71,72] This correlates with the pharmacokinetic properties of the individual antimicrobials. Treatment with spectinomycin has poor efficacy at eradicating pharyngeal gonorrhoea.[40,56-60]

***Recommended treatment for pharyngeal infection***

Ceftriaxone 500 mg IM as a single dose **together with** azithromycin 2 g oral single dose [IV; C].

***Alternative regimens***

Ceftriaxone 500 mg IM as a single dose [IV; C]. This regimen is only an alternative option if azithromycin is not available or patient is unable to take oral medication.

Alternative treatments for pharyngeal infection when there is a history of penicillin anaphylaxis or cephalosporin allergy and fluoroquinolone or azithromycin resistance are excluded by appropriate laboratory susceptibility testing:

- Ciprofloxacin 500 mg as a single oral dose or ofloxacin 400 mg as a single oral dose or azithromycin 2 g as a single oral dose.

***Therapy of genital, anorectal and pharyngeal gonococcal infection when extended-spectrum cephalosporin resistance identified***

- Ceftriaxone 1 g IM as a single dose **together with** azithromycin 2 g oral single dose [IV, C].
- Gentamicin 240 mg IM as a single dose **together with** azithromycin 2 g oral as single dose [IV, C]. This combination is currently under clinical study and may be valuable if infection persists after treatment with ceftriaxone.[73,74] Gentamicin has been successfully used in Malawi, Africa for many years (mainly in syndromic management administered together with doxycycline)[75] and high in-vitro susceptibility in Europe has been proven.[76] However, randomized, quality assured clinical trials need to confirm the efficacy of this treatment regimen.

***Therapy of gonococcal infections in pregnancy or when breastfeeding***

- Recommended treatment[77]

  Ceftriaxone 500 mg IM as a single dose [Ib; A].

***Alternative regimen***

Spectinomycin 2 g IM as a single dose (has poor efficacy for treatment of pharyngeal gonorrhoea).[40,56-60]

The safety of azithromycin in pregnancy has not been confirmed but clinical experience indicates that it may be safely used. It should only be used under medical supervision if the expected benefit to the mother is thought to be greater than the possible risk to the foetus.[78] Azithromycin passes into breast milk and is not recommended whilst breast feeding. Pregnant and breastfeeding women should not be treated with fluoroquinolone or tetracycline antimicrobials.

***Therapy of gonococcal infections in patients with penicillin allergy***

Third-generation cephalosporins show negligible cross-allergy with penicillins and allergy to these cephalosporins is rare.[79,80] If allergy is not excluded and third-generation cephalosporins still need to be given, the patient should be under medical supervision for at least 30 minutes.

- Recommended treatment for patients with a history of penicillin anaphylaxis or cephalosporin allergy:

  Spectinomycin 2 g IM as a single dose [Ib; A] together with Azithromycin 2 g oral single dose.

  Alternative treatments in patients with known penicillin anaphylaxis or cephalosporin allergy when fluoroquinolone or azithromycin sensitivity has been confirmed by appropriate laboratory susceptibility testing:

  Ciprofloxacin 500 mg oral as a single dose or ofloxacin 400 mg oral as a single dose or azithromycin 2 g as a single oral dose [Ib; B].

***Therapy for upper genital tract gonococcal infection***

***Gonococcal epididymo-orchitis***

- Recommended treatments when gonorrhoea is diagnosed in a man with acute epididymo-orchitis:

  Ceftriaxone 500 mg IM as a single dose **together with** doxycycline 100 mg oral dose twice daily for 10-14 days [IV; C].

  Ciprofloxacin 500 mg as a single oral dose may be used as an alternative to ceftriaxone when sensitivity confirmed by appropriate laboratory susceptibility testing.
  (see also European Guideline on Epididymo-orchitis)

***Gonococcal pelvic inflammatory disease***

- Recommended treatments when gonorrhoea is the suspected/possible cause of PID:

  Ceftriaxone 500 mg IM as a single dose **together with** doxycycline 100 mg oral dose twice daily **together with** metronidazole 400 mg oral dose twice daily for 14 days [IV; C].
  (see also European Guideline on Pelvic Infection).

***Therapy for disseminated gonococcal infection***

There have been no clinical trials on the treatment of disseminated gonococcal infection (DGI) since the progressive development of antimicrobial resistance by *N. gonorrhoeae*. Treatment is based on current antimicrobial sensitivity data, observational data from case series and the principals of treating septicaemia. Hospitalization is recommended for initial therapy.[11,12,57,59,81,82]

- Recommended treatment [IV; C]:

  Initial therapy:

  1. Ceftriaxone 1 g IM or IV every 24 hours.
  2. Spectinomycin 2 g IM every 12 hours.

  Therapy should continue for 7 days, but may be switched 24-48 hours after symptoms improve to one of the following oral regimens:

  Cefixime 400 mg oral dose twice daily or if fluoroquinolone sensitivity is confirmed by appropriate laboratory susceptibility testing:

Ciprofloxacin 500 mg oral dose or ofloxacin 400 mg oral dose, twice daily.

***Therapy for gonococcal conjunctivitis***

A three day systemic regimen is recommended as the cornea may be involved and is relatively avascular [IV; C].[57] The eye should be irrigated with sterile saline solution once.

• Ceftriaxone 500 mg IM as a single dose daily for 3 days.

• If history of penicillin anaphylaxis or cephalosporin allergy:

Spectinomycin 2 g IM as a single dose daily for 3 days.

Or, if antibiotic susceptibility testing at laboratory has excluded resistance:

Azithromycin 2 g oral as a single dose **together with** doxycycline 100 mg oral dose twice daily for 1 week **together with** ciprofloxacin 250 mg oral dose daily for 3 days [IV; C]

***Therapy for ophthalmia neonatorum (gonococcal neonatal conjunctivitis)[58]***

The eye should be irrigated frequently with sterile saline solution.

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

**CONTACT TRACING AND MANAGEMENT OF SEX PARTNER(S)**

- Sex partners should be contacted and offered testing together with treatment and counseling for gonorrhoea and chlamydial infection [IV; C];
- For cases of gonorrhoea, all sex partners within the preceding 60 days of onset of symptoms or diagnosis should be evaluated and treated [IV; C].[57-60] If a patient's last sexual contact 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, exclude re-infection and ensure partner notification [IV; C];
- A test of cure is recommended in all cases to identify persisting infection and emerging resistance.[16] Test of cure is particularly important to perform to ensure effective

eradication of pharyngeal infection, which is substantially harder to treat than genital and anorectal infections.[56-60,71,72] When symptoms persist after treatment, culture is recommended to identify persisting infection and for antimicrobial sensitivity testing and may be performed 3-7 days after completion of therapy, possibly supplemented a week later with a NAAT for increased sensitivity if culture is negative. Tests of cure in asymptomatic patients can be performed with a NAAT 2 weeks after completion of treatment and ideally, all positives should be cultured and antibiotic susceptibility testing performed before further treatment is given [IV; C].[83,84]

## IDENTIFICATION, CONFIRMATION AND REPORTING OF TREATMENT FAILURES

The importance of identification, confirmation and reporting of failures with recommended treatment regimens are stressed and described in detail in the recently published WHO Global Action Plan,[50] ECDC European Response Plan,[51] and U.S. CDC Response Plan.[52] Ideally, as much clinical and laboratory data as possible should be collected and reported on treatment failures, including a detailed clinical history (including all antimicrobial treatments given), the exclusion of reinfection, highly discriminative molecular epidemiological typing of pre-treatment and post-treatment gonococcal isolates/NAAT sample (identifying indistinguishable isolates/genetic variant), and phenotypic susceptibility and genetic susceptibility (isolates contain genetic resistance determinants) in the gonococcal isolates to the used treatment. For details regarding identification, confirmation and reporting of treatment failures in Europe, see the ECDC Response Plan.[51]

## NOTIFICATION

Infections with *N. gonorrhoeae* should be notified to local, regional and national authorities as mandated by statute. The ECDC is responsible for the European Union-wide surveillance of communicable diseases including gonorrhoea.

## 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.



**LIST OF CONTRIBUTING ORGANISATIONS**

This guideline has been produced on behalf of the following organisations: the European Branch of the International Union against Sexually Transmitted Infections (IUSTI Europe); the European Academy of Dermatology and Venereology (EADV); the European Dermatology Forum (EDF); the Union of European Medical Specialists (UEMS). The European Centre for Disease Prevention and Control (ECDC) and the European Office of the World Health Organisation (WHO-Europe) also contributed to its development.

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**REFERENCES**

1. World Health Organization. Global incidence and prevalence of selected curable sexually transmitted infections - 2008. Geneva: World Health Organization; 2012. (http://www.who.int/reproductivehealth/publications/rtis/2008_STI_estimates.pdf) (accessed 30 October 2012).
2. European Centre for Disease Prevention and Control (ECDC). Sexually transmitted infections in Europe, 1990-2010. Stockholm, ECDC. 2012. (http://www.ecdc.europa.eu/en/publications/Publications/201206-Sexually-Transmitted-Infections-Europe-2010.pdf) (accessed 30 October 2012).

3. GRASP Steering Group. The gonococcal resistance to antimicrobials programme (GRASP) year 2010 report. London: Health Protection Agency 2011. (http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1316016752917) (accessed 30 October 2012).
4. Risley CL, Ward H, Choudhury B, Bishop CJ, Fenton KA, Spratt BG, *et al*. Geographical and demographic clustering of gonorrhoea in London. *Sex Transm Infect* 2007;**83**:481-7.
5. Hook EW III, Handsfield HH. Gonococcal infections in the adult. In Holmes KK, Sparling PF, *et al* (eds.), *Sexually Transmitted Diseases* 4th ed. New York, NY. McGraw Hill 2008; 627-45.
6. Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. *Genitourin Med* 1996;**72**:422-6.
7. Lewis DA, Bond M, Butt KD, Smith CP, Shafi MS, Murphy SM. A one-year survey of gonococcal infection seen in the genitourinary medicine department of a London district general hospital. *Int J STD AIDS* 1999;**10**:588-94.
8. Barlow D, Phillips I. Gonorrhoea in women: diagnostic, clinical and laboratory aspects. *Lancet* 1978;**1**:761-4.
9. Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, Klausner JD. Prevalence of rectal, urethral and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California 2003. *Clin Infect Dis* 2005;**41**:67-74.
10. Peters RPH, Nijsten N, Mutsaers J, Jansen CL, Morre SA, van Leeuwen AP. Screening of oropharynx and anorectum increases prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection in female STD clinic visitors. *Sex Transm Dis* 2011;**38**:783-7.
11. Bleich AT, Sheffield JS, Wendel GD Jr, Sigman A, Cunningham FG. Disseminated gonococcal infection in women. *Obstet Gynecol* 2012;**119**:597-602.
12. O'Brien JP, Goldenberg DL, Rice PA. Disseminated gonococcal infection: a prospective analysis of 49 patients and a review of pathophysiology and immune mechanisms. *Medicine* 1983;**62**:395-406.
13. Taylor SN, DiCarlo RP, Martin DH. Comparison of methylene blue/gentian violet stain to Gram's stain for the rapid diagnosis of gonococcal urethritis in men. *Sex Trans Dis* 2011;**38**:995-6.
14. Jephcott AE. Microbiological diagnosis of gonorrhoea. *Genitourin Med* 1997;**73**: 245-52.
15. Unemo M, Golparian D, Hestner A. Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, Sweden, July 2010. *Euro Surveill* 2011;**16**(6):p11=19792.
16. Whiley DM, Goire N, Lahra MM, Donovan B, Limnios AE, Nissen MD, Sloots TP. The ticking time bomb: escalating antibiotic resistance in *Neisseria gonorrhoeae* is a public health disaster in waiting. *J Antimicrob Chemother* 2012;**67**:2059-61.
17. Cook RL, Hutchison SL, Østergaard L, Braithwaite RS, Ness RB. Systematic Review: Non-invasive testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae. Ann Intern Med* 2005;**142**:914-25.
18. Whiley DM, Garland SM, Harnett G, Lum G, Smith DW, Tabrizi SN, *et al*. Exploring 'best practice' for nucleic acid detection of *Neisseria gonorrhoeae*. *Sexual Health* 2008;**5**:17-23.
19. Harryman L, Scofield S, Macleod J, Carrington D, Williams OM, Fernandes A, Horner P. Comparative performance of culture using swabs transported in Amies medium and the Aptima Combo 2 nucleic acid amplification test in detection of *Neisseria gonorrhoeae*

from genital and extra-genital sites: a retrospective study. *Sex Transm Infect* 2012;**88**:127-31.
20. Van Dyck E, Ieven M, Pattyn S, Van Damme L, Laga M. Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by enzyme immunoassay, culture and three nucleic acid amplification tests. *J Clin Microbiol* 2001;**39**:1751-6.
21. Van der Pol B, Ferrero DV, Buck-Barrington L, Hook EW 3rd, Lenderman C, Quinn TC, *et al*. Multicenter evaluation of the BDProbeTec ET system for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in urine specimens, female endocervical and male urethral swabs. *J Clin Microbiol* 2001;**39**:1008-16.
22. Moncada J, Schachter J, Hook EW 3rd, Ferrero D, Gaydos C, Quinn T, *et al*. The effect of urine testing in evaluations of the sensitivity of the Gen-Probe APTIMA Combo 2 Assay on endocervical swabs for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Sex Trans Dis* 2004;**31**:273-7.
23. Chernesky MA, Martin DH, Hook EW, Willis D, Jordan J, Wang S, *et al*. Ability of new APTIMA CT and APTIMA GC Assays to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in male urine and urethral swabs. *J Clin Microbiol* 2005;**43**:127-31.
24. Schachter J, Chernesky MA, Willis DE, Fine PM, Martin DH, Fuller D, *et al*. Vaginal swabs are the specimens of choice when screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*: results from a multicenter evaluation of the APTIMA assays for both infections. *Sex Trans Dis* 2005;**32**:725-8.
25. Ison C. GC NAATs: is the time right? *Sex Transm Infect* 2006;**82**:515.
26. Association of Public Health Laboratories. Laboratory diagnostic testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Expert consultation meeting summary report; January 13-15, 2009; Atlanta, GA. Silver Spring, MD: Association of Public Health Laboratories; 2009. (http://www.aphl.org/aphlprograms/infectious/std/documents/ctgclabguidelinesmeetingreport.pdf) (accessed 30 October 2012).
27. Smith DW, Tapsall JW, Lum G. Guidelines for the use and interpretation of nucleic acid detection tests for *Neisseria gonorrhoeae* in Australia: a position paper on behalf of the Public Health Laboratory Network. *Commun Dis Intell* 2005;**29**:358-65.
28. Department of Health, Health Protection Agency and BASHH Feb 2010. Guidance for gonorrhoea testing in England and Wales. (Available from: http://www.bashh.org/guidelines (2010 HPA guidance on Gonorrhoea testing in England & Wales) (accessed 30 October 2012).
29. Page-Shafer K, Graves A, Kent C, Bals JE, Zapitz VM, Klausner JD. Increased sensitivity of DNA amplification testing for the detection of pharyngeal gonorrhoea in men who have sex with men. *Clin Infect Dis* 2002;**34**:173-6.
30. McNally LP, Templeton DJ, Jin F, Grulich AE, Donovan B, Whiley DM, *et al*. Low positive predictive value of a nucleic acid amplification test for nongenital *Neisseria gonorrhoeae* infection in homosexual men. *Clin Infect Dis* 2008;**47**:e25-7.
31. Schachter J, Moncada J, Liska S, Shayevich C, Klausner JD. Nucleic acid amplification tests in the diagnosis of chlamydial and gonococcal infections in the oropharynx and rectum in men who have sex with men. *Sex Trans Dis* 2008;**35**:637-42.
32. Ota KV, Tamari IE, Smieja M, Jamieson F, Jones KE, Towns L, *et al*. Detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in pharyngeal and rectal specimens using the BD Probetec ET system, the Gen-Probe Aptima Combo 2 assay and culture. *Sex Trans Infect* 2009;**85**:182-6.

33. Alexander S. The challenges of detecting gonorrhoea and chlamydia in rectal and pharyngeal sites: could we, should we, be doing more? *Sex Trans Infect* 2009;**85**: 159-60.
34. Bachmann LH, Johnson RE, Cheng H, Markowitz L, Papp JR, Palella FJ Jr, Hook EW 3rd. Nucleic acid amplification tests for diagnosis of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* rectal infections. *J Clin Microbiol* 2010;**48**:1827-32.
35. Mimiaga MJ, Helms DJ, Reisner SL, Grasso C, Bertrand T, Mosure DJ, *et al*. Gonococcal, chlamydia, and syphilis infection positivity among MSM attending a large primary care clinic, Boston, 2003 to 2004. *Sex Transm Dis* 2009;**36**:507-11.
36. Palmer H, Mallinson H, Wood RL, Herring AJ. Evaluation of the specificities of five DNA amplification methods for the detection of *Neisseria gonorrhoeae*. *J Clin Microbiol* 2003;**41**:835-7.
37. Tabrizi SN, Unemo M, Limnios AE, Hogan TR, Hjelmevoll SO, Garland SM, Tapsall J. Evaluation of six commercial nucleic acid amplification tests for the detection of *Neisseria gonorrhoeae* and other Neisseria species. *J Clin Microbiol* 2011;**49**:3610-5.
38. Lavelle SJ, Jones KE, Mallinson H, Webb AMC. Finding, confirming, and managing gonorrhea in a population screened for chlamydia using the Gen-Probe Aptima Combo2 assay. *Sex Trans Infect* 2006;**82**:221-4.
39. Jin F, Prestage GP, Mao L, Kippax SC, Pell CM, Donovan B, *et al*. Incidence and risk factors for urethral and anal gonorrhoea and chlamydia in a cohort of HIV-negative homosexual men: the Health in Men study. *Sex Trans Infect* 2007;**83**:113-9.
40. Tapsall JW, Ndowa F, Lewis DA, Unemo M. Meeting the public health challenge of multidrug- and extensively drug-resistant *Neisseria gonorrhoeae*. *Expert Rev Anti Infect Ther* 2009;**7**:821-34.
41. European Centre for Disease Prevention and Control (ECDC). Gonococcal antimicrobial susceptibility surveillance in Europe 2010. Stockholm: ECDC 2012. (http://ecdc.europa.eu/en/publications/Publications/1206-Gonococcal-AMR.pdf) (accessed 30 October 2012).
42. Chisholm S, Mouton J, Lewis D, Nichols T, Ison C, Livermore D. Cephalosporin MIC creep among gonococci: time for a pharmacodynamic rethink? *J Antimicrob Chemother* 2010;**65**:2141-8.
43. Ohnishi M, Golparian D, Shimuta K, Saika T, Hoshina S, Iwasaku K, *et al*. Is *Neisseria gonorrhoeae* initiating a future era of untreatable gonorrhea? Detailed characterization of the first strain with high-level resistance to ceftriaxone. *Antimicrob Agents Chemother* 2011;**55**:3538-45.
44. Unemo M, Golparian D, Nicholas R, Ohnishi M, Gallay A, Sednaoui P. High-level cefixime- and ceftriaxone-resistant *N. gonorrhoeae* in France: novel *penA* mosaic allele in a successful international clone causes treatment failure. *Antimicrob Agents Chemother* 2012;**56**:1273-80.
45. Unemo M, Golparian D, Syversen G, Vestrheim DF, Mol H. Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010. *Euro Surveill* 2010;**15**(47):pii=19721.
46. Ison CA, Hussey J, Sankar KN, Evans J, Alexander S. Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. *Euro Surveill* 2011;**16**(14):p11=19833.
47. Unemo M, Golparian D, Stary A, Eigentler A. First *Neisseria gonorrhoeae* strain with resistance to cefixime causing gonorrhoea treatment failure in Austria. *Euro Surveill* 2011;**16**(43):pii=19998.

48. Unemo M, Golparian D, Potočnik M, Jeverica S. Treatment failure of pharyngeal gonorrhoea with internationally recommended first-line ceftriaxone verified in Slovenia, September 2011. *Euro Surveill* 2012;**17**(25):pii=20200.
49. Forsyth S, Penney P, Rooney G. Cefixime-resistant *Neisseria gonorrhoeae* in the UK: a time to reflect on practice and recommendations. *Int J STD AIDS* 2011;**22**:296-7.
50. World Health Organization (WHO), Department of Reproductive Health and Research. Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. Geneva: WHO; 2012. p. 1-36. (http://whqlibdoc.who.int/publications/2012/9789241503501_eng.pdf) (accessed 30 October 2012).
51. European Centre for Disease Prevention and Control (ECDC). Response plan to control and manage the threat of multidrug-resistant gonorrhoea in Europe. Stockholm: ECDC; 2012. p. 1-23. (http://www.ecdc.europa.eu/en/publications/Publications/1206-ECDC-MDR-gonorrhoea-response-plan.pdf) (accessed 30 October 2012).
52. Centers for Disease Control and Prevention (CDC). Cephalosporin-Resistant *Neisseria gonorrhoeae* Public Health Response Plan. 2012. p. 1-43. (http://www.cdc.gov/std/gonorrhea/default.htm) (accessed 30 October 2012).
53. Furuya R, Nakayama H, Kanayama A, Saika T, Iyoda T, Tatewaki M, *et al*. In vitro synergistic effects of double combinations of beta-lactams and azithromycin against clinical isolates of *Neisseria gonorrhoeae*. *J Infect Chemotherapy* 2006;**12**:172-6.
54. Sathia L, Ellis B, Phillip S, Winston A, Smith A. Pharyngeal gonorrhoea – is dual therapy the way forward? *Int J STD AIDS* 2007;**18**:647-8.
55. Golden M, Kerani R, Shafii T, Whittington W, Holmes K. Does azithromycin co-treatment enhance the efficacy of oral cephalosporins for pharyngeal gonorrhea? Presented at: 18th International Society for STD Research (ISSTDR) Conference, London, UK, June 2009.
56. Moran JS, Levine WC. Drugs of choice in the treatment of uncomplicated gonococcal infection. *Clin Infect Dis* 1995;**20**(Suppl 1):S47-65.
57. Bignell C, Fitzgerald M, BASHH Guideline Development Group. UK national guideline for the management of gonorrhoea in adults, 2011. *Int J STD AIDS* 2011;**22**:541-7.
58. Centers for Disease Control and Prevention (CDC). Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR* 2010;**59**(No. RR-12):49-55.
59. Centers for Disease Control and Prevention (CDC). Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR Morb Mortal Wkly Rep* 2012;**61**:590-4.
60. Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhoea in adults in the United States. *Clin Infect Dis* 2007;**44**:S84-101.
61. Ison CA, Mouton JW, Jones K, Fenton KA, Livermore DA. Which cephalosporin for gonorrhoea? *Sex Transm Infect* 2004;**80**:386-8.
62. Moran JS. Ciprofloxacin for gonorrhea – 250 mg or 500 mg? *Sex Trans Dis* 1996;**23**:165-7.
63. Handsfield HH, Dalu ZA, Martin DH, Douglas JM Jr, McCarty JM, Schlossberg D. Multicenter trial of single-dose azithromycin vs ceftriaxone in the treatment of uncomplicated gonorrhoea. *Sex Trans Dis* 1994;**21**:107-11.

64. Bignell C, Garley J. Azithromycin in the treatment of infection with *Neisseria gonorrhoeae*. *Sex Transm Infect* 2010;**86**:422-6.
65. Palmer HM, Young H, Winter A, Dave J. Emergence and spread of azithromycin-resistant *Neisseria gonorrhoeae* in Scotland. *J Antimicrob Chemother* 2008;**62**:490-4.
66. Chisholm SA, Neal TJ, Alawattegama AB, Birley HDL, Howe RA, Ison CA. Emergence of high-level azithromycin resistance in *Neisseria gonorrhoeae* in England and Wales. *J Antimicrob Chemother* 2009;**64**:353-8.
67. Chisholm SA, Dave J, Ison CA. High-level azithromycin resistance occurs in *Neisseria gonorrhoeae* as a result of a single point mutation in the 23S rRNA genes. *Antimicrob Agents Chemother* 2010;**54**:3812-6.
68. Starnino S, Stefanelli P; *Neisseria gonorrhoeae* Italian Study Group. Azithromycin-resistant *Neisseria gonorrhoeae* strains recently isolated in Italy. *J Antimicrob Chemother* 2009;**63**:1200-4.
69. Young H, Moyes A, McMillan A. Azithromycin and erythromycin resistant *Neisseria gonorrhoeae* following treatment with azithromycin. *Int J STD AIDS* 1997;**8**:299-302.
70. Tapsall JW, Schultz TR, Limnios EA, Donovan B, Lum G, Mulhall BP. Failure of azithromycin therapy in gonorrhoea and discorrelation with laboratory parameters. *Sex Trans Dis* 1998;**25**:505-8.
71. Ota KV, Fisman DN, Tamari IE, Smieja M, Ng LK, Jones KE, *et al*. Incidence and treatment outcomes of pharyngeal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections in men who have sex with men: a 13-year retrospective cohort study. *Clin Infect Dis* 2009;**48**:1237-43.
72. Moran JS. Treating uncomplicated *Neisseria gonorrhoeae* infections: is the anatomic site of infection important? *Sex Trans Dis* 1995;**22**:39-47.
73. Ross JDC, Lewis DA. Cephalosporin resistant *Neisseria gonorrhoeae*: time to consider gentamicin? *Sex Transm Infect* 2012;**88**:6-8.
74. Dowell D, Kirkcaldy RD. Effectiveness of gentamicin for gonorrhoea treatment: systematic review and meta-analysis. *Sex Transm Infect* 2012 Aug 23. [Epub ahead of print]
75. Brown LB, Krysiak R, Kamanga G, Mapanje C, Kanyamula H, Banda B, *et al*. *Neisseria gonorrhoeae* antimicrobial susceptibility in Lilongwe, Malawi, 2007. *Sex Transm Dis* 2010;**37**:169-72.
76. Chisholm SA, Quaye N, Cole MJ, Fredlund H, Hoffmann S, Jensen JS, *et al*. An evaluation of gentamicin susceptibility of *Neisseria gonorrhoeae* isolates in Europe. *J Antimicrob Chemother* 2011;**66**:592-5.
77. Ramus RM, Sheffield JS, Mayfield JA, Wendel GD. A randomised trial that compared oral cefixime and intramuscular ceftriaxone for the treatment of gonorrhoea in pregnancy. *Am J Obstet Gynecol* 2001;**185**:629-32.
78. Sandoz Limited. SPC on Azithromycin 28/09/2010. (http://www.medicines.org.uk/EMC/medicine/21720/SPC/Azithromycin+500mg+Tablets/#PREGNANCY) (accessed 30 October 2012).
79. Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: A meta-analysis. *Otolaryngol Head Neck Surg* 2007;**136**:340-7.
80. Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. *Am J Med* 2008;**121**:572-6.

81. Wise CM, Morris CR, Wasilauskas BL, Salzer WL. Gonococcal arthritis in an era of increasing penicillin resistance. Presentations and outcomes in 41 recent cases (1985-1991). *Arch Intern Med* 1994;**154**:2690-5.
82. Thompson SE. Treatment of disseminated gonococcal infections. *Sex Transm Dis* 1979;**6**(Suppl 1):181-4.
83. Hjelmevoll SO, Olsen ME, Sollid JU, Haaheim H, Melby KK, Moi H, *et al*. Appropriate time for test-of-cure when diagnosing gonorrhoea with a nucleic acid amplification test. *Acta Derm Venereol* 2012;**92**:316-9.
84. Bachmann LH, Desmond RA, Stephens J, Hughes A, Hook EW 3rd. Duration of persistence of gonococcal DNA detected by ligase chain reaction in men and women following recommended therapy for uncomplicated gonorrhea. *J Clin Microbiol* 2002;**40**:3596–601.

## APPENDIX 1

### LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials.

Ib Evidence obtained from at least one randomised controlled trial.

IIa Evidence obtained from at least one well designed study without randomisation.

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 randomised 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 randomised 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 absence of directly applicable studies of good quality.

APPENDIX 2

SEARCH STRATEGY

A Medline search was conducted in May 2012 using PubMed for articles published since the development of the second European guideline on the management of gonorrhoea in adults in 2008 (published in 2009). Search headings were kept broad (gonorrhoea and *Neisseria 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.

APPENDIX 3

DECLARATIONS OF INTEREST:

Chris Bignell: None

Magnus Unemo: None

Jørgen S. Jensen: None