INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
0(0) 1–17

DOI: 10.1177/0956462420949126
journals.sagepub.com/home/std
SAGE

2020 European guideline for the diagnosis and treatment of gonorrhoea in adults

M Unemo[1], JDC Ross[2], AB Serwin[3], M Gomberg[4], M Cusini[5] and JS Jensen[6]

Abstract

Gonorrhoea is a major public health concern globally. Increasing incidence and sporadic ceftriaxone-resistant cases, including treatment failures, are growing concerns. The 2020 European gonorrhoea guideline provides up-to-date evidence-based guidance regarding the diagnosis and treatment of gonorrhoea. The updates and recommendations emphasize significantly increasing gonorrhoea incidence; broad indications for increased testing with validated and quality-assured nucleic acid amplification tests and culture; dual antimicrobial therapy including high-dose ceftriaxone and azithromycin (ceftriaxone 1 g plus azithromycin 2 g) OR ceftriaxone 1 g monotherapy (ONLY in well-controlled settings, see guideline for details) for uncomplicated gonorrhoea when the antimicrobial susceptibility is unknown; recommendation of test of cure (TOC) in all gonorrhoea cases to ensure eradication of infection and identify resistance; and enhanced surveillance of treatment failures when recommended treatment regimens have been used. Improvements in access to appropriate testing, test performance, diagnostics, antimicrobial susceptibility surveillance and treatment, and follow-up of gonorrhoea patients are essential in controlling gonorrhoea and to mitigate the emergence and/or spread of ceftriaxone resistance and multidrug-resistant and extensively drug-resistant gonorrhoea. For detailed background, evidence base and discussions, see the background review for the present 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults (Unemo M, et al. Int J STD AIDS. 2020).

Keywords

Neisseria gonorrhoeae, gonorrhoea, sexually transmitted infection, Europe, management, diagnosis, antimicrobial resistance, treatment

Date received: 14 July 2020; accepted: 16 July 2020

The present evidence-based guideline represents an updated version of the '2012 European guideline on the diagnosis and treatment of gonorrhoea in adults'.[1] For detailed background, evidence base and discussions, see the background review for the present 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults (Unemo M, et al. Int J STD AIDS. 2020).

Aetiology, transmission, and epidemiology

- Gonorrhoea (gonococcal infection) is caused by the obligate human pathogenic, Gram-negative bacterium *Neisseria gonorrhoeae*;[2]
- Infection predominantly involves the epithelium of the urethra, endocervix, rectum, oropharynx, and

[1]WHO Collaborating Centre for Gonorrhoea and other STIs, National Reference Laboratory for STIs, Department of Laboratory Medicine, Microbiology, Örebro University Hospital and Faculty of Medicine and Health, Örebro University, Örebro, Sweden
[2]University Hospital Birmingham NHS Foundation Trust, Birmingham, UK
[3]Department of Dermatology and Venereology, Medical University of Białystok, Białystok, Poland
[4]Moscow Scientific and Practical Center of Dermatovenereology and Cosmetology, Moscow, Russia
[5]Department of Dermatology, Fondazione IRCCS Ca' Granda Ospedale Policlinico, Milano, Italy
[6]Infection Preparedness, Research Unit for Reproductive Tract Microbiology, Statens Serum Institut, Copenhagen, Denmark

Corresponding author:
M Unemo, WHO Collaborating Centre for Gonorrhoea and other STIs, National Reference Laboratory for STIs, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden.
Email: magnus.unemo@regionorebrolan.se

conjunctivae. Infection can ascend to the upper genital tract to cause pelvic inflammatory disease (PID) and epididymo-orchitis;[1–3]
- Transmission is by direct inoculation of infected secretions from one mucosa to another, i.e., genital-urogenital, urogenital-anorectal, oro-urogenital, or oro-anal contact, or by mother-to-child transmission at birth;[1–7]
- In the European Union (EU)/European Economic Area (EEA), gonorrhoea is the second (after *Chlamydia trachomatis* infection) most frequently reported bacterial sexually transmitted infection (STI), and the incidence has increased by ~240% since 2008.[8] In 2018, 76% of gonorrhoea cases were reported in men,[8] reflecting the high prevalence in men who have sex with men (MSM) and the higher proportion of diagnosed symptomatic urogenital infections in men. In 2018, the highest incidence of gonorrhoea in the EU/EEA was among 25–34 year olds, closely followed by 15–24 year olds and, in many countries, there is a disproportionate burden of infection in MSM and/or ethnic minority groups.[8–10]

Clinical features[1–3,11–16]

Symptoms and physical signs of gonorrhoea reflect localised inflammation of infected mucosal surfaces in the urogenital tract and several other STIs cause similar symptoms.

Symptoms

- In men, acute urethritis is predominant with symptoms of urethral discharge (>80%) and dysuria (>50%), usually starting within 2–8 days of exposure. Asymptomatic urethral infection in men is rare (<10% of infections);
- In women, endocervical and urethral infection include symptoms such as increased or altered vaginal discharge (≤50%), lower abdominal pain (≤25%), dysuria (10–15%), and occasionally intermenstrual bleeding or menorrhagia. Endocervical infection is frequently asymptomatic (≥50%);
- Rectal and oropharyngeal infections in men and women are usually asymptomatic. Rare symptoms include anal discharge and perianal/anal pain or discomfort and sore throat, respectively.

Physical signs

- In men, mucopurulent urethral discharge is most common, which may be accompanied by erythema of the urethral meatus;
- In women, urogenital 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 and sequelae

- PID in women, potentially resulting in ectopic pregnancy and infertility, and epididymo-orchitis in men are complications of infection ascending to the upper genital tract;
- Gonococcal bacteraemia is generally rare,[17,18] but can be more common in high-prevalent gonorrhoea areas and may be expected to increase when the gonorrhoea incidence increases.[19] This is usually manifested by skin lesions, fever, arthralgia, acute arthritis, and tenosynovitis (disseminated gonococcal infection [DGI]).[3,17–21]

Indications for testing [2C]

- Symptoms or signs of urethral discharge in men;
- Cervical or vaginal discharge with a risk factor for STI (age <30 years, new sexual contact in the last year, or more than one partner in the last year);[8,22–24]
- Mucopurulent cervicitis;
- Persons newly diagnosed with other STIs;
- Sexual contact of persons with an STI or PID;
- Acute epididymo-orchitis in a male aged <40 years or with other risk factors for STIs (e.g., new sexual contact in the last year, or more than one partner in the last year);[8,22–24]
- Acute pelvic pain or signs of PID;
- When performing an STI screen in young adults (<25 years of age) or MSM;
- When performing an STI screen in individuals with new or multiple recent sexual contacts;
- Purulent conjunctivitis in a neonate or adult;
- Mother of a newborn with ophthalmia neonatorum;
- Unplanned termination of pregnancy in areas or populations of high gonorrhoea prevalence;
- Any intrauterine interventions or manipulations in areas or populations of high gonorrhoea prevalence.[25,26]

Testing and diagnosis

- **Diagnosis** of uncomplicated gonorrhoea is established by identification of *N. gonorrhoeae* in urogenital, rectal, oropharyngeal, or ocular secretions;[2,27]
- *N. gonorrhoeae* can be detected by nucleic acid amplification tests (NAATs) or culture. The bacterium can also be visualized by microscopy of a stained anogenital tract smear to facilitate rapid diagnosis in symptomatic patients;
- **Microscopy (×1000)** using Gram or methylene blue staining for identification of characteristic

intracellular diplococci within polymorphonuclear leukocytes offers adequate sensitivity (90-95%) and specificity (>99%) as a rapid diagnostic test in symptomatic men with urethral discharge [1C].[1–3,12,27,28] Microscopy has a low sensitivity in asymptomatic men (50-75%) and from endocervical (16-50%) or rectal (≤40%) sites, and microscopy is not recommended as a test of exclusion in these patients [1C].[1–3,12,14,27–31] Microscopy is also not recommended for detection of oropharyngeal gonorrhoea due to low specificity and sensitivity;

- **Culture**, including appropriate species confirmation, is a highly specific test, and relatively sensitive for urogenital specimens, provided that specimen collection, transport, storage, and culture procedures are optimised. However, the sensitivity of culture for rectal and oropharyngeal specimens is significantly lower.[1,2,27,32] Diagnostic culture is appropriate for endocervical, urethral, rectal, oropharyngeal and conjunctival specimens but not for urine or vaginal swabs.[1,2,27] Ideally, all gonococcus-positive individuals diagnosed by NAAT should have cultures performed before initiation of gonorrhoea treatment to permit antimicrobial resistance (AMR) testing and surveillance to be performed. Selective culture media containing antimicrobials such as vancomycin, colistin, nystatin, and trimethoprim are recommended [1C].[2,27,30] Culture (ideally supplemented with a NAAT for optimal sensitivity), including AMR testing, should also be performed in patients with proven infection (i.e. positive test of cure [TOC]) or in the presence of symptoms following treatment with a recommended regimen;[1–3,27,33]
- **NAATs** are the recommended diagnostic tests for symptomatic and asymptomatic individuals,[1,2,34–38] however, culture of individuals with urogenital symptoms and in gonococcal NAAT-positive individuals prior to treatment to obtain isolates for AMR testing is also encouraged. NAATs are more sensitive than culture (particularly for oropharyngeal and rectal specimens); less demanding in specimen quality, transportation and storage; offer testing on a wider range of specimen types; and show high sensitivity (>95%) in both symptomatic and asymptomatic gonorrhoea.[1,2,27,32–52]

In men, urine (up to 20 mL sampled >1 h after previous micturition) is preferable, providing a high sensitivity and non-invasive sampling.[1,2,36,42,52]

In women, vulvo-vaginal swabs (health care worker- or self-collected) are recommended due to their superior sensitivity and being less invasive since they do not require a speculum examination [1A].[1,2,34–38,44,51–55]

- **NAATs** are significantly more sensitive than culture for detection of rectal and oropharyngeal gonorrhoea,[1,2,27,32,35–38,46,49,50,56–62] and appropriately-validated and quality-assured NAATs are recommended for testing and/or screening for infections at these sites.[1,2,35–38,63,64] However, most commercially available gonococcal NAATs are not licensed for testing oropharyngeal and rectal specimens, and differ in their sensitivity and especially specificity,[1,2,27,33,37,65–69] particularly when examining oropharyngeal specimens due to the frequent presence of non-gonococcal *Neisseria* species.
- **NAAT confirmatory testing:** The positive predictive value (PPV) of NAAT testing to detect *N. gonorrhoeae* should exceed 90%. The PPV is highly influenced by the gonorrhoea prevalence in the tested population and the specificity of the NAAT.[1,2,27,65–67] If the diagnostic NAAT used does not display a PPV exceeding 90%, positive specimens should be confirmed, i.e. by repeat testing with a NAAT targeting another genetic sequence, particularly if oropharyngeal specimens are tested [1C];[1,2,27,35,36,63,64,66,67,70–72]
- **Point-of-care tests (POCTs):** rapid, validated and quality-assured POCTs for diagnosis of gonorrhoea with sufficient sensitivity compared to NAATs are still lacking; however, several NAAT-based POCTs with high sensitivity and specificity are in late development (https://www.who.int/reproductivehealth/topics/rtis/Diagnostic-Landscape-for-STIs-2019.pdf).[2,73–75]
- **Testing of rectal and oropharyngeal specimens** should be routine in MSM, considered in women who are sexual contacts of gonorrhoea patients [1C], and be guided based on sexual history, risk and symptoms or signs in all other patients.[1,36,76–85]
- **Testing of pooled specimens** (oropharyngeal, rectal, and urine/urogenital) is not recommended, due to potentially decreased sensitivity,[1,36,86–89] increased complexity, including risk of cross-contamination of sample, and lack of approval by US Food and Drug Administration (FDA) or other regulatory agencies.

Management of patients

Information, explanation and advice for the patient

- Patients with gonorrhoea should be advised to abstain from sexual contact (or if this is not possible to consistently use barrier contraception) for 14 days (seven days if ceftriaxone monotherapy)[1,36,37] after they and their sexual partners have completed ceftriaxone plus azithromycin dual treatment and their symptoms have resolved [2D]. This is to limit possible re-exposure in the presence of residual azithromycin;

- Patients (and their sexual partners) should be given information (verbal and written) about their infection, including details about transmission, prevention, complications, and treatment [1D];
- A patient information leaflet is available in different languages from IUSTI (https://iusti.org/patient-information/).
- Patients with verified gonorrhoea (and their sexual contacts) are recommended to be offered testing for other STIs, e.g. including *C. trachomatis*, *Mycoplasma genitalium* (only in symptomatic patients and always including macrolide resistance testing), syphilis, HBV, HCV, and HIV [1C].

Therapy[1,36,37,90–107]

For detailed background, evidence base and discussions regarding gonorrhoea therapy and antimicrobial resistance in *N. gonorrhoeae*, see the background review for the present guideline (Unemo M, et al. Int J STD AIDS. 2020).[1,36,37,90–206]

Briefly, ceftriaxone plus azithromycin dual therapy aims to provide cure for all gonorrhoea cases and, accordingly, to delay the emergence and/or spread of multi-drug resistance and particularly ceftriaxone resistance. It has very high cure rates; effectively targets both intracellular and extracellular bacteria;[117] has likely been involved in decreasing the level of resistance to extended-spectrum cephalosporins (ESCs; mainly ceftriaxone and cefixime) internationally[118–122] and inhibiting spread of ESC-resistant and azithromycin-resistant gonococcal strains (because concurrent resistance to ceftriaxone and azithromycin has been exceedingly rare globally [https://www.ecdc.europa.eu/en/publications-data]).[118,120–122,138] This dual therapy also effectively eradicates concomitant *C. trachomatis* infections[1,37,123] and a proportion of *M. genitalium* infections, and adherence appears high.[124] Ceftriaxone 1 g effectively cures ceftriaxone-susceptible anogenital and oropharyngeal gonorrhoea.[99,100] However, failures to treat ceftriaxone-resistant infections, particularly oropharyngeal gonorrhoea, have occurred also with ceftriaxone 1 g,[138] and additional treatment failures can be expected when using ceftriaxone monotherapy for currently circulating gonococcal strains.[138–148] ESCs combined with another anti-gonococcal antimicrobials, including azithromycin, can more effectively cure gonorrhoea, including oropharyngeal infection.[1,93,106,107,119,138,152–154] Azithromycin 2 g, but not azithromycin 1 g, effectively cures azithromycin-susceptible gonococcal infections, including in the oropharynx.[1,36,94,126,127,153,154] Nevertheless, azithromycin 2 g single oral dose may also result in more gastrointestinal side effects, particularly if taken on an empty stomach,[95,96,154] although the reported incidence of gastrointestinal side effects varies widely between studies.[153,162,163] Dividing the dose of azithromycin to give it over a longer period of time reduces the high and sustained tissue concentration, but also reduces the risk of gastrointestinal side effects.[117,155–161]

Recent published randomised controlled clinical trials (RCTs) on the treatment of gonorrhoea are few and do not address the rapidly evolving situation of gonococcal AMR. Treatment regimens recommended in this guideline are based on early clinical efficacy trials, pharmacokinetic/pharmacodynamic (PK/PD) considerations,[152] *in vitro* AMR surveillance data,[118,120–122,138] case reports of verified treatment failures,[110,111,138] and expert opinion. Significant variations between different European countries in STI health care, patient and partner management, including follow up, and gonococcal AMR and AMR surveillance exist. Accordingly, national adoption of the European gonorrhoea guideline based on comprehensive, recent, quality-assured AMR data and an effective patient management strategy, e.g. including mandatory TOC, locally can be reasonable.[1,165,206]

Indications for therapy [1C]

- Identification of characteristic intracellular diplococci within polymorphonuclear leukocytes in a sample from a urogenital site, by Gram-stained or methylene blue-stained 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 sexual contact has confirmed gonorrhoea,[207] mother of a neonate with verified gonorrhoea, and can be considered following sexual assault. When giving treatment based on epidemiological grounds, specimen(s) for laboratory testing should be collected;
- On demonstration of a purulent urethral discharge in men or mucopurulent cervicitis in women when rapid diagnostic tests such as microscopy are not available and after specimen collection for laboratory testing. In this circumstance, empirical treatment covering also *C. trachomatis* infection should be considered.

Recommended treatment for uncomplicated *N. gonorrhoeae* infections of the urethra, cervix and rectum in adults and adolescents when the antimicrobial susceptibility of the infection is unknown[1,36,37,91,93,97–104,117]

- Ceftriaxone 1 g intramuscularly (IM) as a single dose **together with** azithromycin 2 g as a single oral dose [1C]

- If gastrointestinal side effects are anticipated: ceftriaxone 1 g IM single dose **plus** azithromycin 1 g oral dose followed by azithromycin 1 g oral dose 6–12 h later may be used to limit gastrointestinal side effects[117,161]

NOTE: Azithromycin tablets should not be taken on an empty stomach due to possible gastrointestinal side effects. If required, a snack or crackers can be given to patients before taking the azithromycin tablets.[153,154,208] For patients perceived to be at risk of vomiting, an anti-emetic can be provided.[91]

OR

- Ceftriaxone 1 g IM as a single dose [2C]

NOTE: Only recommended in settings where:

(i) comprehensive, recent and quality-assured local *in vitro* ceftriaxone susceptibility testing has shown lack of ceftriaxone resistance;
(ii) TOC is mandatory;
(iii) the patient is considered very likely to return for TOC;
(iv) doxycycline 100 mg oral dose twice daily for 7 days is administered at the same time to cover any concomitant *C. trachomatis* infection, if *C. trachomatis* infection has not been excluded by NAAT.

In other settings, ceftriaxone 1 g IM monotherapy is only an alternative option if azithromycin is not available or patient is unable to take oral medication.

Treatment when patient has history of severe hypersensitivity (e.g. anaphylaxis) to any β-lactam antimicrobial (penicillins, cephalosporins, monobactams or carbapenems)[1,36,37]

Third-generation cephalosporins, such as ceftriaxone, show negligible cross-allergy with penicillins and allergy to these cephalosporins is rare.[166–170]

Recommended treatment.

- Spectinomycin 2 g IM as a single dose [1B] **together with** azithromycin 2 g as a single oral dose [1C]
- If gastrointestinal side effects are anticipated: spectinomycin 2 g IM single dose **plus** azithromycin 1 g oral dose followed by azithromycin 1 g oral dose 6-12 h later may be used[117,161]

NOTE: See use of azithromycin 2 g for treatments of uncomplicated *N. gonorrhoeae* infections of the urethra, cervix and rectum.

Alternative treatment. For susceptible gonococcal infections, early clinical trials demonstrated that ciprofloxacin (500 mg) had high efficacy.[97,98,171] Accordingly, this is an alternative treatment when the infection has been confirmed to be susceptible to ciprofloxacin; using phenotypic AMR testing or validated and quality-assured molecular *gyrA*-based fluoroquinolone resistance testing (only for anogenital samples due to potential cross-reactions with commensal *Neisseria* species in pharyngeal samples)[63,172–175,209–211]:

- Ciprofloxacin 500 mg as a single oral dose [1B]
- Gentamicin 240 mg IM as a single dose **together with** azithromycin 2 g as a single oral dose [1B]
- If gastrointestinal side effects are anticipated: gentamicin 240 mg IM single dose **plus** azithromycin 1 g oral dose followed by azithromycin 1 g oral dose 6–12 h later may be used[117,161]

NOTE: The European Medicines Agency (EMA) has alerted a risk of serious side effects associated with the use of quinolone/fluoroquinolone antibiotics.[176] Ciprofloxacin should be avoided in people who have previously had serious side effects with any quinolone, and it should be used with caution in those aged >60 years, taking a corticosteroid, having kidney disease, and who have had an organ transplantation. However, the single ciprofloxacin 500 mg oral dose likely limits the risk of side effects. See note regarding use of azithromycin 2 g for treatments of uncomplicated *N. gonorrhoeae* infections of the urethra, cervix and rectum.

Treatment when administration of an intramuscular injection is contraindicated or refused

Multiple reports of cefixime treatment failures, PK/PD investigations, and *in vitro* resistance levels have raised serious concerns over the adequacy of 400 mg of cefixime for treatment, particularly for monotherapy and treatment of oropharyngeal gonorrhoea (https://www.ecdc.europa.eu/en/publications-data).[110,111,138,152,178–180]

Recommended treatment.

- Cefixime 400 mg as a single oral dose **together with** azithromycin 2 g as a single oral dose [1B]
- If gastrointestinal side effects are anticipated: cefixime 400 mg single oral dose **plus** azithromycin 1 g oral dose followed by azithromycin 1 g oral dose 6-12 h later may be used[117,161]

NOTE: See use of azithromycin 2 g for treatments of uncomplicated *N. gonorrhoeae* infections of the urethra, cervix and rectum.

Alternative treatment. When the infection has been confirmed before treatment to be susceptible to ciprofloxacin; using phenotypic AMR testing or validated and quality-assured molecular *gyrA*-based fluoroquinolone resistance testing (only for anogenital samples)[63,172–175,209–211]:

- Ciprofloxacin 500 mg as a single oral dose [1B].

NOTE: Co-infection with *C. trachomatis* is common in young (<30 years) heterosexual patients and MSM with gonorrhoea.[1,8,9,36,37] If treatment for gonorrhoea does not include azithromycin, doxycycline 100 mg oral dose twice daily for 7 days should be considered for possible *C. trachomatis* co-infection unless co-infection has been excluded with NAAT testing.[1,36,37]

Treatment for gonococcal infection of the pharynx or when such infection has not been excluded

Many antimicrobials, including ceftriaxone, have a lower efficacy in curing oropharyngeal gonorrhoea compared to urogenital and anorectal infection.[1,36,37,97,98,105,110,111,126,138,149,164,165,177–186]

Recommended treatment.
- Ceftriaxone 1 g IM as a single dose **together with** azithromycin 2 g as a single oral dose [1D]
- If gastrointestinal side effects are anticipated: ceftriaxone 1 g IM single dose **plus** azithromycin 1 g oral dose followed by azithromycin 1 g oral dose 6-12 h later may be used[117,161]

NOTE: See use of azithromycin 2 g for treatments of uncomplicated *N. gonorrhoeae* infections of the urethra, cervix and rectum.

Alternative regimens.
- Ceftriaxone 1 g IM as a single dose [2D]

NOTE: This regimen is only an option if azithromycin is not available or patient is unable to take oral medication.

- Ciprofloxacin 500 mg as a single oral dose [1B]

NOTE: This regimen is only an alternative for treatment when the infection has been confirmed before treatment to be susceptible; using phenotypic AMR testing or validated and quality-assured molecular *gyrA*-based fluoroquinolone resistance testing (only for anogenital samples).[63,172–175,209–211]

Recommended treatment for genital, anorectal and oropharyngeal gonococcal infection when ceftriaxone resistance identified[1,92,153,154]

The management of patients with ceftriaxone-resistant gonorrhoea or verified treatment failures following other recommended antimicrobial regimens requires advice from specialist STI clinicians and microbiologists, and should include sexual contact notification and follow-up with TOC. Where relevant, these cases should be notified to local, regional and/or national authorities as mandated by statute. Three-site testing for *N. gonorrhoeae*, including culture and AMR testing, is recommended for all patients with ceftriaxone-resistant gonorrhoea. AMR testing, when available, should inform further treatment.

- Ceftriaxone 1 g IM as a single dose **together with** azithromycin 2 g as a single oral dose [1D], i.e. when ceftriaxone monotherapy, a lower ceftriaxone dose, or another treatment regimen was given initially.
- Spectinomycin 2 g IM as a single dose [1B] **together with** azithromycin 2 g as a single oral dose [1C]
- Gentamicin 240 mg IM as a single dose **together with** azithromycin 2 g as a single oral dose [1B]

The high efficacy (100% [95%CI 95–100%]) of the gentamicin 240 mg plus azithromycin 2 g regimen for treatment of anogenital and oropharyngeal gonorrhoea was confirmed in two recent RCTs.[153,154] Notable, gentamicin 240 mg IM combined with only 1 g of azithromycin orally is suboptimal to eradicate rectal (90%) and oropharyngeal gonorrhoea (82%).[126]

NOTE: See use of azithromycin 2 g for treatments of uncomplicated *N. gonorrhoeae* infections of the urethra, cervix and rectum.

- Ertapenem 1 g IM once daily for three days [2D]

This treatment has only been used in a very small number of patients with oropharyngeal gonorrhoea resistant to a regimen of ceftriaxone with or without azithromycin.[138,146,149]

Treatment for gonococcal infections in pregnancy or when breastfeeding[199–201]

Recommended treatment.
- Ceftriaxone 1 g IM as a single dose **together with** azithromycin 2 g as a single oral dose [1D]

- If gastrointestinal side effects are anticipated: ceftriaxone 1 g IM single dose **plus** azithromycin 1 g oral dose followed by azithromycin 1 g oral dose 6-12 h later may be used[117,161]

Alternative regimen.

- Spectinomycin 2 g IM as a single dose **together with** azithromycin 2 g as a single oral dose [1D]
- If gastrointestinal side effects are anticipated: spectinomycin 2 g IM single dose **plus** azithromycin 1 g oral dose followed by azithromycin 1 g oral dose 6-12 h later may be used[117,161]

NOTE: See use of azithromycin 2 g for treatments of uncomplicated *N. gonorrhoeae* infections of the urethra, cervix and rectum.

- Ceftriaxone 1 g IM as a single dose [2D]

NOTE: Pregnancy does not significantly affect the efficacy of treatment. Pregnant and breastfeeding women should not be treated with fluoroquinolones or tetracyclines. The safety of azithromycin 2 g in pregnancy cannot be completely guaranteed but clinical experience indicates that it can be used safely. However, 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.[202]

Treatment for upper genital tract gonococcal infection

Epididymo-orchitis

- See the 'European guideline on the management of epididymo-orchitis' (https://iusti.org/treatment-guidelines/).

Pelvic inflammatory disease

- See the 'European guideline for the management of pelvic inflammatory disease' (https://iusti.org/treatment-guidelines/. . . . .).

Recommended treatment for disseminated gonococcal infection [2D]

There have been no clinical trials on the treatment of DGI since the progressive development of gonococcal AMR. Recommended treatment is based on current AMR data, observational data from case series, and the principals of treating septicaemia. Hospitalization is recommended for initial therapy,[1,17,20,36,37,203,204] and gonococcal culture and AMR testing should be performed.

Initial therapy:

- Ceftriaxone 1 g IM or intravenously (IV) every 24 hours **OR**
- Cefotaxime 1 g IV every 8 hours **OR**
- Spectinomycin 2 g IM every 12 hours.

Therapy should continue for 7 days, but may be switched 24–48 hours after substantial clinical improvement to one of the following oral regimens guided by AMR testing:

- Cefixime 400 mg oral dose twice daily **OR**
- Ciprofloxacin 500 mg oral dose twice daily.

NOTE: Ciprofloxacin should only be used when the infection has been confirmed before treatment to be susceptible; using phenotypic AMR testing or validated and quality-assured molecular *gyrA*-based fluoroquinolone resistance testing (only for anogenital samples).[63,172–175,209–211]

Recommended treatment for gonococcal conjunctivitis[1,36,37,205]

There is a lack of recent clinical data for treatment of gonococcal conjunctivitis. The eye should be irrigated frequently with sterile saline solution.

- Ceftriaxone 1 g IM as a single dose **together with** azithromycin 2 g as a single oral dose [2D]
- If gastrointestinal side effects are anticipated: ceftriaxone 1 g IM single dose **plus** azithromycin 1 g oral dose followed by azithromycin 1 g oral dose 6-12 h later may be used[117,161]

NOTE: See use of azithromycin 2 g for treatments of uncomplicated *N. gonorrhoeae* infections of the urethra, cervix and rectum.

Recommended treatment for ophthalmia neonatorum (gonococcal neonatal conjunctivitis)[1,36,37]

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

Recommended treatment for people living with HIV[1,36,37]

People living with HIV with gonorrhoea should be treated in an identical way to HIV-negative individuals.

Recommended treatment for uncomplicated Neisseria meningitidis infection of the urethra[212–214]

Individuals with uncomplicated urethritis caused by *N. meningitidis* should be treated in an identical way to patients with gonococcal urethritis.

Sexual contact notification and management of sex contact(s)

- Sexual contact notification should be performed and documented by appropriately trained professionals at the time of diagnosis to prevent reinfection and reduce onwards transmission [1B];
- Sexual contacts should be contacted and offered (and encouraged to have) testing for gonorrhoea (and other STIs) together with antimicrobial treatment if appropriate (i.e. if positive *N. gonorrhoeae* test or clinician considers contacts will not return for treatment after testing results are available) and receive counseling for gonorrhoea and other STIs [1D];
- All sexual contact(s) within the preceding 3 months of onset of symptoms or diagnosis should be tested and treated if positive [2D].[1,36,37,207] See the 'European guidelines for the management of partners of persons with sexually transmitted infections' (https://iusti.org/treatment-guidelines/).

Follow-up and test of cure

- Assessment after treatment is recommended to confirm eradication of infection, compliance with therapy, enquire about adverse effects, resolution of symptoms and signs, take a sexual history to explore the possibility of re-infection, and pursue partner notification and health promotion [1D];
- A TOC is recommended in all cases to identify persisting infection (possible treatment failure) and emerging AMR.[1,33,138,206] When symptoms and/or signs persist after treatment, culture is recommended to identify persisting infection and for AMR testing, and should be performed 3-7 days after completion of therapy, possibly supplemented a week later with a NAAT for increased sensitivity if culture is negative. TOC in asymptomatic patients can be performed with a NAAT 2 weeks after completion of treatment and ideally, all TOC-positive patients should be cultured and AMR testing performed before further treatment is given.[32,215,216] A positive TOC can be due to treatment failure, but also reinfection or, when NAATs are used, residual nucleic acid from non-viable gonococci, and needs to be followed up and interpreted in the clinical context [2C].[32,215,216]

Identification, confirmation and reporting of treatment failures

The surveillance of possible and confirmed failures with recommended treatment regimens should be enhanced, as detailed in the ECDC Response Plan.[206] As much clinical and laboratory data as feasible should be collected and reported on treatment failures, including a detailed clinical history (including all antimicrobial treatments given), the exclusion of reinfection, whole genome sequencing of pre-treatment and post-treatment gonococcal isolates or other highly discriminative molecular epidemiological typing of NAAT specimens (identifying indistinguishable isolates/genetic variants) and phenotypic and/or molecular assessment of resistance (AMR determinants) to the prescribed treatment using the gonococcal isolates or NAAT specimens.[206,217]

Notification

Gonorrhoea cases should be notified to local, regional and national authorities as mandated by statute. The ECDC is responsible for the EU/EEA-wide gonorrhoea surveillance.

Composition of the European STI guidelines editorial board

The current composition of the European STI Guidelines Editorial Board can be found at: https://iusti.org/wp-content/uploads/2019/12/Editorial_Board.pdf.

Search strategy

The present guideline was produced according to the protocol for production and revision of European STI guidelines, which has been written and approved by the IUSTI European STI Guidelines Editorial Board (https://iusti.org/wp-content/uploads/2020/04/ProtocolForProduction2020.pdf). A Medline search was conducted up to June 2020 using PubMed for articles published since the development of the 2012 European gonorrhoea guideline.[1] Search headings were kept broad (i) gonorrhoea, iii) gonorrhea or ii) *Neisseria gonorrhoeae* to include epidemiology, diagnosis, antimicrobial susceptibility/resistance, therapy, clinical trials, prevention, and control. Only publications and abstracts in the English language were considered. The Cochrane Library was searched for all entries related to gonorrhoea/gonorrhea or *Neisseria gonorrhoeae*. Relevant STI guidelines produced by the WHO (www.who.int), US Centers for Disease Control and Prevention (www.cdc.gov/std/) and the British

Association for Sexual Health and HIV (www.bashh.org) were also reviewed.

Levels of evidence and grading of recommendations

Levels of evidence and grading of recommendations that were used in the present guideline can be found in the protocol for production and revision of European STI guidelines at: https://iusti.org/wpcontent/uploads/2019/12/Euro_Guidelines_Protocol_2010.pdf

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.

Proposed date of revision

2023.

Authors' note

A list of contributing organisations can be found at: https://iusti.org/treatment-guidelines/

Acknowledgements

The authors are grateful to Chris Bignell for being the first author of the superseded 2012 European gonorrhoea guidelines,[1] and for valuable input on the present guideline to Fabian Kong, Keith Radcliffe, Raj Patel, Derek Freedman, Sébastien Fouere, Gianfranco Spiteri, and Iryna Boiko.

Declaration of conflicting interests

JR reports personal fees from GSK Pharma, Mycovia, and Nabriva Therapeutics as well as ownership of shares in GSK Pharma and AstraZeneca Pharma.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

M Unemo https://orcid.org/0000-0003-1710-2081
JS Jensen https://orcid.org/0000-0002-7464-7435

References

1. Bignell C and Unemo M; European STI Guidelines Editorial Board. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS* 2013; 24: 85–92.
2. Unemo M, Seifert HS, Hook EW 3rd, et al. Gonorrhoea. *Nat Rev Dis Primers* 2019; 5: 79.
3. Hook EW III and Handsfield HH. Gonococcal infections in the adult. In: Holmes KK and Sparling PF (eds) *Sexually transmitted diseases*. 4th ed. New York, NY: McGraw-Hill, 2008, pp. 627–645.
4. Cornelisse VJ, Williamson D, Zhang L, et al. Evidence for a new paradigm of gonorrhoea transmission: cross-sectional analysis of *Neisseria gonorrhoeae* infections by anatomical site in both partners in 60 male couples. *Sex Transm Infect* 2019; 95: 437–442.
5. Cornelisse VJ, Zhang L, Law M, et al. Concordance of gonorrhoea of the rectum, pharynx and urethra in same-sex male partnerships attending a sexual health service in Melbourne, Australia. *BMC Infect Dis* 2018; 18: 95.
6. Cornelisse VJ, Bradshaw CS, Chow EPF, et al. Oropharyngeal gonorrhea in absence of urogenital gonorrhea in sexual network of male and female participants, Australia, 2018. *Emerging Infect Dis* 2019; 25: 1373–1376.
7. Fairley CK, Cornelisse VJ, Hocking JS, et al. Models of gonorrhoea transmission from the mouth and saliva. *Lancet Infect Dis* 2019; 19: e360–e366.
8. European Centre for Disease Prevention and Control. Surveillance atlas of infectious diseases, http://atlas.ecdc.europa.eu/public/index.aspx (accessed 27 July 2020).
9. GRASP Steering Group. Antimicrobial resistance in *Neisseria gonorrhoeae* in England and Wales. Key findings from the gonococcal resistance to antimicrobials surveillance programme (GRASP 2018), https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/834924/GRASP__2018_report.pdf (accessed 27 July 2020).
10. Risley CL, Ward H, Choudhury B, et al. Geographical and demographic clustering of gonorrhoea in London. *Sex Transm Infect* 2007; 83: 481–487.
11. Reddy BSN, Khandpur S, Sethi S, et al. Gonococcal infections. In: Gupta S and Kumar B (eds) *Sexually transmitted infections*. 2nd ed. New Delhi, India: Elsevier, 2012, pp.473–493.
12. Sherrard J and Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. *Genitourin Med* 1996; 72: 422–426.
13. Lewis DA, Bond M, Butt KD, et al. 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: 588–594.
14. Barlow D and Phillips I. Gonorrhoea in women: diagnostic, clinical and laboratory aspects. *Lancet* 1978; 1: 761–764.
15. Kent CK, Chaw JK, Wong W, et al. 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.
16. Peters RPH, Nijsten N, Mutsaers J, et al. Screening of oropharynx and anorectum increases prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection in female STD clinic visitors. *Sex Transm Dis* 2011; 38: 783–787.
17. O'brien JP, Goldenberg DL and Rice PA. Disseminated gonococcal infection: a prospective analysis of 49 patients and a review of pathophysiology and immune mechanisms. *Medicine* 1983; 62: 395–406.
18. Belkacem A, Caumes E, Ouanich J, et al. Changing patterns of disseminated gonococcal infection in France: cross-sectional data 2009–2011. *Sex Transm Infect* 2013; 89: 613–615.
19. Birrell JM, Gunathilake M, Singleton S, et al. Characteristics and impact of disseminated gonococcal infection in the "top end" of Australia. *Am J Trop Med Hyg* 2019; 101: 753–760.
20. Bleich AT, Sheffield JS, Wendel GD Jr, et al. Gonococcal infection in women. *Obstet Gynecol* 2012; 119: 597–602.
21. Roth A, Mattheis C, Muenzner P, et al. Innate recognition by neutrophil granulocytes differs between *Neisseria gonorrhoeae* strains causing local or disseminating infections. *Infect Immun* 2013; 81: 2358–2370.
22. Unemo M, Bradshaw CS, Hocking JS, et al. Sexually transmitted infections: challenges ahead. *Lancet Infect Dis* 2017; 17: e235–e279.
23. Abraha M, Egli-Gany D and Low N. Epidemiological, behavioural, and clinical factors associated with antimicrobial-resistant gonorrhoea: a review. *F1000Res* 2018; 7: 400.
24. Kirkcaldy RD, Weston E, Segurado AC, et al. Epidemiology of gonorrhoea: a global perspective. *Sex Health* 2019; 16: 401–411.
25. Grentzer JM, Peipert JF, Zhao Q, et al. Risk-based screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* prior to intrauterine device insertion. *Contraception* 2015; 92: 313–318.
26. Sufrin CB and Averbach SH. Testing for sexually transmitted infections at intrauterine device insertion: an evidence-based approach. *Clin Obstet Gynecol* 2014; 57: 682–693.
27. Unemo M, Ison C. Gonorrhoea. In: Unemo M, Ballard R, et al. (eds) *Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus*. 2nd ed. Geneva, Switzerland: World Health Organization, 2013, pp.21–54.
28. Taylor SN, DiCarlo RP and 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: 995–996.
29. Thorley N and Radcliffe K. The performance and clinical utility of cervical microscopy for the diagnosis of gonorrhoea in women in the era of the NAAT. *Int J STD AIDS* 2015; 26: 656–660.
30. Jephcott AE. Microbiological diagnosis of gonorrhoea. *Genitourin Med* 1997; 73: 245–252.
31. Forni J, Miles K and Hamill M. Microscopy detection of rectal gonorrhoea in asymptomatic men. *Int J STD AIDS* 2009; 20: 797–798.
32. Wind CM, Schim van der Loeff MF, Unemo M, et al. Test of cure for anogenital gonorrhoea using modern RNA-based and DNA-based nucleic acid amplification tests: a prospective cohort study. *Clin Infect Dis* 2016; 62: 1348–1355.
33. Whiley DM, Goire N, Lahra MM, et al. The ticking time bomb: escalating antibiotic resistance in *Neisseria gonorrhoeae* is a public health disaster in waiting. *J Antimicrob Chemother* 2012; 67: 2059–2061.
34. Cook RL, Hutchison SL, Østergaard L, et al. Systematic review: non-invasive testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Ann Intern Med* 2005; 142: 914–925.
35. Whiley DM, Garland SM, Harnett G, et al. Exploring 'best practice' for nucleic acid detection of *Neisseria gonorrhoeae*. *Sex Health* 2008; 5: 17–23.
36. Fifer H, Saunders J, Soni S, et al. 2018 UK national guideline for the management of infection with *Neisseria gonorrhoeae*. *Int J STD AIDS* 2020; 31: 4–15.
37. Workowski KA and Bolan GA; CDC. Sexually transmitted diseases treatment guidelines. *MMWR Recomm Rep* 2015; 64: 1–137.
38. Centers for disease control and prevention. Recommendations for the laboratory-based detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*–2014. *MMWR Recomm Rep* 2014; 63: 1–19.
39. Harryman L, Scofield S, Macleod J, et al. 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: 27–31.
40. Van Dyck E, Ieven M, Pattyn S, et al. Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by enzyme immunoassay, culture and three nucleic acid amplification tests. *J Clin Microbiol* 2001; 39: 1751–1756.
41. Van Der Pol B, Ferrero DV, Buck-Barrington L, 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: 1008–1016.
42. Moncada J, Schachter J, Hook EW 3rd, 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 Transm Dis* 2004; 31: 273–277.
43. Chernesky MA, Martin DH, Hook EW, 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: 127–131.
44. Schachter J, Chernesky MA, Willis DE, 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: 725–728.
45. Ison C. GC NAATs: is the time right? *Sex Transm Infect* 2006; 82: 515.
46. Cornelisse VJ, Chow EP, Huffam S, et al. Increased detection of pharyngeal and rectal gonorrhea in men who have sex with men after transition from culture to nucleic acid amplification testing. *Sex Transm Dis* 2017; 44: 114–117.
47. Van Der Pol B, Hook EW 3rd, Williams JA, et al. Performance of the BD CTQx and GCQx amplified assays on the BD viper LT compared with the BD viper XTR system. *Sex Transm Dis* 2015; 42: 521–523.
48. Geelen TH, Rossen JW, Beerens AM, et al. Performance of cobas(R) 4800 and m2000 real-time assays for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in rectal and self-collected vaginal specimen. *Diagn Microbiol Infect Dis* 2013; 77: 101–105.
49. Bachmann LH, Johnson RE, Cheng H, et al. Nucleic acid amplification tests for diagnosis of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* rectal infections. *J Clin Microbiol* 2010; 48: 1827–1832.
50. Bachmann LH, Johnson RE, Cheng H, et al. Nucleic acid amplification tests for diagnosis of *Neisseria gonorrhoeae* oropharyngeal infections. *J Clin Microbiol* 2009; 47: 902–907.
51. Lunny C, Taylor D, Hoang L, et al. Self-collected versus clinician-collected sampling for chlamydia and gonorrhea screening: a systemic review and Meta-analysis. *PLoS One* 2015; 10: e0132776.
52. Coorevits L, Traen A, Bingé L, et al. Identifying a consensus sample type to test for *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium, Trichomonas vaginalis* and human papillomavirus. *Clin Microbiol Infect* 2018; 24: 1328–1332.
53. Stewart CM, Schoeman SA, Booth RA, et al. Assessment of self taken swabs versus clinician taken swab cultures for diagnosing gonorrhoea in women: single centre, diagnostic accuracy study. *BMJ* 2012; 345: e8107.
54. Boiko I, Golparian D, Krynytska I, et al. High prevalence of *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and particularly *Trichomonas vaginalis* diagnosed using US FDA-approved Aptima molecular tests and evaluation of conventional routine diagnostic tests in Ternopil, Ukraine. *APMIS* 2019; 127: 627–634.
55. Van Der Pol B, Taylor SN, Liesenfeld O, et al. Vaginal swabs are the optimal specimen for detection of genital *Chlamydia trachomatis* or *Neisseria gonorrhoeae* using the Cobas 4800 CT/NG test. *Sex Transm Dis* 2013; 40: 247–250.
56. Page-Shafer K, Graves A, Kent C, et al. Increased sensitivity of DNA amplification testing for the detection of pharyngeal gonorrhoea in men who have sex with men. *Clin Infect Dis* 2002; 34: 173–176.
57. McNally LP, Templeton DJ, Jin F, 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–e27.
58. Schachter J, Moncada J, Liska S, et al. 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: 637–642.
59. Ota KV, Tamari IE, Smieja M, 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 Transm Infect* 2009; 85: 182–186.
60. Mimiaga MJ, Helms DJ, Reisner SL, 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: 507–511.
61. Cosentino LA, Danby CS, Rabe LK, et al. Use of nucleic acid amplification testing for diagnosis of extragenital sexually transmitted infections. *J Clin Microbiol* 2017; 55: 2801–2807.
62. Bristow CC, McGrath MR, Cohen AC, et al. Comparative evaluation of 2 nucleic acid amplification tests for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* at extragenital sites. *Sex Transm Dis* 2017; 44: 398–400.
63. Smith DW, Tapsall JW and 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: 358–365.
64. Hughes G, Ison C, Field N, et al. Guidance for the detection of gonorrhoea in England. Public Health England, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/405293/170215_Gonorrhoea_testing_guidance_REVISED__2_.pdf (2014, accessed 27 July 2020).
65. Palmer H, Mallinson H, Wood RL, et al. Evaluation of the specificities of five DNA amplification methods for the detection of *Neisseria gonorrhoeae*. *J Clin Microbiol* 2003; 41: 835–837.
66. Tabrizi SN, Unemo M, Limnios AE, et al. Evaluation of six commercial nucleic acid amplification tests for the detection of *Neisseria gonorrhoeae* and other Neisseria species. *J Clin Microbiol* 2011; 49: 3610–3615.
67. Golparian D, Boräng S, Sundqvist M, et al. Evaluation of the new BD max GC Real-Time PCR assay, analytically and clinically as a supplementary test for the BD ProbeTec GC Qx amplified DNA assay, for molecular detection of *Neisseria gonorrhoeae*. *J Clin Microbiol* 2015; 53: 3935–3937.
68. Ison CA, Golparian D, Saunders P, et al. Evolution of *Neisseria gonorrhoeae* is a continuing challenge for molecular detection of gonorrhoea: false negative gonococcal *porA* mutants are spreading internationally. *Sex Transm Infect* 2013; 89: 197–201.
69. Golparian D, Tabrizi SN and Unemo M. Analytical specificity and sensitivity of the APTIMA Combo 2 and APTIMA GC assays for detection of commensal neisseria species and *Neisseria gonorrhoeae* on the

Gen-Probe panther instrument. *Sex Transm Dis* 2013; 40: 175–178.
70. Pope CF, Hay P, Alexander S, et al. Positive predictive value of the Becton Dickinson VIPER system and the ProbeTec GC Q x assay, in extracted mode, for detection of *Neisseria gonorrhoeae*. *Sex Transm Infect* 2010; 86: 465–469.
71. Whiley DM and Lahra MM; National Neisseria Network. Review of 2005 public health laboratory network *Neisseria gonorrhoeae* nucleic acid amplification tests guidelines. *Commun Dis Intell Q Rep* 2015; 39: E42–E45.
72. Field N, Clifton S, Alexander S, et al. Confirmatory assays are essential when using molecular testing for *Neisseria gonorrhoeae* in low-prevalence settings: insights from the third national survey of sexual attitudes and lifestyles (Natsal-3). *Sex Transm Infect* 2015; 91: 338–341.
73. Guy RJ, Causer LM, Klausner JD, et al. Performance and operational characteristics of point-of-care tests for the diagnosis of urogenital gonococcal infections. *Sex Transm Infect* 2017; 93: S16–S21.
74. Toskin I, Govender V, Blondeel K, et al. Call to action for health systems integration of point-of-care testing to mitigate the transmission and burden of sexually transmitted infections. *Sex Transm Infect* 2020; 96: 342–347.
75. Gaydos CA and Melendez JH. Point-by-point progress: gonorrhea point of care tests [published online ahead of print. *Expert Rev Mol Diagn* 2020; 1–11.
76. van Liere GAFS, Dukers-Muijrers NHTM, Levels L, et al. High proportion of anorectal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* after routine universal urogenital and anorectal screening in women visiting the sexually transmitted infection clinic. *Clin Infect Dis* 2017; 64: 1705–1710.
77. van Liere GA, Hoebe CJ, Niekamp AM, et al. Standard symptom- and sexual history-based testing misses anorectal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in swingers and men who have sex with men. *Sex Transm Dis* 2013; 40: 285–289.
78. van Liere GA, Hoebe CJ and Dukers-Muijrers NH. Evaluation of the anatomical site distribution of chlamydia and gonorrhoea in men who have sex with men and in high-risk women by routine testing: cross-sectional study revealing missed opportunities for treatment strategies. *Sex Transm Infect* 2014; 90: 58–60.
79. Anschuetz GL, Paulukonis E, Powers R, et al. Extragenital screening in men who have sex with men diagnoses more chlamydia and gonorrhea cases than urine testing alone. *Sex Transm Dis* 2016; 43: 299–301.
80. Moncada J, Shayevich C, Philip SS, et al. Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in rectal and oropharyngeal swabs and urine specimens from men who have sex with men with Abbott's M2000 RealTime. *Sex Transm Dis* 2015; 42: 650–651.
81. den Heijer CDJ, Hoebe CJPA, van Liere GAFS, et al. A comprehensive overview of urogenital, anorectal and oropharyngeal *Neisseria gonorrhoeae* testing and diagnoses among different STI care providers: a cross-sectional study. *BMC Infect Dis* 2017; 17: 290.
82. Trebach JD, Chaulk CP, Page KR, et al. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* among women reporting extragenital exposures. *Sex Transm Dis* 2015; 42: 233–239.
83. Dombrowski JC. Do women need screening for extragenital gonococcal and chlamydial infections? *Sex Transm Dis* 2015; 42: 240–242.
84. Wallace H, Loftus-Keeling M, Ward H, et al. O022 rectal chlamydia infection in women – have we been missing the point? *Sex Transm Infect* 2016; 92: A8.
85. Wilson J, Wallace H, Loftus-Keeling M, et al. 4 Clinician-taken extra-genital samples for gonorrhoea and chlamydia in women and MSM compared with self-taken samples analysed separately and self-taken pooled samples. *Sex Transm Infect* 2017; 93: A26.
86. Sultan B, White JA, Fish R, et al. The "3 in 1" study: pooling self-taken pharyngeal, urethral, and rectal samples into a single sample for analysis for detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in men who have sex with men. *J Clin Microbiol* 2016; 54: 650–656.
87. Durukan D, Read TRH, Bradshaw CS, et al. Pooling pharyngeal, anorectal and urogenital samples for screening asymptomatic men who have sex with men for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *J Clin Microbiol* 2020; 58: e01969–19.
88. Badman SG, Bell SFE, Dean JA, et al. Reduced sensitivity from pooled urine, pharyngeal and rectal specimens when using a molecular assay for the detection of chlamydia and gonorrhoea near the point of care. *Sex Health* 2020; 17: 15–21.
89. De Baetselier I, Vuylsteke B, Yaya I, et al. To pool or not to pool samples for sexually transmitted infections detection in men who have sex with men? An evaluation of a new pooling method using the GeneXpert instrument in West-Africa. *Sex Transm Dis* 2020; 47: 556–561.
90. Romanowski B, Robinson J and Wong T. Gonococcal infections chapter. https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/std-mts/sti-its/cgsti-ldcits/assets/pdf/section-5-6-eng.pdf (2013, accessed 29 July 2020).
91. Australasian Sexual Health Alliance (ASHA). Gonorrhoea. http://www.sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea#management (2018, accessed 29 July 2020).
92. World Health Organization (WHO). *WHO guidelines for the treatment of Neisseria gonorrhoeae*. Geneva: WHO, 2016.
93. Unemo M and Workowski K. Dual antimicrobial therapy for gonorrhoea: what is the role of azithromycin? *Lancet Infect Dis* 2018; 18: 486–488.
94. Bignell C and Garley J. Azithromycin in the treatment of infection with *Neisseria gonorrhoeae*. *Sex Transm Infect* 2010; 86: 422–426.
95. Handsfield HH, Dalu ZA, Martin DH, et al. Multicenter trial of single-dose azithromycin vs ceftriaxone in the treatment of uncomplicated gonorrhoea. *Sex Trans Dis* 1994; 21: 107–111.

96. Mensforth S and Ross JDC. Should we still use azithromycin for gonorrhoea treatment? *Sex Health* 2019; 16: 442–448.
97. Moran JS and Levine WC. Drugs of choice in the treatment of uncomplicated gonococcal infection. *Clin Infect Dis* 1995; 20: S47–S65.
98. Newman LM, Moran JS and Workowski KA. Update on the management of gonorrhoea in adults in the United States. *Clin Infect Dis* 2007; 44: S84–101.
99. Ito S, Yasuda M, Hatazaki K, et al. Microbiological efficacy and tolerability of a single-dose regimen of 1 g of ceftriaxone in men with gonococcal urethritis. *J Antimicrob Chemother* 2016; 71: 2559–2562.
100. Muratani T, Inatomi H, Ando Y, et al. Single dose 1 g ceftriaxone for urogenital and pharyngeal infection caused by *Neisseria gonorrhoeae*. *Int J Urol* 2008; 15: 837–842.
101. Japanese Society of Sexually Transmitted Infections. Gonococcal infection. Sexually transmitted infections, diagnosis and treatment guidelines 2011. *Jpn J Sex Transm Dis* 2011; 2252–59 (in Japanese).
102. Boiko I, Golparian D, Krynytska I, et al. Antimicrobial susceptibility of *Neisseria gonorrhoeae* isolates and treatment of gonorrhoea patients in Ternopil and Dnipropetrovsk regions of Ukraine, 2013–2018. *APMIS* 2019; 127: 503–509.
103. Unemo M, Shipitsyna E and Domeika M; Eastern European Sexual and Reproductive Health (EE SRH) Network Antimicrobial Resistance Group. Recommended antimicrobial treatment of uncomplicated gonorrhoea in 2009 in 11 east European countries: implementation of a *Neisseria gonorrhoeae* antimicrobial susceptibility programme in this region is crucial. *Sex Transm Infect* 2010; 86: 442–444.
104. Tapsall JW. Implications of current recommendations for third-generation cephalosporin use in the WHO Western pacific region following the emergence of multiresistant gonococci. *Sex Transm Infect* 2009; 85: 256–258.
105. Moran JS. Treating uncomplicated *Neisseria gonorrhoeae* infections: is the anatomic site of infection important? *Sex Transm Dis* 1995; 22: 39–47.
106. Hananta IPY, De Vries HJC, van Dam AP, et al. Persistence after treatment of pharyngeal gonococcal infections in patients of the STI clinic, Amsterdam, The Netherlands, 2012–2015: a retrospective cohort study. *Sex Transm Infect* 2017; 93: 467–471.
107. Sathia L, Ellis B, Phillip S, et al. Pharyngeal gonorrhoea – is dual therapy the way forward? *Int J STD AIDS* 2007; 18: 647–648.
108. Unemo M and Shafer WM. Antimicrobial resistance in *Neisseria gonorrhoeae* in the 21st century: past, evolution, and future. *Clin Microbiol Rev* 2014; 27: 587–613.
109. Golparian D, Harris SR, Sánchez-Busó L, et al. Genomic evolution of *Neisseria gonorrhoeae* since the preantibiotic era (1928–2013): antimicrobial use/misuse selects for resistance and drives evolution. *BMC Genomics* 2020; 21: 116.
110. Unemo M and Nicholas RA. Emergence of multidrug-resistant, extensively drug-resistant and untreatable gonorrhea. *Future Microbiol* 2012; 7: 1401–1422.
111. Unemo M. Current and future antimicrobial treatment of gonorrhoea – the rapidly evolving *Neisseria gonorrhoeae* continues to challenge. *BMC Infect Dis* 2015; 15: 364.
112. Barbee LA, Soge OO, Holmes KK, et al. In vitro synergy testing of novel antimicrobial combination therapies against *Neisseria gonorrhoeae*. *J Antimicrob Chemother* 2014; 69: 1572–1578.
113. Pereira R, Cole MJ and Ison CA. Combination therapy for gonorrhoea: in vitro synergy testing. *J Antimicrob Chemother* 2013; 68: 640–643.
114. Wind CM, de Vries HJ and van Dam AP. Determination of in vitro synergy for dual antimicrobial therapy against resistant *Neisseria gonorrhoeae* using etest and agar dilution. *Int J Antimicrob Agents* 2015; 45: 305–308.
115. Furuya R, Nakayama H, Kanayama A, et al. In vitro synergistic effects of double combinations of beta-lactams and azithromycin against clinical isolates of *Neisseria gonorrhoeae*. *J Infect Chemother* 2006; 12: 172–176.
116. Singh V, Bala M, Bhargava A, et al. In vitro efficacy of 21 dual antimicrobial combinations comprising novel and currently recommended combinations for treatment of drug resistant gonorrhoea in future era. *PLoS One* 2018; 13: e0193678.
117. Kong FYS, Horner P, Unemo M, et al. Pharmacokinetic considerations regarding the treatment of bacterial sexually transmitted infections with azithromycin: a review. *J Antimicrob Chemother* 2019; 74: 1157–1166.
118. Harris SR, Cole MJ, Spiteri G, et al. Public health surveillance of multidrug-resistant clones of *Neisseria gonorrhoeae* in Europe: a genomic survey. *Lancet Infect Dis* 2018; 18: 758–768.
119. Barbee LA, Kerani RP, Dombrowski JC, et al. A retrospective comparative study of 2-drug oral and intramuscular cephalosporin treatment regimens for pharyngeal gonorrhea. *Clin Infect Dis* 2013; 56: 1539–1545.
120. Cole MJ, Spiteri G, Jacobsson S, et al. Is the tide turning again for cephalosporin resistance in *Neisseria gonorrhoeae* in Europe? Results from the 2013 European surveillance. *BMC Infect Dis* 2015; 15: 321.
121. Cole MJ, Spiteri G, Jacobsson S, et al. Overall low extended-spectrum cephalosporin resistance but high azithromycin resistance in *Neisseria gonorrhoeae* in 24 European countries, 2015. *BMC Infect Dis* 2017; 17: 617.
122. Day MJ, Spiteri G, Jacobsson S, et al. Stably high azithromycin resistance and decreasing ceftriaxone susceptibility in *Neisseria gonorrhoeae* in 25 European countries, 2016. *BMC Infect Dis* 2018; 18: 609.
123. Horner PJ. Azithromycin antimicrobial resistance and genital *Chlamydia trachomatis* infection: duration of therapy may be the key to improving efficacy. *Sex Transm Infect* 2012; 88: 154–156.

124. Unemo M, Clarke E, Boiko I, et al.; ECCG Core Group. Adherence to the 2012 European gonorrhoea guideline in the WHO European region according to the 2018–19 international union against sexually transmitted infections European collaborative clinical group gonorrhoea survey. *Int J STD AIDS* 2020; 31: 69–76.
125. Fifer H, Cole M, Hughes G, et al. Sustained transmission of high-level azithromycin-resistant *Neisseria gonorrhoeae* in England: an observational study. *Lancet Infect Dis* 2018; 18: 573–581.
126. Ross JDC, Brittain C, Cole M, et al. Gentamicin compared with ceftriaxone for the treatment of gonorrhoea (G-ToG): a randomised non-inferiority trial. *Lancet* 2019; 393: 2511–2520.
127. Tapsall JW, Schultz TR, Limnios EA, et al. Failure of azithromycin therapy in gonorrhoea and discorrelation with laboratory parameters. *Sex Trans Dis* 1998; 25: 505–508.
128. Cole MJ, Tan W, Fifer H, et al. Gentamicin, azithromycin and ceftriaxone in the treatment of gonorrhoea: the relationship between antibiotic MIC and clinical outcome. *J Antimicrob Chemother* 2020; 75: 449–457.
129. Unemo M and Jensen JS. Antimicrobial-resistant sexually transmitted infections: gonorrhoea and *Mycoplasma genitalium*. *Nat Rev Urol* 2017; 14: 139–152.
130. Crokaert F, Hubloux A and Cauchie P. A phase I determination of azithromycin in plasma during a 6-week period in normal volunteers after a standard dose of 500mg once daily for 3 days. *Clin Drug Investig* 1998; 16: 161–166.
131. Zheng S, Matzneller P, Zeitlinger M, et al. Development of a population pharmacokinetic model characterizing the tissue distribution of azithromycin in healthy subjects. *Antimicrob Agents Chemother* 2014; 58: 6675–6684.
132. Matzneller P, Krasniqi S, Kinzig M, et al. Blood, tissue, and intracellular concentrations of azithromycin during and after end of therapy. *Antimicrob Agents Chemother* 2013; 57: 1736–1742.
133. Clifton S, Town K, Furegato M, et al. Is previous azithromycin treatment associated with azithromycin resistance in *Neisseria gonorrhoeae*? A cross-sectional study using national surveillance data in England. *Sex Transm Infect* 2018; 94: 421–426.
134. Kenyon C, Buyze J, Spiteri G, et al. Population-level antimicrobial consumption is associated with decreased antimicrobial susceptibility in *Neisseria gonorrhoeae* in 24 European countries: an ecological analysis. *J Infect Dis* 2020; 221: 1107–1116.
135. Kirkcaldy RD, Bartoces MG, Soge OO, et al. Antimicrobial drug prescription and *Neisseria gonorrhoeae* susceptibility, United States, 2005–2013. *Emerging Infect Dis* 2017; 23: 1657–1663.
136. Olesen SW, Torrone EA, Papp JR, et al. Azithromycin susceptibility among *Neisseria gonorrhoeae* isolates and seasonal macrolide use. *J Infect Dis* 2019; 219: 619–623.
137. Wind CM, de Vries E, Schim van der Loeff MF, et al. Decreased azithromycin susceptibility of *Neisseria gonorrhoeae* isolates in patients recently treated with azithromycin. *Clin Infect Dis* 2017; 65: 37–45.
138. Unemo M, Lahra MM, Cole M, et al. World health organization global gonococcal antimicrobial surveillance program (WHO GASP): review of new data and evidence to inform international collaborative actions and research efforts. *Sex Health* 2019; 16: 412–425.
139. Nakayama S, Shimuta K, Furubayashi K, et al. New ceftriaxone- and multidrug-resistant *Neisseria gonorrhoeae* strain with a novel mosaic *penA* gene isolated in Japan. *Antimicrob Agents Chemother* 2016; 60: 4339–4341.
140. Lahra MM, Martin I, Demczuk W, et al. Cooperative recognition of internationally disseminated ceftriaxone-resistant *Neisseria gonorrhoeae* strain. *Emerg Infect Dis* 2018; 24: 735–740.
141. Lefebvre B, Martin I, Demczuk W, et al. Ceftriaxone-resistant *Neisseria gonorrhoeae*, Canada, 2017. *Emerg Infect Dis* 2018; 24: 381–383.
142. Terkelsen D, Tolstrup J, Johnsen CH, et al. Multidrug-resistant *Neisseria gonorrhoeae* infection with ceftriaxone resistance and intermediate resistance to azithromycin, Denmark. *Euro Surveill* 2017; 22: 17-00659.
143. Poncin T, Fouere S, Braille A, et al. Multidrug-resistant *Neisseria gonorrhoeae* failing treatment with ceftriaxone and doxycycline in France, November 2017. *Euro Surveill* 2018; 23: 1800264.
144. Golparian D, Rose L, Lynam A, et al. Multidrug-resistant *Neisseria gonorrhoeae* isolate, belonging to the internationally spreading Japanese FC428 clone, with ceftriaxone resistance and intermediate resistance to azithromycin, Ireland, August 2018. *Euro Surveill* 2018: 23: 1800617.
145. Ko KKK, Chio MTW, Goh SS, et al. First case of ceftriaxone-resistant multidrug-resistant *Neisseria gonorrhoeae* in Singapore. *Antimicrob Agents Chemother* 2019; 63: e02624-18.
146. Eyre DW, Town K, Street T, et al. Detection in the United Kingdom of the *Neisseria gonorrhoeae* FC428 clone, with ceftriaxone resistance and intermediate resistance to azithromycin, October to December 2018. *Euro Surveill* 2019; 24: 1900147.
147. Lee K, Nakayama SI, Osawa K, et al. Clonal expansion and spread of the ceftriaxone-resistant *Neisseria gonorrhoeae* strain FC428, identified in Japan in 2015, and closely related isolates. *J Antimicrob Chemother* 2019; 74: 1812–1819.
148. Chen SC, Han Y, Yuan LF, et al. Identification of internationally disseminated ceftriaxone-resistant *Neisseria gonorrhoeae* strain FC428, China. *Emerging Infect Dis* 2019; 25: 1427–1429.
149. Eyre DW, Sanderson ND, Lord E, et al. Gonorrhoea treatment failure caused by a *Neisseria gonorrhoeae* strain with combined ceftriaxone and high-level azithromycin resistance, England, February 2018. *Euro Surveill* 2018; 23: 1800323.
150. Jennison AV, Whiley D, Lahra MM, et al. Genetic relatedness of ceftriaxone-resistant and high-level azithromycin resistant *Neisseria gonorrhoeae* cases, United

Kingdom and Australia, February to April 2018. *Euro Surveill* 2019; 24: 1900118.
151. Hernando Rovirola C, Spiteri G, Sabidó M, et al. Antimicrobial resistance in *Neisseria gonorrhoeae* isolates from foreign-born population in the European gonococcal antimicrobial surveillance programme. *Sex Transm Infect* 2020; 96: 204–210.
152. Chisholm S, Mouton J, Lewis D, et al. Cephalosporin MIC creep among gonococci: time for a pharmacodynamic rethink? *J Antimicrob Chemother* 2010; 65: 2141–2148.
153. Rob F, Klubalová B, Nyčová E, et al. Gentamicin 240 mg plus azithromycin 2 g vs. ceftriaxone 500 mg plus azithromycin 2 g for treatment of rectal and pharyngeal gonorrhoea: a randomized controlled trial. *Clin Microbiol Infect* 2020; 26: 207–212.
154. Kirkcaldy RD, Weinstock HS, Moore PC, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. *Clin Infect Dis* 2014; 59: 1083–1091.
155. Girard D, Finegan SM, Dunne MW, et al. Enhanced efficacy of single-dose versus multi-dose azithromycin regimens in preclinical infection models. *J Antimicrob Chemother* 2005; 56: 365–371.
156. Canada P. *Zithromax product information*. Quebec, Canada: Pfizer, 2013.
157. Di Paolo A, Barbara C, Chella A, et al. Pharmacokinetics of azithromycin in lung tissue, bronchial washing, and plasma in patients given multiple oral doses of 500 and 1000 mg daily. *Pharmacol Res* 2002; 46: 545–550.
158. Amsden GW, Nafziger AN and Foulds G. Pharmacokinetics in serum and leukocyte exposures of oral azithromycin, 1,500 milligrams, given over a 3- or 5-day period in healthy subjects. *Antimicrob Agents Chemother* 1999; 43: 163–165.
159. Kong F. Is the current treatment of urogenital and anorectal chlamydia infection appropriate? 2017.
160. Foulds G and Johnson RB. Selection of dose regimens of azithromycin. *J Antimicrob Chemother* 1993; 31: 39–50.
161. Read TRH, Fairley CK, Murray GL, et al. Outcomes of resistance-guided sequential treatment of *Mycoplasma genitalium* infections: a prospective evaluation. *Clin Infect Dis* 2019; 68: 554–560.
162. Hook EW 3rd, Martin DH, Stephens J, et al. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. *Sex Transm Dis* 2002; 29: 486–490.
163. Takahashi S, Kiyota H, Ito S, et al. Clinical efficacy of a single two gram dose of azithromycin extended release for male patients with urethritis. *Antibiotics (Basel)* 2014; 3: 109–120.
164. Alirol E, Wi TE, Bala M, et al. Multidrug-resistant gonorrhea: a research and development roadmap to discover new medicines. *PLoS Med* 2017; 14: e1002366.
165. Tapsall JW, Ndowa F, Lewis DA, et al. Meeting the public health challenge of multidrug- and extensively drug-resistant *Neisseria gonorrhoeae*. *Expert Rev Anti Infect Ther* 2009; 7: 821–834.
166. Pichichero ME and Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: a meta-analysis. *Otolaryngol Head Neck Surg* 2007; 136: 340–347.
167. Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. *Am J Med* 2008; 121: 572–576.
168. Zagursky RJ and Pichichero ME. Cross-reactivity in beta-lactam allergy. *J Allergy Clin Immunol Pract* 2018; 6: 72–81.e1.
169. Novalbos A, Sastre J, Cuesta J, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. *Clin Exp Allergy* 2001; 31: 438–443.
170. Romano A, Gaeta F, Valluzzi RL, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. *J Allergy Clin Immunol* 2010; 126: 994–999.
171. Moran JS. Ciprofloxacin for gonorrhea – 250 mg or 500 mg? *Sex Transm Dis* 1996; 23: 165–167.
172. Pond MJ, Hall CL, Miari VF, et al. Accurate detection of *Neisseria gonorrhoeae* ciprofloxacin susceptibility directly from genital and extragenital clinical samples: towards genotype-guided antimicrobial therapy. *J Antimicrob Chemother* 2016; 71: 897–902.
173. Allan-Blitz LT, Wang X and Klausner JD. Wild-type gyrase a genotype of *Neisseria gonorrhoeae* predicts in vitro susceptibility to ciprofloxacin: a systematic review of the literature and meta-analysis. *Sex Transm Dis* 2017; 44: 261–265.
174. Allan-Blitz LT, Humphries RM, Hemarajata P, et al. Implementation of a rapid genotypic assay to promote targeted ciprofloxacin therapy of *Neisseria gonorrhoeae* in a large health system. *Clin Infect Dis* 2017; 64: 1268–1270.
175. Hadad R, Cole MJ, Ebeyan S, et al. Evaluation of the SpeeDx *ResistancePlus*® GC and SpeeDx GC 23S 2611 (beta) molecular assays for prediction of antimicrobial resistance/susceptibility to ciprofloxacin and azithromycin in *Neisseria gonorrhoeae J Antimicrob Chemother* 2020. In press.
176. European Medicines Agency. Review of quinolone- and fluoroquinolone-containing medicinal products, https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products (2018, accessed 29 July 2020).
177. Gratrix J, Bergman J, Egan C, et al. Retrospective review of pharyngeal gonorrhea treatment failures in Alberta. *Sex Transm Dis* 2013; 40: 877–879.
178. Allen VG, Mitterni L, Seah C, et al. *Neisseria gonorrhoeae* treatment failure and susceptibility to cefixime in Toronto, Canada. *JAMA* 2013; 309: 163–170.
179. Barbee LA, Nayak SU, Blumer JL, et al. A phase 1 pharmacokinetic and safety study of extended-duration, high-dose cefixime for cephalosporin-resistant *Neisseria gonorrhoeae* in the pharynx. *Sex Transm Dis* 2018; 45: 677–683.
180. Lewis DA. Will targeting oropharyngeal gonorrhoea delay the further emergence of drug-resistant *Neisseria gonorrhoeae* strains? *Sex Transm Infect* 2015; 91: 234–237.

181. Taylor SN, Marrazzo J, Batteiger BE, et al. Single-dose zoliflodacin (ETX0914) for treatment of urogenital gonorrhea. *N Engl J Med* 2018; 379: 1835–1845.
182. Ota KV, Fisman DN, Tamari IE, 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: 1237–1243.
183. Fifer H, Natarajan U, Jones L, et al. Failure of dual antimicrobial therapy in treatment of gonorrhea. *N Engl J Med* 2016; 374: 2504–2506.
184. Ohnishi M, Golparian D, Shimuta 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: 3538–3545.
185. Taylor SN, Morris DH, Avery AK, et al. Gepotidacin for the treatment of uncomplicated urogenital gonorrhea: a phase 2, randomized, dose-ranging, single-oral dose evaluation. *Clin Infect Dis* 2018; 67: 504–512.
186. Barbee LA, Soge OO, Morgan J, et al. Gentamicin alone inadequate to eradicate *Neisseria gonorrhoeae* from the pharynx. *Clin Infect Dis*. Epub ahead of print 12 November 2019. DOI:10.1093/cid/ciz1109.
187. Ohnishi M, Watanabe Y, Ono E, et al. Spread of a chromosomal cefixime-resistant *penA* gene among different *Neisseria gonorrhoeae* lineages. *Antimicrob Agents Chemother* 2010; 54: 1060–1067.
188. Igawa G, Yamagishi Y, Lee KI, et al. *Neisseria cinerea* with high ceftriaxone MIC is a source of ceftriaxone and cefixime resistance-mediating *penA* sequences in *Neisseria gonorrhoeae*. *Antimicrob Agents Chemother* 2018; 62: 17. e02069-17.
189. Blandizzi C, Malizia T, Lupetti A, et al. Periodontal tissue disposition of azithromycin in patients affected by chronic inflammatory periodontal diseases. *J Periodontol* 1999; 70: 960–966.
190. Foulds G, Shepard RM and Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. *J Antimicrob Chemother* 1990; 25: 73–82.
191. Chisholm SA, Quaye N, Cole MJ, et al. An evaluation of gentamicin susceptibility of *Neisseria gonorrhoeae* isolates in Europe. *J Antimicrob Chemother* 2011; 66: 592–595.
192. Mann LM, Kirkcaldy RD, Papp JR, et al. Susceptibility of *Neisseria gonorrhoeae* to gentamicin-gonococcal isolate surveillance project, 2015. *Sex Transm Dis* 2018; 45: 96–98.
193. Bala M, Singh V, Philipova I, et al. Gentamicin in vitro activity and tentative gentamicin interpretation criteria for the CLSI and calibrated dichotomous sensitivity disc diffusion methods for *Neisseria gonorrhoeae*. *J Antimicrob Chemother* 2016; 71: 1856–1859.
194. Liu JW, Xu WQ, Zhu XY, et al. Gentamicin susceptibility of *Neisseria gonorrhoeae* isolates from 7 provinces in China. *Infect Drug Resist* 2019; 12: 2471–2476.
195. Unemo M, Golparian D, Limnios A, et al. In vitro activity of ertapenem versus ceftriaxone against *Neisseria gonorrhoeae* isolates with highly diverse ceftriaxone MIC values and effects of ceftriaxone resistance determinants: ertapenem for treatment of gonorrhea? *Antimicrob Agents Chemother* 2012; 56: 3603–3609.
196. Yang F, Yan J, Zhang J, et al. Evaluation of alternative antibiotics for susceptibility of gonococcal isolates from China. *Int J Antimicrob Agents* 2020; 55: 105846.
197. Quaye N, Cole MJ and Ison CA. Evaluation of the activity of ertapenem against gonococcal isolates exhibiting a range of susceptibilities to cefixime. *J Antimicrob Chemother* 2014; 69: 1568–1571.
198. Lagacé-Wiens PRS, Adam HJ, Laing NM, et al. Antimicrobial susceptibility of clinical isolates of *Neisseria gonorrhoeae* to alternative antimicrobials with therapeutic potential. *J Antimicrob Chemother* 2017; 72: 2273–2277.
199. Ramus RM, Sheffield JS, Mayfield JA, et al. A randomised trial that compared oral cefixime and intramuscular ceftriaxone for the treatment of gonorrhoea in pregnancy. *Am J Obstet Gynecol* 2001; 185: 629–632.
200. Brocklehurst P. Antibiotics for gonorrhoea in pregnancy. *Cochrane Database Syst Rev* 2002; 2: CD000098.
201. Cavenee MR, Farris JR, Spalding TR, et al. Treatment of gonorrhea in pregnancy. *Obstet Gynecol* 1993; 81: 33–38.
202. Sandoz Limited. SPC on azithromycin, www.medicines.org.uk/EMC/medicine/21720/SPC/Azithromycin+500mg+Tablets/#PREGNANCY (accessed 27 July 2020).
203. Wise CM, Morris CR, Wasilauskas BL, et al. Gonococcal arthritis in an era of increasing penicillin resistance. Presentations and outcomes in 41 recent cases (1985-1991). *Arch Intern Med* 1994; 154: 2690–2695.
204. Thompson SE. Treatment of disseminated gonococcal infections. *Sex Transm Dis* 1979; 6: 181–184.
205. Haimovici R and Roussel TJ. Treatment of gonococcal conjunctivitis with single-dose intramuscular ceftriaxone. *Am J Ophthalmol* 1989; 107: 511–514.
206. European Centre for Disease Prevention and Control (ECDC). *Response plan to control and manage the threat of multi- and extensively drug-resistant gonorrhoea in* Europe, www.ecdc.europa.eu/en/publications-data/response-plan-control-and-manage-threat-multi-and-extensively-drug-resistant (accessed 27 July 2020).
207. Tiplica GS, Radcliffe K, Evans C, et al. 2015 European guidelines for the management of partners of persons with sexually transmitted infections. *J Eur Acad Dermatol Venereol* 2015; 29: 1251–1257.
208. Hook EW, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. *J Infect Dis* 2010; 201: 1729–1735.
209. Sadiq ST, Mazzaferri F and Unemo M. Rapid accurate point-of-care tests combining diagnostics and antimicrobial resistance prediction for *Neisseria gonorrhoeae* and *Mycoplasma genitalium*. *Sex Transm Infect* 2017; 93: S65–S68.

210. Low N and Unemo M. Molecular tests for the detection of antimicrobial resistant *Neisseria gonorrhoeae*: when, where, and how to use? *Curr Opin Infect Dis* 2016; 29: 45–51.
211. Donà V, Low N, Golparian D, et al. Recent advances in the development and use of molecular tests to predict antimicrobial resistance in *Neisseria gonorrhoeae*. *Expert Rev Mol Diagn* 2017; 17: 845–859.
212. Bazan JA, Peterson AS, Kirkcaldy RD, et al. Notes from the field: Increase in *Neisseria meningitidis*-associated urethritis among men at two sentinel clinics – Columbus, Ohio, and Oakland county, Michigan, 2015. *MMWR Morb Mortal Wkly Rep* 2016; 65: 550–552.
213. Bazan JA, Turner AN, Kirkcaldy RD, et al. Large cluster of *Neisseria meningitidis* urethritis in Columbus, Ohio, 2015. *Clin Infect Dis* 2017; 65: 92–99.
214. Retchless AC, Kretz CB, Chang HY, et al. Expansion of a urethritis-associated *Neisseria meningitidis* clade in the United States with concurrent acquisition of *N. gonorrhoeae* alleles. *BMC Genomics* 2018; 19: 176.
215. Hjelmevoll SO, Olsen ME, Sollid JU, et al. Appropriate time for test-of-cure when diagnosing gonorrhoea with a nucleic acid amplification test. *Acta Derm Venereol* 2012; 92: 316–319.
216. Bachmann LH, Desmond RA, Stephens J, et al. 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: 3596–3601.
217. Buckley C, Beatson SA, Limnios A, et al. Whole-genome sequencing as an improved means of investigating *Neisseria gonorrhoeae* treatment failures. *Sex Health* 2019; 16: 500–507.