Expert Committee recommendation

The Expert Committee endorsed the inclusion of the following medicines for use in sexually transmitted infections: • Neisseria gonorrhoeae: first-choice therapy is ceftriaxone in combination with azithromycin and second-choice therapy is cefixime in combination with azithromycin, or gentamicin or spectinomycin. • Chlamydia trachomatis: first-choice therapy is azithromycin or doxycycline. • Trichomonas vaginalis: first-choice therapy is metronidazole. • Syphilis: first-choice therapy is benzathine benzylpenicillin or procaine benzylpenicillin (EMLc) or benzylpenicillin, and second-choice therapy is procaine benzylpenicillin (EML). The Expert Committee recommended the addition of erythromycin eye ointment to Section 21.1 of the EMLc for use in Chlamydia trachomatis and Neisseria gonorrhoeae as first-choice therapy in neonates for both infections.

Background

Although there are a range of causative agents of urethritis, or inflammation of the urethra, the focus here is sexually transmitted infections (STIs). The McMaster application targeted comparative empirical therapy or comparative antimicrobials for Gonococcus and Chlamydia trachomatis, the two most common pathogens in infectious urethritis; syphilis was also included. The application from the WHO Department of Reproductive Health and Research was based on updated WHO treatment guidelines for gonorrhoea, syphilis and chlamydia. STIs represent a major burden of disease worldwide and have significant negative effects on well-being. Gonorrhoea, syphilis and chlamydia often go undiagnosed and, if untreated, can result in serious complications such as pelvic inflammatory disease, infertility, ectopic pregnancy and miscarriage. Risk of infection with HIV is also increased in patients infected with gonorrhoea, syphilis or chlamydia.
For treatment of urethritis due to C. trachomatis, one review of 23 randomized controlled trials (RCTs, 2384 participants) compared azithromycin with doxycycline and reported a non-significant summary estimate in favour of doxycycline (absolute risk benefit 1.5%; 95% confidence interval (CI) −0.1% to 3.1%) (1). An earlier review (12 RCTs; 1543 participants) also reported no difference between these two antibiotics for microbiological cure rates (risk difference 0.01; 95% CI −0.01 to −0.02%) (2). However, another systematic review by the same first author found that clinical cure was significantly lower in studies since 2009 (67%) than in those before 2009 (85%), which raises the question of how useful azithromycin remains given the increase in observed resistance rates (3). The risk–benefit profile of doxycycline and the lower clinical cure rates in more recent studies with azithromycin support the use of doxycycline. This was confirmed by a recent non-inferiority trial, which reported that failure rates (0 in the doxycycline group, 5 in the azithromycin group) exceeded the margin for non-inferiority and concluded that non-inferiority was not established (4). Nevertheless, azithromycin still appears to be the best choice if adherence to a multi-day regimen is a concern. A review of single-dose azithromycin versus erythromycin and amoxicillin for C. trachomatis urethritis during pregnancy (8 RCTs; 587 participants) found no difference in treatment success between the two groups (odds ratio (OR) 1.46; 95% CI 0.56–3.78) (5). Fewer adverse events were seen with azithromycin than with erythromycin (OR 0.11; 95% CI 0.07–0.18); erythromycin is thus not an ideal treatment for this indication given its poor risk–benefit profile. Two systematic reviews comparing azithromycin with benzathine benzylpenicillin for syphilis were identified (6, 7). The newer review (3 RCTs) reported no difference (6) but confidence intervals exceeded those defined in the application for non-inferiority; the older, 2008, review (4 RCTs) showed better serological cure with benzathine benzylpenicillin (OR 1.75; 95% CI 1.03–2.97) (7). The applicant considered that the evidence favours doxycycline over azithromycin for C. trachomatis urethritis and shows a questionable advantage of benzathine benzylpenicillin over azithromycin for the treatment of syphilis.

### Guidelines

Given the increase in fluoroquinolone resistance in gonococcal infections, the highest-ranked guidelines specific for urethritis, developed by the European Association of Urology, recommend ceftriaxone or cefixime, 800 mg, plus azithromycin for empirical treatment (8). They list azithromycin as the preferred antibiotic for Chlamydia and Mycoplasma infection and doxycycline as the preferred choice for Ureaplasma urealyticum. The European guidelines on the management of non-gonococcal urethritis recommend doxycycline as the preferred antibiotic, and tetracycline or azithromycin as alternatives (9). Azithromycin is a second-line agent and is recommended for Mycoplasma genitalium infection; it should not be used routinely because of concern about macrolide resistance in M. genitalium. For persistent or recurrent non-gonococcal urethritis, if doxycycline was used as the first-line treatment, azithromycin and metronidazole can be used if Trichomonas vaginalis is prevalent in the local population. However, if azithromycin was used as first-line treatment, the recommended regimen is moxifloxacin and metronidazole. United Kingdom guidelines for the management of non-gonococcal urethritis recommend doxycycline as the most effective treatment option, or a single dose of azithromycin with ofloxacin as an alternative (10). Guidelines from CDC (Centers for Disease Control and Prevention) include erythromycin, levofloxacin, or ofloxacin as alternatives to first-line regimens of azithromycin or doxycycline (11). The 2016 guideline on syphilis published by WHO (12) recommends benzathine benzylpenicillin, or procaine benzylpenicillin as the next best alternative, for first-line treatment of both adults and children. Alternatives for patients who are allergic to penicillin include doxycycline. The use of ceftriaxone or azithromycin or erythromycin is discouraged unless there are no other options. Aqueous benzylpenicillin is recommended for congenital syphilis, with procaine benzylpenicillin as an alternative. The United Kingdom guidelines from 2015 also recommend benzathine benzylpenicillin as first-line therapy, and azithromycin or doxycycline as a second-line alternative, with a caution about increasing resistance to macrolides (13). Other alternative regimens include ceftriaxone and amoxicillin, and erythromycin only if no other options are available. For neurosyphilis, procaine benzylpenicillin with concomitant probenecid is recommended as first choice. For congenital syphilis, again, aqueous benzylpenicillin and procaine benzylpenicillin are options. Recommendations in the 2015 CDC guideline are essentially identical (11). However, the CDC recommends aqueous crystalline benzylpenicillin as first-line treatment for neurosyphilis, rather than procaine benzylpenicillin and probenecid, which are recommended as an alternative. WHO guidelines - Neisseria gonorrhoeae: The 2016 WHO guidelines for the treatment of Neisseria gonorrhoeae (14) make the following recommendations: Genital and anorectal gonococcal infections • Dual therapy: – ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g orally as a single dose; OR – cefixime 400 mg orally as a single dose plus azithromycin 1 g orally as a single dose. • Single therapy: – ceftriaxone 250 mg IM as a single dose – cefixime 400 mg orally as a single dose – spectinomycin 2 g IM as a single dose. Oropharyngeal gonococcal infections • Dual therapy: – ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g orally as a single dose; OR –
Committee considerations

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Committee considered the various antibiotics proposed in the applications, aligning recommendations to WHO STI guidelines for combination therapy (gonorrhoea) and including additional second-choice medicines (gentamicin and spectinomycin). Recommended first- and second-choice antibiotics are reported below.
EML recommendations: Gonococcal infection

First choice
- ceftriaxone
  - co-prescribed with azithromycin

Second choice
- cefixime
  - co-prescribed with azithromycin
- spectinomycin
- gentamicin