Benzylpenicillin

Essential medicine status

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.1. Access group antibiotics

ATC codes: J01CE01

Indication	Syphilis ICD11 code: 1A6Z
INN	Benzylpenicillin
Medicine type	Chemical agent
Antibiotic groups	A ACCESS
List type	Core
Formulations	**Parenteral > General injections > unspecified:** 600 mg in vial powder for injection (=1 million IU as sodium or potassium salt) ; 3 g in vial powder for injection (=5 million IU as sodium or potassium salt)
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Benzylpenicillin
DrugBank	Benzylpenicillin

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.

Summary of evidence

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 infection 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 lymecycline, 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 − cefixime 400 mg orally as a single dose plus azithromycin 1 g orally as a single dose. • Single therapy: − ceftriaxone 250 mg IM as single dose. Retreatment after treatment failure • Dual therapy with one of the following combinations − ceftriaxone 500 mg IM as a single dose plus azithromycin 2 g orally as a single dose − cefixime 800 mg orally as a single dose plus azithromycin 2 g orally as a single dose − gentamicin 240 mg IM as a single dose plus azithromycin 2 g orally as a single dose − spectinomycin 2 g IM as a single dose (if not an oropharyngeal infection) plus azithromycin 2 g orally as a single dose. Gonococcal ophthalmia neonatorum • Treatment with one of the following options: − ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose − kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose − spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose. Ocular

prophylaxis of gonococcal ophthalmia neonatorum • Treatment with one of the following options: − tetracycline hydrochloride 1% eye ointment − erythromycin 0.5% eye ointment − povidone iodine 2.5% solution (water-based) − silver nitrate 1% solution − chloramphenicol 1% eye ointment. WHO guidelines - Treponema pallidum and congenital syphilis: The 2016 WHO guidelines for the treatment of Treponema pallidum (syphilis) (12) make the following recommendations: Early syphilis (primary, secondary and early latent syphilis of not more than 2 years' duration) – adults and adolescents • Treatment with one of the following options: − benzathine benzylpenicillin 2.4 million units once IM, over no treatment − benzathine benzylpenicillin 2.4 million units once IM, over procaine benzylpenicillin 1.2 million units daily IM for 10–14 days. • When benzathine or procaine penicillin cannot be used: − doxycycline 100 mg twice daily orally for 14 days; OR − ceftriaxone 1 g IM once daily for 10–14 days; OR − azithromycin 2 g once orally (special circumstances). Early syphilis (primary, secondary and early latent syphilis of not more than 2 years' duration) – pregnant women • Treatment with one of the following options: − benzathine benzylpenicillin 2.4 million units once IM, over no treatment − benzathine benzylpenicillin 2.4 million units once IM, over procaine benzylpenicillin 1.2 million units IM once daily for 10 days. • With caution, when benzathine or procaine benzylpenicillin cannot be used: − erythromycin 500 mg orally four times daily for 14 days; OR − ceftriaxone 1 g IM once daily for 10–14 days; OR − azithromycin 2 g once orally. Late syphilis (infection of more than 2 years' duration without evidence of treponemal infection – adults and adolescents • Treatment with one of the following options: − benzathine benzylpenicillin 2.4 million units IM once weekly for 3 consecutive weeks, over no treatment. − benzathine benzylpenicillin 2.4 million units IM once weekly for 3 consecutive weeks, over procaine benzylpenicillin 1.2 million units IM once daily for 20 days. • When benzathine or procaine penicillin cannot be used: − doxycycline 100 mg twice daily orally for 30 days. Late syphilis (infection of more than 2 years' duration without evidence of treponemal infection – pregnant women • Treatment with one of the following options: − benzathine benzylpenicillin 2.4 million units IM once weekly for 3 consecutive weeks, over no treatment − benzathine benzylpenicillin 2.4 million units IM once weekly for 3 consecutive weeks, over procaine benzylpenicillin 1.2 million units IM once daily for 20 days. • With caution, when benzathine or procaine benzylpenicillin cannot be used: − erythromycin 500 mg orally four times daily for 30 days. Congenital syphilis in infants • Treatment with one of the following options: − benzylpenicillin 100 000–150 000 U/kg IV daily for 10–15 days − procaine benzylpenicillin 50 000 U/kg single dose IM daily for 10–15 days. WHO guidelines - Chlamydia trachomatis: The 2016 WHO guidelines for the treatment of Chlamydia trachomatis (15) make the following recommendations: Uncomplicated genital chlamydia • Treatment with one of the following options: − azithromycin 1 g orally as a single dose − doxycycline 100 mg orally twice a day for 7 days. • OR one of the following alternatives: − tetracycline 500 mg orally four times a day for 7 days − erythromycin 500 mg orally twice a day for 7 days − ofloxacin 200–400 mg orally twice a day for 7 days. Anorectal chlamydial infection • In order of preference: − doxycycline 100 mg orally twice a day for 7 days − azithromycin 1 g orally as a single dose. Genital chlamydial infection in pregnant women • In order of preference: − azithromycin 1 g orally as a single dose − amoxicillin 500 mg orally three times a day for 7 days − erythromycin 500 mg orally twice a day for 7 days. Lymphogranuloma venereum • In order of preference: − doxycycline 100 mg orally twice daily for 21 days − azithromycin 1 g orally, weekly for 3 weeks. Chlamydial ophthalmia neonatorum • In order of preference: − azithromycin 20 mg/kg per day orally, one dose daily for 3 days − erythromycin 50 mg/kg per day orally, in four divided doses daily for 14 days. Ocular prophylaxis of chlamydial ophthalmia neonatorum • Treatment with one of the following options: − tetracycline hydrochloride 1% eye ointment − erythromycin 0.5% eye ointment − povidone iodine 2.5% solution − silver nitrate 1% solution − chloramphenicol 1% eye ointment.

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: Syphilis

First choice	Second choice
benzylpenicillin	procaine benzylpenicillin
benzathine benzylpenicillin	

1. Kong FY, Tabrizi SN, Law M, Vodstrcil LA, Chen M, Fairley CK et al. Azithromycin versus doxycycline for the treatment of genital chlamydia infection: a meta-analysis of randomized controlled trials. Clin Infect Dis. 2014;59(2):193–205.
2. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. Sex Transm Dis. 2002;29(9):497–502.
3. Lau A, Bradshaw CS, Lewis D, Fairley CK, Chen MY, Kong FY et al. The efficacy of azithromycin for the treatment of genital Mycoplasma genitalium: a systematic review and meta-analysis. Clin Infect Dis. 2015;61(9):1389–99.
4. Geisler WM, Uniyal A, Lee JY, Lensing SY, Johnson S, Perry RC et al. Azithromycin versus doxycycline for urogenital Chlamydia trachomatis infection. N Engl J Med. 2015;373(26):2512–21.
5. Pitsouni E, Iavazzo C, Athanasiou S, Falagas ME. Single-dose azithromycin versus erythromycin or amoxicillin for Chlamydia trachomatis infection during pregnancy: a meta-analysis of randomised controlled trials. Int J Antimicrob Agents. 2007;30(3):213–21.
6. Bai ZG, Wang B, Yang K, Tian JH, Ma B, Liu Y et al. Azithromycin versus penicillin G benzathine for early syphilis. Cochrane Database Syst Rev. 2012;(6):CD007270.
7. Bai ZG, Yang KH, Liu YL, Tian JH, Ma B, Mi DH et al. Azithromycin vs. benzathine penicillin G for early syphilis: a meta-analysis of randomized clinical trials. Int J STD AIDS. 2008;19(4):217–21.
8. Grabe M, Bartoletti R, Bjerklund Johansen TE, Cai T, Çek M, Köves B et al. Guidelines on urological infections2015. Arnhem, Netherlands: European Association of Urology; 2015 (http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf, accessed 21 March 2017).
9. Horner PJ, Blee K, Falk L, van der Meijden W, Moi H. 2016 European guideline on the management of non-gonococcal urethritis. Int J STD AIDS. 2016;27(11):928–37.
10. Horner P, Blee K, O'Mahony C, Muir P, Evans C, Radcliffe K. 2015 UK national guideline on the management of non-gonococcal urethritis. Int J STD AIDS. 2016;27(2):85–96.
11. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64(RR-03):1–137.
12. WHO guidelines for the treatment of Treponema pallidum (syphilis) Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf?ua=1, accessed 21 March 2017).
13. Kingston M, French P, Higgins S, McQuillan O, Sukthankar A, Stott C et al. UK national guidelines on the management of syphilis 2015. Int J STD AIDS. 2016;27(6):421–46.
14. WHO guidelines for the treatment of Neisseria gonorrhoeae. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/246114/1/9789241549691-eng.pdf?ua=1, accessed 21 March 2017).
15. WHO guidelines for the treatment of Chlamydia trachomatis. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/246165/1/9789241549714-eng.pdf?ua=1, accessed 21 March 2017).