# Azithromycin

Section: 21. Ophthalmological preparations > 21.1. Ophthalmological preparations > Anti-infective agents

EMLc | ATC codes: S01AA26

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| **Indication** | Trachoma ICD11 code: 1C23.Z |
| **INN** | Azithromycin |
| **Medicine type** | Chemical agent |
| **Antibiotic groups** | WATCH |
| **List type** | Core |
| **Formulations** | **Local > Ophthalmological > Solution (eye drops):** 1.5% eye drops |
| **EML status history** | First added in 2013 (TRS 985)<br>Changed in 2021 (TRS 1035) |
| **Sex** | All |
| **Age** | Also recommended for children |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Wikipedia** | Azithromycin |
| **DrugBank** | Azithromycin |

## Expert Committee recommendation

The Expert Committee noted that infections of the eye and surrounding structures are frequent around the world and are an important cause of blindness. Given increasing concerns about overuse of antibiotics, the emergence of antimicrobial resistance and the need to guarantee prompt access to highly beneficial treatments, the Expert Committee noted the importance of revising and updating the Model Lists to provide clear information on the use of antibiotics in ocular infections. With regard to conjunctivitis, topical anti-infective medicines currently included on the Model Lists are gentamicin and tetracycline (each with a square box). The Committee noted that based on the evidence and guidelines reviewed in the application, topical antibiotics are indicated for moderate to severe infection and can be considered in mild cases. The available evidence does not make it possible to identify specific, preferred antibiotics for this indication. The Committee therefore endorsed the current listings for gentamicin and tetracycline, and recommended that the indications for ofloxacin be expanded to include the treatment of conjunctivitis. For trachoma, a specific type of conjunctivitis caused by certain serovars of C. trachomatis, the treatment of choice is a single oral dose of azithromycin. Topical azithromycin or topical tetracycline are also indicated. The Committee also endorsed the current listings on the EML and EMLc for oral and topical azithromycin and for topical tetracycline for the treatment of trachoma. For infectious keratitis, topical anti-infective medicines currently included on the Model Lists are ofloxacin and tetracycline (each with a square box). The Committee noted that based on the evidence and guidelines reviewed in the application, topical fluoroquinolones are indicated for infectious keratitis. The Committee therefore endorsed the current square box listing for ofloxacin for this indication. No change was recommended for the listing of tetracycline. The Committee

noted that systemic antibiotics may be indicated in certain situations (e.g. with lesions close to the limbus) but the available evidence could not identify specific, preferred antibiotics. The Committee therefore did not endorse listing for systemic antibiotics for infectious keratitis. For endophthalmitis, the Committee acknowledged the lack of high-quality evidence for antibiotic choice and specific recommendations in guidelines. Based on common practice and the range of pathogens, the application proposed ceftriaxone plus vancomycin for systemic treatment, and vancomycin and ceftazidime by intravitreal administration for the empiric treatment of bacterial endophthalmitis. The Committee acknowledged that intravitreal treatment requires specialist training and adequate infrastructure to ensure safe administration. Given that bacterial endophthalmitis is a serious, sight-threatening infection, the Expert Committee recommended the current listings for ceftazidime, ceftriaxone and vancomycin be extended to include the indication of bacterial endophthalmitis as first-choice treatment options.

## Background

Topical ophthalmological antibacterial medicines currently included in the Model Lists are summarized below: Azithromycin eye drops 1.5% (trachoma) Erythromycin eye ointment 0.5% (infections due to Chlamydia trachomatis or Neisseria gonorrhoeae) Gentamicin eye drops 0.3% (blepharitis, conjunctivitis) Ofloxacin eye drops 0.3% (infectious keratitis) Tetracycline eye ointment 1% (blepharitis, conjunctivitis, infectious keratitis, trachoma) Oral azithromycin is currently included in the Model Lists as a systemic single-dose treatment for trachoma. Ceftazidime and ceftriaxone and vancomycin are included in the Model Lists for other indications.

## Public health relevance

Conjunctivitis is an inflammation or infection of the conjunctiva characterized by dilatation of the conjunctival vessels and typically with associated discharge. Most episodes are from viral infection, with bacteria being the second most common cause. In children, however, bacterial infections can be more common than viral infections. The most common bacterial pathogens causing bacterial conjunctivitis are Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. M. catarrhalis is a frequent bacterial cause of conjunctivitis in children. Infectious keratitis is an infection of the cornea and an important cause of visual impairment and blindness. It predominantly affects people in developing countries as well as contact lens users in developed countries. The mainstay of diagnosis is a Gram staining and culture of corneal samples to guide targeted treatment. The most common pathogens are: Pseudomonas sp., Staphylococcus sp., Streptococcus sp. and other Gram-negative organisms. Endophthalmitis can be exogenous (postoperative, trauma) or endogenous. Cataract surgery is the most common source of exogenous endophthalmitis with the most common causative pathogens being Gram-positive bacteria (Staphylococcus sp. or three Streptococcus sp.) while Gram-negative bacteria are a less common cause. Endogenous endophthalmitis is caused by bacterial pathogens in about half of the cases, mostly by Gram-positive bacteria (Staphylococcus sp. or Streptococcus sp.). In East Asia, Klebsiella pneumoniae is reported to be the leading pathogen responsible for endogenous endophthalmitis. Microbiological diagnosis through tap biopsy or vitrectomy is required to guide targeted antibiotic treatment. Surgical debridement and/or pars plana vitrectomy is in general required if the infection spreads beyond the choroid into the vitreous. Antibiotics can be administered by topical, subconjunctival, intravitreal, and/or systemic routes.

## Benefits

The application presented the results of a search for systematic reviews and meta-analyses of antibiotic therapy for ocular infections. Conjunctivitis Four systematic reviews were identified, including two on antibiotics for bacterial conjunctivitis (1,2) and two specific to the management of Chlamydia trachomatis conjunctivitis (trachoma) (3,4). A Cochrane systematic review summarized eleven randomized controlled trials (2116 patients) that compared topical antibiotics to placebo for acute bacterial conjunctivitis (1). The topical antibiotics used included azithromycin, bacitracin, besifloxacin, ciprofloxacin, chloramphenicol, fusidic acid, moxifloxacin, norfloxacin and polymyxin. The authors reported a modest benefit from topical antibiotics (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.15 to 1.61) for early clinical resolution (day 2–5), and similarly for late resolution (RR 1.21, 95% CI 1.10 to 1.33) (day 6–10). There were no serious outcomes in either study arm. An individual patient-data meta-analysis of three randomized controlled trials (626 patients) also compared topical antibiotics

with placebo for acute infective conjunctivitis (2). Antibiotics included chloramphenicol and fusidic acid. Cure was more likely at day 7 with antibiotic treatment (risk difference 0.08, 95% CI 0.01 to 0.04), and for those with purulent discharge and mild severity of eye redness in subgroup analysis. The effect was, however, modest and, given that the infection is largely self-limiting, the authors recommended the use of topical antibiotics only in selected patients. Neither of these two systematic reviews identified studies of head-to-head comparison of different antibiotics; therefore no systematic review data are available to guide the choice of antibiotics. A Cochrane systematic review of antibiotic treatment for trachoma included nine studies (1961 patients) comparing topical antibiotics with placebo, eight studies (1583 patients) comparing oral and topical antibiotics, and four cluster-randomized studies comparing oral azithromycin with delayed or no treatment (3). There was a benefit from antibiotics versus no treatment (RR 0.78, 95% CI 0.69 to 0.89) for cure after 3 months, but no statistically significant benefit after 12 months of follow-up (RR 0.74, 95% CI 0.55 to 1.0). No interaction effect was seen between studies comparing either topical or systemic antibiotics with placebo, nor was there a benefit from systemic versus topical antibiotics in studies comparing the two modes of application at 3 months (RR 0.97, 95% CI 0.81 to 1.16). However, a comparison between systemic azithromycin and topical tetracycline favoured azithromycin (RR 0.76, 95% CI 0.59 to 0.99) for the 12-month outcome of active trachoma, while there was no difference at 3 months (no effect size was reported). A systematic review and meta-analysis of three randomized controlled trials and nine observational studies (292 patients) evaluated antibiotic treatment in neonates with chlamydial conjunctivitis (4). The authors assessed the efficacy of various doses of systemic macrolides. Only cure rates of each study were reported with no direct comparisons. The only regimen that appeared to result in a lower cure rate compared to the other regimens reported was a single-dose treatment of azithromycin (60% cure rate), while a 3-day course of azithromycin and any of the regimens using 10–14 days of erythromycin had similar cure rates. No firm conclusions could be drawn on which antibiotic or regimen would be the most appropriate to use. A short course of azithromycin may be beneficial because of less concern about adherence when compared with a 14-day course of erythromycin. The cure rate of 60% in the study that used a single dose of azithromycin should be considered in the context of the original study which was a small observational study in only five neonates. Keratitis Two systematic reviews on antibiotic treatment for bacterial keratitis were identified (5,6). One review included eight randomized controlled trials and five observational studies that compared topical fluoroquinolones (ciprofloxacin, lemofloxacin, levofloxacin, moxifloxacin and ofloxacin) with a combination of an aminoglycoside (amikacin, gentamicin or tobramycin) plus cephalosporin (cefazolin, cefalotin, cefamandole, cefuroxime or cephaloridine) for treatment of (suspected) bacterial keratitis (5). No difference was found in achieving the primary outcome of healing between the treatment groups in the randomized controlled trials (odds ratio (OR) 1.05, 95% CI 0.64 to 1.73) but a benefit for fluoroquinolones was seen in observational studies (OR 2.37, 95% CI 1.08 to 5.21). When combining the study designs, no statistically significant effect was found (OR 1.47, 95% CI 0.90 to 2.41). When limited to microbiologically confirmed bacterial keratitis, no statistically significant benefit was seen for fluoroquinolones (OR 1.20, 95% CI 0.48 to 3.0). In the randomized controlled trials, there were fewer adverse events that were mild, while one observational study suggested a higher risk of perforations in the fluoroquinolone group, a finding not corroborated in other studies. The second review included 16 randomized controlled trials (1823 participants) that compared different topical antibiotics for the treatment of bacterial keratitis (6). No statistically significant difference in treatment success, time to cure or serious complications (including corneal perforation) between the groups was identified. Fluoroquinolones were found to be better tolerated in terms of ocular discomfort and chemical conjunctivitis than aminoglycoside–cephalosporin combinations (RR 0.20, 95% CI 0.10 to 0.41). However, fluoroquinolones increase the risk of corneal precipitates compared with the aminoglycoside–cephalosporin combinations (RR 24.4, 95% CI 4.68 to 126.9). Endophthalmitis No systematic reviews could be identified.

## Additional evidence

The application presented the results of a search for clinical practice guidelines on the use of antibiotics for ocular infections. Conjunctivitis Five clinical practice guidelines were identified (7–11). The guideline by Azari and Barney, based on a systematic review of conjunctivitis diagnosis and treatment, mentions several options for management of uncomplicated bacterial conjunctivitis: no treatment, delayed treatment, or immediate antibiotic

treatment (7). The likely benefits of treatment are: shorter duration of symptoms; decrease in transmissibility; and earlier return to school. If a decision is made to treat, any broad-spectrum antibiotic eye drops can be viewed as equally effective (e.g. aminoglycosides, fluoroquinolones, macrolides and sulfonamides) given the lack of direct comparisons. The Médecins Sans Frontières guideline recommends cleaning eyes four times daily with boiled water with 0.9% sodium chloride, and to apply 1% tetracycline eye ointment twice daily for 7 days for suspected bacterial conjunctivitis, i.e. where there is abundant and purulent secretions, eyelids stuck together and unilateral at onset (8). The Conjunctivitis Preferred Practice Pattern® of the American Academy of Ophthalmology recommends considering topical agents for mild bacterial conjunctivitis, and obtaining a swab to guide targeted topical treatment given that methicillin-resistant S. aureus is a more frequently detected pathogen in severe conjunctivitis (9). No specific antibiotics are recommended because of the lack of data on benefit of one antibiotic over another. For trachoma, the guideline recommends either a single dose of azithromycin 1 g orally or doxycycline 100 mg twice daily for 7 days. The Australian guideline on the management of C. trachomatis eye infection recommends a single dose of azithromycin at 20 mg/kg body weight up to 1000 mg (10). Bhosai et al. also recommend the use azithromycin with the same single dose for the treatment of trachoma (12). The use of topical tetracycline ointment was discouraged because of adherence concerns. This is in keeping with a WHO guideline published in 2016 that was not formally included in this review as the guideline covers the entire spectrum of C. trachomatis infections and only touches briefly on trachoma (11). Keratitis Two clinical practice guidelines on this topic were identified (13,14). The United Kingdom College of Optometrists guideline on management of microbial keratitis recommends monotherapy with either topical levofloxacin or moxifloxacin, and to add (unspecified) systemic antibiotics if the lesion is close to the limbus (13). The Royal Victorian eye and ear hospital guideline on the management of microbial keratitis recommends the use of hourly topical fluoroquinolones (ofloxacin 3 mg/mL) at least for the first 48 hours and then to reduce the frequency gradually (14). Endophthalmitis Guidelines published by the United Kingdom College of Optometrists focused specifically on postsurgical endophthalmitis (15). No specific antibiotics are recommended and only general recommendations for management are provided (including the use of unspecified topical and systemic antibiotics). A guidance document by the American Academy of Ophthalmology on endogenous endophthalmitis recommends a wide spectrum of possible systemic antibiotics depending on the (suspected) pathogen that have a good penetration into the vitreous humour, for example, aminoglycosides, clindamycin, fluoroquinolones, and third-generation cephalosporins (16). Options for intravitreal therapy in the guidance, if indicated, include ceftazidime (2.25 mg/0.1 mL) and vancomycin (1.0 mg/0.1 mL). Amikacin (0.4 mg/0.1 mL) and clindamycin (1.0 mg/0.1 mL) are suggested as alternative antibiotics if the primary regimen cannot be used.

## Other considerations

Conjunctivitis If bacterial conjunctivitis is suspected, treatment with topical antibiotics is indicated for moderate to severe infection and can also be considered in mild cases. No specific topical antibiotic can be recommended because of the lack of direct comparisons; therefore, the choice for empiric antibiotics should be based on local availability. Topical antibiotics containing fluoroquinolone are proposed (e.g. ofloxacin). For trachoma, the treatment of choice is oral azithromycin as a single dose of 1 g (or 20 mg/kg body-weight in children) because of the potentially better efficacy and adherence with the single-dose regimen. Keratitis Topical fluoroquinolones (e.g. ofloxacin) are recommended for (suspected) bacterial keratitis. As there are no recommendations for specific agents, the choice depends on local availability. Antibiotics should be adjusted based on culture results, if possible. Adding systemic antibiotics should be considered in addition to topical antibiotics if the lesion is close to the limbus. However, no recommendation can be made on the type of systemic antibiotic. Endophthalmitis No specific recommendations can be made given the lack of systematic reviews and the non-specific recommendations in the guidelines identified. Empiric antibiotic choice must target the most common pathogens (Gram-positive bacteria). For systemic treatment, given the range of pathogens, ceftriaxone plus vancomycin are proposed. For intravitreal administration, vancomycin and ceftazidime are proposed.

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