EML Application on eye infections

Applicants: Dr. Mark Loeb, Dr. Dominik Mertz

McMaster University

Correspondence: Dr. Mark Loeb, McMaster University, 1280 Main St West, MDCL 3200, Hamilton, Ontario, Canada L8S 4K1; loebm@mcmaster.ca

Background

The WHO Essential Medicine List (EML) lists the most efficacious and safe medicines to treat illnesses that are considered high priority, including antibiotics. However, most antibiotics were listed decades ago and a comprehensive review of all the antibiotics listed over the past 40 years has never been done. Given increasing concerns about overuse of antibiotics, the emergence of antimicrobial resistance and the need to guarantee prompt access to highly beneficial treatments, revising and updating the list is an important priority.

Applications for revisions to the Model List are accepted every 2 years and are by single agent. However, similarly to what has been done for cancer in 2015, a syndrome-based approach was agreed as the best option. We have revised the list based on common syndromes to date and have now done this for eye infections. All potentially relevant antibiotics for use across low, middle and high-income countries, were considered. The working group and the EML Secretariat a priori reasoned on the guiding principles to prioritize the selection of antibiotics: safety and efficacy, resistance, feasibility, parsimony.

As in our previous work on the original 21 syndromes [1], this review of the evidence was supplemented by a systematic search and synthesis of clinical practice guidelines. We placed a relative high value on evidence and guideline recommendations that can be applicable to a majority of patients and settings. The proposal will be presented for review by the WHO Expert Committee. It is acknowledged that local antibiotic resistance patterns are critical when selecting antibiotics and must be given strong consideration.

Rationale to consider eye infections for the EML

In this document, we consider eye infections, including localized bacterial infections affecting the conjunctiva (conjunctivitis), the cornea (keratitis), and intra-ocular infections (endophthalmitis). Infections of the skin and soft tissue surrounding the eye are out of scope (e.g. periorbital cellulitis), as is disseminated gonococcal infection with eye involvement. Both systemic and topic antibiotics for treatment are considered. 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 *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* which is a frequent bacterial cause in children. Infectious keratitis is an infection of the cornea and a major cause of visual impairment and blindness. It predominantly affects people in developing countries as well as contact lenses users in developed countries. The mainstay of diagnosis is a gram stain and culture of corneal samples to guide targeted treatment. The most common pathogens are: Pseudomonas sp., Staphylococcus sp., Streptococcus sp., and other gram negatives. Endophthalmitis can be exogenous (post-operative, trauma) or endogenous. Cataract surgery is the most common source of exogenous endophthalmitis with the most common pathogens being gram positive (Staphylococcus sp. or

Streptococcus sp) while gram-negatives are less common. Endogenous endophthalmitis is caused by bacterial pathogens in roughly half of the cases, mostly by gram-positives (Staphylococcus sp. or Streptococcus sp) while in East Asia, *K. pneumoniae* is reported to be the leading pathogen. Microbiological diagnosis through tap 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 via topical, subconjunctival, intravitreal, and/or systemic routes.

Methods

Data search and retention of Systematic Review and Meta-analysis evidence

A search for systematic reviews and meta-analyses of antibiotic therapy for eye infections was conducted. We searched for systematic reviews and meta-analyses of randomized controlled trials (RCTs) from 1996 to September 9, 2020 that reported comparisons between different antibiotics and/or antibiotic classes and/or comparisons to placebo for eye infections. We did not apply language restrictions and searched three databases (MEDLINE/PubMed, EMBASE, Cochrane Database of Systematic Reviews). For relevant clinical practice guidelines (CPGs), a search of all databases was conducted.

Screening of titles and abstracts, full-texts, as well as subsequent data abstraction, was conducted independently and in duplicate, followed by consensus discussion where there was disagreement, and with third party adjudication if needed. Following the electronic database searching and prior to the initiation of the formal screening of citations, a calibration exercise to ensure that screeners were uniform in their screening approach was conducted. For data abstraction, our focus was on comparative effectiveness evidence and we retrieved data on all reported outcomes (primary and secondary) in which cumulative estimates were reported. We further included any instance of a reported outcome with only one RCT.

Ranking of Systematic Reviews and Meta-analyses

We ranked the quality of evidence for each systematic review and meta-analysis on the basis of the study characteristics included in the review and the conduct of the review itself. Individual study characteristics included aspects of internal validity, such as risk of bias, as well as precision, while the publication date was a function of the review itself. We used the following five variables to develop a score for each systematic review or meta-analysis in order to rank them on overall quality of evidence: i) the judged quality assessment of the systematic review's evidence taking into account author's assessment and our assessment using GRADE. Note, our judged quality assessment involved a global assessment that included issues around potential for risk of bias e.g. randomization, blinding, data loss, publication bias, heterogeneity of the study estimates, whether Risk of Bias (RoB) was assessed with a valid technique, study selection and abstraction/RoB performed in duplicate/independently, comprehensive literature search, possible conflict of interest) ii) sample size of studies where reported, iii) number of events where reported and particularly for categorical/dichotomous data, iv) number of studies per outcome,

and v) publication year. The judged quality of evidence variable included abstracting the risk of bias and level of evidence assessments reported by authors (e.g. Cochrane's Risk of Bias tool, the Jadad 5-point scale, GRADE methods). Using the five variables, we assigned each variable (in duplicate and independently using consensus to address disagreement) a rating of either high, moderate, low, and very low for each variable and assigned an ordinal score (high= 1.0, moderate =0.75, low=0.5, very low= 0.25). We averaged the score for each review. We then ranked the studies based on these mean scores which we multiplied by 100 (i.e. percentage) for ease of comprehension.

In deciding upon the list of antibiotics, we considered all relevant outcomes reported in the systematic reviews on eye infections. We planned to give more weight to patient important outcomes, mild to moderate harms, and lastly surrogate markers.

Search and retention of Clinical Practice Guidelines

We reviewed well accepted international CPGs. These included clinical practice guidelines from North America and Europe. We reasoned that clinical practice guidelines might offer complementary information on the use of antibiotics for eye infections, particularly given the context of antibiotic resistance and for circumstances where RCTs in systematic reviews and meta-analyses were not designed to address superiority of one or more antibiotics compared to others. We defined clinical practice guidelines as documents that provide recommendations on the management of infectious disease syndromes and optimal AB use. These documents must have contained an explicit methodology section which provided sufficient detail of how they were developed, such as an explicit search strategy, evidence quality assessment, and the method used to make recommendations.

Ranking of Clinical Practice Guidelines

For our approach, we ranked the clinical practice guidelines using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument, which is designed to evaluate the process of practice guideline development and the quality of reporting.[2] We used 11 of the 23 AGREE II items (see Appendix Table 1) as these were the only items pertinent to our objective. Standard AGREE II methodology for scoring was used where the maximum possible score is based on the number of items by the number of assessors, the minimum possible score based on the minimum score by the number of items by the number of assessors, and the scaling of domains to arrive at an overall percentage. We used two assessors for this step and judged a scaled percentage of ≤70% to be low, 71 to 79 to be moderate, and scores ≥ 80% to be high.

Conjunctivitis

Synopsis of published evidence

We identified 4 systematic review[3-6]. Two systematic reviews were on antibiotics for bacterial conjunctivitis (Sheikh et al. and Jefferis et al.), and two were specific to the management of *C. trachoma*tis conjunctivitis ("trachoma", Evans et al., and Zikic et al.).

Of the two identified, the better quality SR on bacterial conjunctivitis was the Cochrane systematic review by Sheikh et al. (score 0.7). This review summarized 11 RCTs (2116 patients) that compared topical antibiotics to placebo [5]. Topical antibiotics used included azithromycin, polymyxin, bacitracin, moxifloxacin, besifloxacin, ciprofloxacin, norfloxacin, fusidic acid, and chloramphenicol. The authors reported a modest benefit of topical antibiotics (RR 1.36, 1.15-1.61) for early clinical resolution (day 2-5), and similarly, RR 1.21 (1.10-1.33) for late resolution (day 6-10). There were no serious outcomes in either study arm.

The other SR on bacterial conjunctivitis was by Jefferis et al. (score 0.675), an individual patient-data meta-analysis (IPDMA) of 3 RCTs with 626 patients, also comparing topical antibiotics to placebo [4]. Antibiotics included chloramphenicol and fusidic acid. Cure was more likely at day 7 with antibiotic treatment (risk difference 0.08, 0.01-0.04), and in particular, for those with purulent discharge and mild severity of eye redness in subgroup analysis. The effect however was modest, and given that the infection is largely self-limiting, the authors recommended to use topical antibiotics only in selected patients.

Neither of these two systematic reviews identified studies of head-to-head comparison, therefore there is no systematic review data to guide the choice of antibiotics.

Of the two systematic reviews for antibiotic management of trachoma, the Cochrane review by Evans et al. had a higher score (0.725)[3]. This study included 14 RCTs with 1961 patients comparing topic antibiotics to placebo. They found a benefit of antibiotics versus no treatment (RR 0.78, 0.69-0.89) for cure after 3 months, but not a statistically significant benefit after 12 months of follow-up (RR 0.74, 0.55-1.0). There was no interaction effect between studies comparing either topical or systemic antibiotics to placebo, nor was there a benefit of systemic versus topical antibiotics in studies comparing the two modes of application at 3 months (RR 0.97, 0.81-1.16). However, a comparison between systemic azithromycin and topical tetracycline favoured the former (RR 0.76, 0.59-0.99) for the 12 months outcome of active trachoma, while there was no difference at the 3 months (no effect size was reported).

The other systematic review on trachoma by Zikic et al included 3 RCTs and 9 observational studies, with a total of 292 neonates with chlamydial conjunctivitis [6]. 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 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 to use preferentially. A short course of azithromycin may be beneficial due to less concern about

adherence when compared to a 14-day course of erythromycin. The cure rate of 60% in the one study that used a single dose of azithromycin should be considered in the context of the original study which was a small observation study with a n of 5 neonates.

Synopsis of guidelines

A total of 5 CPGs were identified [7-11]. Among the 3 CPGs on bacterial conjunctivitis, the guideline by Azari et al (score 66.9) was of the highest quality [9]. They provide a no treatment, delayed treatment, or immediate antibiotic treatment option for uncomplicated bacterial conjunctivitis. The benefit of treatment is likely a shorter duration of symptoms, a decrease in transmissibility, and earlier return to school. They conclude that if a decision is made to treat, any broad-spectrum antibiotic eyedrops can be viewed as equally effective given the lack of head-to-heat comparisons (e.g. aminoglycosides, fluoroquinolones, macrolides, sulfonamides).

The Medicine Sans Frontiers guideline (score 65.6) recommends cleaning eyes 4x times daily with boiled water of 0.9% sodium chloride, and to apply 1% tetracycline eye ointment twice daily for 7 days for suspected bacterial conjunctivitis (abundant and purulent secretions, eyelids stuck together, unilateral at onset) [7].

Finally, the American Academy of Ophtalmology “Conjunctivitis Preferred Practice Pattern” recommends to consider topical agents for mild bacterial conjunctivitis, and obtaining a swab to guide targeted topical treatment given that MRSA is a more frequently detected pathogen in severe conjunctivitis [11]. No specific antibiotics are recommended due to the lack of data of benefit for one over another. For trachoma, the guideline recommends either a single dose of azithromycin 1g orally, or doxycycline 100mg twice daily for 7 days.

The Australian guideline on the management of *C. trachomatis* eye infection score highest among the specific CPGs (score 70.8) [8]. The recommendation is a single-dose of azithromycin at 20mg/kg body weight up to 1000mg. Bhosai et al. (score 68.8) also recommend the use azithromycin with the same single-dose for the treatment of trachoma. The use of topical tetracycline ointment was discouraged due to adherence concerns. This is in keeping with a previously published WHO guideline 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[12].

Conclusions

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 due to a lack of head-to-head comparisons and, therefore, the choice for empiric antibiotics should be based on local availability.

For trachoma, the treatment of choice is an oral single-dose of azithromycin 1g (or 20mg/kg body-weigh in children) given the potentially better efficacy and adherence with the single-dose regimen. An alterative option is doxycycline 100mg twice daily for 7 days (adults, only). Erythromycin is discouraged because of the adverse effects associated with this antibiotic.

Keratitis

Synopsis of systematic reviews

We identified two non-Cochrane systematic reviews on antibiotic treatment of bacterial keratitis [13, 14]. Hanet at al. included RCTs and observational studies comparing topical fluoroquinolones to topical "fortified antibiotics" (typically aminoglycoside plus cephalosporin) for treatment of (suspected) bacterial keratitis [13]. They identified 8 RCTs and 5 observational studies that compared topical fluoroquinolones (ofloxacin, ciprofloxacin, lemofloxacin, moxifloxacin, levofloxacin) to a combination of an aminoglycoside (tobramycin, gentamicin, or amikacin) plus cephalosporin (cefazolin, cefuroxime, cefamandole, cephaloridine, or cephalothin). There was no difference in achieving the primary outcome of healing between the treatment groups in the RCTs (OR 1.05, 0.64-1.73) but a benefit for fluoroquinolones in observational studies (OR 2.37, 1.08-5.21). When combining the study designs, there was no statistically significant effect (OR 1.47, 0.90-2.41). When limited to microbiologically confirmed bacterial keratitis, there was no significant benefit of fluoroquinolones (IR 1.20, 0.48-3.0). In RCTs, there was fewer adverse events which were mild, while one observational study suggested a higher risk of perforations in the fluoroquinolone group, a finding not corroborated in other studies.

McDonald et al. included 16 RCTs (1823 participants) that compared different topical antibiotics [14]. They did not identify a significant difference in treatment success, time to cure, or serious complications (including corneal perforation) between groups. Fluoroquinolones were again found to be better tolerated in terms of ocular discomfort and chemical conjunctivitis than aminoglycoside-cephalosporin combinations (RR 0.20, 0.10-0.41). However, fluoroquinolones increase the risk of corneal precipitates compared to the aminoglycoside-cephalosporin combinations (RR 24.4, 4.68-126.89).

Synopsis of guidelines

We identified two CPGs on this topic [15, 16]. The US College of Optometrists guideline on management of microbial keratitis (score 70.1%) recommend monotherapy with either topical levofloxacin or moxifloxacin, and to add systemic antibiotics (which they do not specify) if the

lesion is close to the limbus [16]. The Royal Victorian eye and ear hospital guideline on the management of microbial keratitis (score 66.9%) recommended the use of hourly topical fluoroquinolones (ofloxacin 3g/ml) at least for the first 48 hours, and then to reduce the frequency step-by-step [15].

Conclusions

Topical fluoroquinolones 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.

Endophthalmitis:

Synopsis of systematic reviews

No systematic reviews could be found.

Synopsis of guidelines

Only one guideline that did meet our criteria of a CPG could be identified, published by the American College of optometrists specifically on post-surgical endophthalmitis (score: 70.1) [17]. It does not however recommend any specific antibiotics, it only provides general recommendations for management which includes topical and systemic antibiotics.

A guideline by the American Academy of Ophthalmology did not meet criteria for being a CPG and its quality was therefore not assessed [18]. This guideline on endogenous endophthalmitis recommends a wide spectrum of possible systemic antibiotics depending on the (suspected) pathogen that have a good penetration into the vitreous (e.g. fluoroquinolones, aminoglycoside, third generation cephalosporins, and clindamycin). Options for intravitreal therapy if indicated include ceftazidime (2.25mg/0.1ml) and vancomycin (1.0mg/0/1ml). Amikacin (0.4mg/0.1ml) and clindamycin (1.0mg/0.1ml) are alternatives if the primary regimen cannot be used.

NHS Sandwell and West Birmingham Hospital guidelines (quality score 67.5%)

Conclusions

No specific recommendations can be made given the lack of systematic reviews and the non-specific recommendations in the identified guideline. Empiric antibiotic choice must target the most common pathogens (gram positives).

Antibiotics selected for EML:

Conjunctivitis and keratitis: fluoroquinolone-containing topical antibiotics (e.g. ofloxacin 3mg/ml).

Trachoma: Azithromycin (oral) for paediatric and adult patients with trachoma (20mg/kg body weight up to 1000mg).

Endophthalmitis:

- Vancomycin plus ceftazidime for intravitreal administration
- For systemic treatment, no specific recommendation are made in the included guidelines, but given the spectrum of pathogens, IV ceftriaxone (2g daily) plus IV vancomycin 15-20mg/kg twice daily) can be used and is the first choice recommended in the Sanford guide.

References

1. *World Health Organization. Essentail Medicines Selection. Comprehensive Review of Antibiotic Medicine.* February 11, 2019]; Available from: https://www.who.int/selection_medicines/committees/expert/21/applications/comprehensive_antibiotics_rev/en/.
2. Brouwers, M.C., et al., *AGREE II: advancing guideline development, reporting and evaluation in health care.* CMAJ, 2010. **182**(18): p. E839-42.
3. Evans, J.R., et al., *Antibiotics for trachoma.* Cochrane Database Syst Rev, 2019. **9**: p. CD001860.
4. Jefferis, J., et al., *Acute infective conjunctivitis in primary care: who needs antibiotics? An individual patient data meta-analysis.* Br J Gen Pract, 2011. **61**(590): p. e542-8.
5. Sheikh, A., et al., *Antibiotics versus placebo for acute bacterial conjunctivitis.* Cochrane Database Syst Rev, 2012(9): p. CD001211.
6. Zikic, A., et al., *Treatment of Neonatal Chlamydial Conjunctivitis: A Systematic Review and Meta-analysis.* J Pediatric Infect Dis Soc, 2018. **7**(3): p. e107-e115.
7. *Medicines Sans Frontiers. Conjunctivitis Guideline.* *https://medicalguidelines.msf.org/viewport/CG/english/conjunctivitis-16689724.html*.
8. *CDNA National Guidelines for the Public Health Management of Trachoma.* *https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-cdna-pubs-trachoma.htm*.
9. Azari, A.A. and N.P. Barney, *Conjunctivitis: a systematic review of diagnosis and treatment.* JAMA, 2013. **310**(16): p. 1721-9.
10. Bhosai, S.J., et al., *Trachoma: an update on prevention, diagnosis, and treatment.* Curr Opin Ophthalmol, 2012. **23**(4): p. 288-95.
11. Varu, D.M., et al., *Conjunctivitis Preferred Practice Pattern(R).* Ophthalmology, 2019. **126**(1): p. P94-P169.
12. *WHO guidelines for the treatment of Chlamydia trachomatis.* *https://www.who.int/reproductivehealth/publications/rtis/chlamydia-treatment-guidelines/en/*.
13. Hanet, M.S., J. Jamart, and A.P. Chaves, *Fluoroquinolones or fortified antibiotics for treating bacterial keratitis: systematic review and meta-analysis of comparative studies.* Can J Ophthalmol, 2012. **47**(6): p. 493-9.
14. McDonald, E.M., et al., *Topical antibiotics for the management of bacterial keratitis: an evidence-based review of high quality randomised controlled trials.* Br J Ophthalmol, 2014. **98**(11): p. 1470-7.
15. *Royal Victorian eye and ear hospital guideline on management of microbial keratitis.* *https://www.eyeandear.org.au/page/Health_Professionals/Knowledge_Portal/Eye_and_Ear_Emergency_Department/CPGs/*.
16. *The US College of Optometrists guideline on management of microbial keratitis.* *https://www.college-optometrists.org/guidance/clinical-management-guidelines/microbial-keratitis-bacterial-fungal-.html*.
17. *The US College of Optometrists guideline on management of endophtalmitis (post-operative).* *https://www.college-optometrists.org/guidance/clinical-management-guidelines/endophthalmitis*.
18. *American Academy of Ophtalmology. Endogenous Endopthalmitis: Diagnosis and Treatment.* *https://www.aao.org/eyenet/article/endogenous-endophthalmitis-diagnosis-treatment*.