Month/Year of Review: November 2014  
Date of Last Review: September 2012

PDL Class: Ophthalmic Antibiotics  
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

<table>
<thead>
<tr>
<th>Preferred Agents</th>
<th>Non-Preferred Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
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<tr>
<td>Gentamicin drops and ointment</td>
<td></td>
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<tr>
<td>Tobramycin drops and Tobramycin (Tobrex®) ointment</td>
<td></td>
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<tr>
<td><strong>Fluoroquinolones</strong></td>
<td></td>
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<tr>
<td>Ciprofloxacin drops and Ciprofloxacin (Ciloxan®) ointment</td>
<td>Besifloxacin (Besivance®) drops</td>
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<tr>
<td>Gatifloxacin (Zymar®) 0.3% drops</td>
<td>Gatifloxacin (Zymaxid®) 0.5% drops</td>
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<tr>
<td>Moxifloxacin (Vigamox®) drops</td>
<td>Levofoxacin (Iquix®) 1.5% drops</td>
</tr>
<tr>
<td>Ofloxacln drops</td>
<td>Levofoxacin 0.5% drops</td>
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<tr>
<td></td>
<td>Moxifloxacin (Moxeza®) 0.5% drops</td>
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<tr>
<td><strong>Macrolides</strong></td>
<td></td>
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<tr>
<td>Erythromycin base ointment</td>
<td>Azithromycin (AzaSite®) drops</td>
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<tr>
<td><strong>Others</strong></td>
<td></td>
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<tr>
<td>Bacitracin/polymyxin B ointment</td>
<td>Bacitracin ointment</td>
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<tr>
<td>Natamycin (Natacyin®) drops</td>
<td>Neomycin/polymyxin B/bacitracin ointment</td>
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<tr>
<td>Neomycin/polymyxin B/gramicidin drops</td>
<td>Sulfacetamide ointment</td>
</tr>
<tr>
<td>PolymyxinB/TMP drops</td>
<td>Chloramphenicol ointment and drops</td>
</tr>
<tr>
<td>Sulfacetamide drops</td>
<td>Oxytetracycline/polymyxin B (Terak®)</td>
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</table>

Previous Conclusions and Recommendations:

1. There is high-quality evidence that there is no difference in efficacy/effectiveness or in safety between agents.
2. Consider at least one medication from each class (aminoglycosides, macrolides, fluoroquinolones and others).
3. Include natamycin as it is the only medication that carries FDA approval for fungal infections.
4. Consider having drops and ointments available.
5. Consider step therapy for 4th and 5th generation fluoroquinolones.
6. Surgical consideration regarding 4th and 5th generation fluoroquinolones which are commonly used pre- and post-op.

Conclusions and Recommendations:

- There is no significant new comparative evidence on the efficacy and safety of agents that changes the previous conclusions.
- No further review of research needed at this time; review comparative costs.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCT’s) comparing ophthalmic antibiotics to placebo or other products was conducted with limits for humans and English. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Care Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in
Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

**New Systematic Reviews:**

A systematic review and meta-analysis by McDonald et al\(^1\) evaluated the efficacy of ophthalmic antibiotics in patients with bacterial keratitis. Randomized controlled trials that compared two or more antibiotics administered for at least 7 days were included. A total of 16 trials with 1,823 participants were included. The primary outcome was treatment success, defined as complete re-epithelialization of the cornea at trial conclusion. There was no evidence of difference in relative risk (RR) of treatment success when moxifloxacin was compared with tobramycin-cefazolin (RR 1.02; 95% CI 0.91 to 1.14), when ciprofloxacin was compared with gentamicin-cefazolin (RR 1.11; 95% CI 0.84 to 1.45), or when moxifloxacin, ofloxacin or ciprofloxacin was compared with aminoglycoside-cephalosporin (RR 0.93: 95% CI 0.64 to 1.36; RR 0.94: 95% CI 0.68 to 1.30; and RR 1.02: 95% CI 0.83 to 1.25, respectively). There was also no difference in risk of treatment success when moxifloxacin, ofloxacin, ciprofloxacin, gatifloxacin or tobramycin-cefazolin were compared with fluoroquinolones (RR 1.02: 95% CI 0.58 to 1.80; RR 0.82: 95% CI 0.57 to 1.16; RR 1.44: 95%: 0.94 to 2.21; RR 0.76: 95% CI 0.40 to 1.44; and RR 1.03: 95% CI 0.85 to 1.24, respectively). When compared as a class, there was no evidence of difference in risk of treatment success between fluoroquinolones and aminoglycoside-cephalosporin (RR 1.01; 95% CI 0.94 to 1.08) in 10 trials with 1,265 participants. No difference was seen in any comparison for the difference in time to cure or risk of serious complications of infections. When compared to aminoglycoside-cephalosporin, ofloxacin significantly reduced the risk of ocular discomfort (RR 0.22; 95% CI 0.13 to 0.39; 2 trials). Tobramycin-cefazolin increased ocular discomfort when compared to fluoroquinolones (RR 3.13; 95% CI 2.13 to 4.60; 3 trials). There was no evidence of significant heterogeneity in any outcome. Risk of bias of each trial was assessed using the Cochrane Risk of Bias tool. The risk of bias overall was low in trials; two trials did not give adequate details on randomization, allocation concealment, or blinding.

Azari et al\(^3\) reviewed the literature available for diagnosis and treatment all types of conjunctivitis. A level of evidence was assigned to treatment recommendations using the following grading system: Level A assigned if there are multiple randomized trials with large numbers of patients, Level B assigned if there are a limited number of randomized trials with small numbers of patients, careful analyses of non-randomized studies, or observational registries, and Level C assigned when expert consensus is the primary basis for the recommendation. For acute bacterial conjunctivitis, tobramycin, besofloxacin, ciprofloxacin, moxifloxacin, ofloxacin, azithromycin, and trimethoprim/polymixin B all have Level A evidence; gentamycin, gatifloxacin, levofloxacin, erythromycin and sulfacetamide all have level B evidence. All treatments for hyperacute bacterial conjunctivitis, viral conjunctivitis, herpes zoster virus and herpes simplex virus are oral medications and have level C evidence.

**New Guidelines:**

*Scottish Intercollegiate Guidelines Network: Antibiotic Prophylaxis in Surgery (Updated April 2014)*\(^4\)

- Grades of Recommendation\(^4\)
  - **Level A** evidence: At least one meta-analysis, systematic review or RCT rated as high quality with very low risk of bias and directly applicable to the target population; or a body of evidence consisting principally of well conducted meta-analyses, systematic reviews or RCTs with low risk of bias directly applicable to the target population and demonstrating overall consistency of results

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Level B evidence: A body of evidence including high quality systematic reviews of case control or cohort studies directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from high quality meta-analyses, systematic reviews or RCTs with low risk of bias

Level C evidence: A body of well conducted case control or cohort studies with low risk of confounding or bias and a moderate probability that the relationship is not causal, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from high quality systematic reviews of case control or cohort studies

Level D evidence: Non-analytic studies (case reports, case series) or expert opinion; or extrapolated evidence from well conducted case control or cohort studies with a low risk or confounding or bias and a moderate probability that the relationship is causal

- **Recommended Indications for surgical antibiotic prophylaxis to prevent skin and soft tissue infections - Ophthalmic**
  - Cataract surgery: Antibiotic prophylaxis is highly recommended (OR 0.36; NNT 451 for endophthalmitis, evidence level 1) (Level A evidence).
  - Glaucoma or corneal grafts: Antibiotic prophylaxis is recommended (Level B evidence, effectiveness inferred from evidence about cataract surgery).
  - Lacrimal surgery: Antibiotic prophylaxis is recommended (OR 0.03, NNT = 9 for wound infection) (Level C evidence).
  - Penetrating eye injury: Antibiotic prophylaxis is recommended (OR 0.20, NNT = 18 for endophthalmitis) (Level B evidence).

**New drugs:**
None

**New Formulations/Indications:**
None

**New FDA safety alerts:**
None
New Trials (Appendix 1):

37 potentially relevant RCTs were evaluated from the literature search. After further review, 34 RCTs did not have a head-to-head comparison and were therefore excluded. The remaining 3 RCTs are briefly described in the table below. Full abstracts are included in Appendix 1.

**Table 1: Description of RCTs**

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blavin et al</td>
<td>Azithromycin TID or tobramycin QID until reepithelialization</td>
<td>Adult patients undergoing penetrating keratoplasty in one eye</td>
<td>Time to reepithelialization</td>
<td>N=46 Similar between tobramycin group (4.14±1.17 days) and azithromycin group (4.13±1.82) (p=0.89)</td>
</tr>
<tr>
<td>Prajna et al</td>
<td>Voriconazole 1% or natamycin 5% applied every hour while awake until reepithelialization then four times daily for at least 3 weeks</td>
<td>Adults with fungal corneal ulcer and visual acuity of 20/40 to 20/400</td>
<td>Best spectacle-corrected visual acuity (BSCVA) at 3 months</td>
<td>N=323 Patients receiving voriconazole did worse than those randomized to receive natamycin (regression coefficient = −0.18; 95% CI, −0.30 to −0.05; P = .006)</td>
</tr>
<tr>
<td>Williams et al</td>
<td>Moxifloxacin 0.5% TID Vs. Polymyxin B-trimethoprim QID</td>
<td>Children aged 1-18 with conjunctivitis</td>
<td>Clinical cure rates at 4-6 days</td>
<td>N=124 Cure rates not different for the two treatment groups (p=0.59)</td>
</tr>
</tbody>
</table>

**References:**

Appendix 1: Abstracts of RCTs


PURPOSE: After keratoplasty, antibiotic eye drops are used to prevent ocular infection until the recipient corneal epithelium has healed. We compared the effects of azithromycin, a new macrolide, with the effect of the standard antibiotics, tobramycin, on the (i) prevention of infection, (ii) epithelial healing, and (iii) ocular tolerance after penetrating keratoplasty.

METHODS: In this prospective, single-center, randomized study, patients undergoing penetrating keratoplasty received postoperative topical dexamethasone and either azithromycin (n=23; Azyter[]; one drop twice daily for 3 days) or tobramycin (n=23; Tobrex[]; 1 drop 4 times daily until complete re-epithelialization). Daily slit-lamp examination with fluorescein was performed, and photographs were taken to digitally assess the re-epithelialized surface area. Daily questionnaires assessed ocular comfort and pain.

RESULTS: There were no cases of infection in either group. The re-epithelialized area of the corneal graft increased at a similar rate in each group, with no difference between the groups on any day. The mean+SD days until complete re-epithelialization did not differ between tobramycin (4.14+1.17) and azithromycin (4.13+1.82) (P=0.89). Superficial punctate keratitis scores were similar for tobramycin (1.39) and azithromycin (1.34). Pain and discomfort scores improved each day after surgery with no differences between the groups on any day.

CONCLUSION: Postkeratoplasty epithelial healing and ocular tolerance were not significantly different between the azithromycin- and tobramycin-treated groups. Our results support the use of azithromycin as an alternative to tobramycin after corneal surgery such as keratoplasty.


OBJECTIVE: To compare topical natamycin vs voriconazole in the treatment of filamentous fungal keratitis.

METHODS: This phase 3, double-masked, multicenter trial was designed to randomize 368 patients to voriconazole (1%) or natamycin (5%), applied topically every hour while awake until reepithelialization, then 4 times daily for at least 3 weeks. Eligibility included smear-positive filamentous fungal ulcer and visual acuity of 20/40 to 20/400.

MAIN OUTCOME MEASURES: The primary outcome was best spectacle-corrected visual acuity at 3 months; secondary outcomes included corneal perforation and/or therapeutic penetrating keratoplasty.

RESULTS: A total of 940 patients were screened and 323 were enrolled. Causative organisms included Fusarium (128 patients [40%]), Aspergillus (54 patients [17%]), and other filamentous fungi (141 patients [43%]). Natamycin treated cases had significantly better 3-month best spectacle-corrected visual acuity than voriconazole-treated cases (regression coefficient=0.18 logMAR; 95% CI, 0.30 to 0.05; P=.006). Natamycin-treated cases were less likely to have perforation or require therapeutic penetrating keratoplasty (odds ratio=0.42; 95% CI, 0.22 to 0.80; P=.009). Fusarium cases fared better with natamycin than with voriconazole (regression coefficient=0.41 logMAR; 95% CI,0.61 to 0.20; P<.001; odds ratio for perforation=0.06; 95% CI, 0.01 to 0.28; P=.001), while non-Fusarium cases fared similarly (regression coefficient=0.02 logMAR; 95% CI, 0.17 to 0.13; P=.81; odds ratio for perforation=1.08; 95% CI, 0.48 to 2.43; P=.86).

CONCLUSIONS: Natamycin treatment was associated with significantly better clinical and microbiological outcomes than voriconazole treatment for smear-positive filamentous fungal keratitis, with much of the difference attributable to improved results in Fusarium cases.

APPLICATION TO CLINICAL PRACTICE: Voriconazole should not be used as monotherapy in filamentous keratitis.


OBJECTIVE: To perform a randomized controlled trial comparing moxifloxacin hydrochloride with polymyxin B-trimethoprim for the treatment of acute conjunctivitis.

STUDY DESIGN: Patients ages 1–18 years old with acute conjunctivitis had cultures performed and were randomized to receive either moxifloxacin hydrochloride or polymyxin B-trimethoprim ophthalmic solution for 7 days. Response to treatment was determined by phone query on day 4–6 and by examination with post-treatment conjunctival culture on day 7–10.

RESULTS: One hundred and twenty-four patients were enrolled. Eighty patients (65%) had recognized pathogens (55 Haemophilus influenzae, 22 Streptococcus pneumoniae, 4 Moraxella catarrhalis) isolated from their conjunctiva. One hundred fourteen (56/62 moxifloxacin and 58/62 polymyxin B-trimethoprim) completed the 4-6 day evaluation, with 43/56 (77%) of the moxifloxacin

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group and 42/58 (72%) of the polymyxin B-trimethoprim group clinically cured according to parents (noninferiority test P = .04). Eighty-nine (39/56 moxifloxacin and 50/58 polymyxin B-trimethoprim) patients completed the 7-10 day evaluation. Clinical cure was observed in 37/39 (95%) of the moxifloxacin and 49/51 (96%) of the polymyxin B-trimethoprim treated groups (noninferiority test P < .01). Clinical cure rates for culture positive and negative conjunctivitis were not different. There was no statistically significant difference in bacteriologic cure rates between the 2 groups.

**CONCLUSIONS:** Polymyxin B-trimethoprim continues to be an effective treatment for acute conjunctivitis with a clinical response rate that does not differ from moxifloxacin. Use of polymyxin B-trimethoprim for the treatment of conjunctivitis would result in significant cost savings compared with fluoroquinolones.