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Month/Year of Review: September 2012
PDL Class: Opthalmic Antibiotics
Literature Search End Date: June week 1, 2012

Date of Last Review: December 2009
Source Document: Provider Synergies (PS)

Current Status of PDL Class:

Preferred Agents	Non-Preferred Agents
Aminoglycosides	
Gentamicin drops and ointment	
Tobramycin drops and Tobramycin (Tobrex®) ointment	
Fluoroquinolones	
Ciprofloxacin drops	Besifloxacin (Besivance®) drops
Gatifloxacin (Zymar®) 0.3% drops	Ciprofloxacin (Ciloxan®) ointment
Levofloxacin 0.5% drops	Gatifloxacin (Zymaxid®) 0.5% drops
Moxifloxacin (Vigamox®) drops	Levofloxacin (Iquix®) 1.5% drops
Ofloxacin drops	
Macrolides	
Erythromycin base ointment	Azithromycin (AzaSite®)
Others	
Bacitracin/polymyxin B ointment	Bacitracin ointment
Natamycin (Natacyn®) drops	Neomycin/polymyxin B/bacitracin ointment
Neomycin/polymyxn B/gramicidin drops	Sulfaetamide ointment
PolymiyxinB/TMP drops	
Sulfacetamide drops	

Previous 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.

Background:
Acute conjunctivitis is usually a benign, self-limited condition or is easily treated. Acute conjunctivitis can be classified as infectious (bacterial or viral) and noninfectious (allergic or nonallergic). Bacterial conjunctivitis is more common in children than in adults.[1] Bacterial conjunctivitis is commonly caused by Staphylococcus aureus, Streptococcus pneuminiae, Haemophilus influenza, and Moraxella catarrhalis. S. aureus infection is common in adults; the other pathogens are common in children.[2] While acute bacterial conjunctivitis is often self-limiting, empiric therapy with opthalmic antibiotics is a common practice.

Methods:
A MEDLINE OVID search was conducted using all ophthalmic antibiotics limited to randomized controlled trials and meta-analysis, English language, and conducted in humans since the literature search conducted for the previous PS review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality 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 Trials:
A total of 18 citations resulted and after review for inclusions, two potentially relevant clinical trials were identified (Appendix 1). A multicenter, randomized, investigator-masked and active-controlled, 15-day study evaluated the clinical efficacy and safety of tobramycin/dexamethasone (TobraDex ST ; 'ST') ophthalmic suspension 0.3%/0.05% compared to azithromycin (Azasite®) ophthalmic solution (1%) in the treatment of moderate to severe blepharitis/ blepharoconjunctivitis. A statistically significant lower mean global score ($p = 0.0002$) was observed in subjects treated with ST compared to subjects treated with azithromycin at Day 8. No serious adverse events were reported during the course of the study in either group. The authors concluded ST provides a fast and effective treatment of acute blepharitis compared to azithromycin. Initial therapy with the combination of tobramycin/dexamethasone provides faster inflammation relief than azithromycin for moderate to severe blepharitis/blepharoconjunctivitis.[3]

Another trial was a multicenter, prospective, randomized, double-masked, vehicle-controlled, parallel-group study evaluated the efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days compared with vehicle (formulation without besifloxacin) in the treatment of adults and children with bacterial conjunctivitis. Of 202 patients randomized to treatment (mean [SD] age, 25.2 [24.3] years; 56.9% female; 76.7% white), 109 had culture-confirmed bacterial conjunctivitis (53 besifloxacin ophthalmic suspension, 56 vehicle). At visit 2, the besifloxacin ophthalmic suspension group had significantly greater rates of clinical resolution compared with the vehicle group (37/53 [69.8%] vs 21/56 [37.5%], respectively; $P < 0.001$), as well as significantly greater rates of bacterial eradication (46/53 [86.8%] vs 32/56 [57.1%]; $P < 0.001$). At visit 3, rates of bacterial eradication were also significantly greater in the besifloxacin ophthalmic suspension group compared with the vehicle group (46/53 [86.8%] vs 39/56 [69.6%]; $P = 0.038$). The incidence of ocular AEs did not differ significantly between treatment groups (4/94 [4.3%] vs 8/98 [8.2%]).[4]

New drugs:
None

New FDA Indications:
None

New FDA safety alerts:
None

New Systematic Reviews:
None identified

Guidelines:
None identified.

Recommendations:

- No further research or review needed at this time.
- Evaluate comparative costs in executive session.

References:

1. Anon. Conjunctivitis. Available at: http://www-uptodate-com.liboff.ohsu.edu/contents/conjunctivitis?source=search_result&search=acute+conjunctivitis&selectedTitle=1%7E150#H20. Accessed June 6, 2012.

2. Friedlaender MH. A review of the causes and treatment of bacterial and allergic conjunctivitis. *Clinical Therapeutics*. 1995;17(5):800–810.

3. Torkildsen GL, Cockrum P, Meier E, et al. Evaluation of clinical efficacy and safety of tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% compared to azithromycin ophthalmic solution 1% in the treatment of moderate to severe acute blepharitis/blepharoconjunctivitis. *Current Medical Research and Opinion*. 2011;27(1):171–178.

4. Silverstein BE, Allaire C, Bateman KM, et al. Efficacy and Tolerability of Besifloxacin Ophthalmic Suspension 0.6% Administered Twice Daily for 3 Days in the Treatment of Bacterial Conjunctivitis: A Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study in Adults and Children. *Clinical Therapeutics*. 2011;33(1):13–26.

Appendix 1

1. Torkildsen GL, Cockrum P, Meier E, Hammonds WM, Silverstein B, Silverstein S. Evaluation of clinical efficacy and safety of tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% compared to azithromycin ophthalmic solution 1% in the treatment of moderate to severe acute blepharitis/blepharoconjunctivitis. *Curr Med Res Opin.* 2011 Jan;27(1):171-8. Epub 2010 Dec 7

   Objective: To evaluate the clinical efficacy and safety of tobramycin/dexamethasone (TobraDex ST ; 'ST') ophthalmic suspension 0.3%/0.05% compared to azithromycin (Azasite) ophthalmic solution (1%) in the treatment of moderate to severe blepharitis/blepharoconjunctivitis.
   Research design and methods: The study was a multicenter, randomized, investigator-masked, and active-controlled, 15-day study. Enrolled in the study were 122 adult subjects (at least 18 years of age) diagnosed with moderate to severe blepharitis/blepharoconjunctivitis, defined by a minimum score of at least '1' for one of the lid signs, one of the conjunctival signs, and one of the symptoms in at least one eye and a minimum global score (total signs and symptoms score) of '5' in the same eye. One group of 61 subjects received ST with instructions to dose 1 drop four times daily (QID) for 14 days. The other group of 61 subjects received azithromycin and dosed with 1 drop twice daily (BID) for 2 days followed by once daily (QD) dosing for 12 days. Visits were conducted at Day 1 (baseline), Day 8 and Day 15. The a priori primary outcome parameter of the study was the seven-item global score defined as the total score of lid margin redness, bulbar conjunctival redness, palpebral conjunctival redness, ocular discharge (0-3 scale), and lid swelling, itchy eyelids, and gritty eyes (0-4 scale). The study utilized standardized, validated photograph control scales developed by Ora, Inc. (Andover, MA).
   Results: A statistically significant lower mean global score ($p = 0.0002$) was observed in subjects treated with ST compared to subjects treated with azithromycin at Day 8. No serious adverse events were reported during the course of the study in either group.
   Conclusion: ST provides a fast and effective treatment of acute blepharitis compared to azithromycin. Initial therapy with the combination of tobramycin/dexamethasone provides faster inflammation relief than azithromycin for moderate to severe blepharitis/blepharoconjunctivitis.

2. Silverstein BE, Allaire C, Bateman KM, Gearinger LS, Morris TW, Comstock TL. Efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days in the treatment of bacterial conjunctivitis: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study in adults and children. *Clin Ther.* 2011 Jan;33(1):13-26.

   Background: Besifloxacin is a topical fluoroquinolone with potent in vitro activity against a broad spectrum of ocular pathogens, including drug-resistant strains. Besifloxacin ophthalmic suspension 0.6% given 3 times daily for 5 days has been reported to be more effective than its vehicle in the treatment of bacterial conjunctivitis. Pharmacokinetic/pharmacodynamic modeling suggests that besifloxacin might also be effective given twice daily.
   Objective: This study evaluated the efficacy and tolerability of besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days compared with vehicle (formulation without besifloxacin) in the treatment of adults and children with bacterial conjunctivitis.
   Method: This was a multicenter, prospective, randomized, double-masked, vehicle-controlled, parallel-group study. Patients aged ≥1 year with bacterial conjunctivitis were randomized to receive besifloxacin ophthalmic suspension or vehicle administered twice daily for 3 days. There were 3 study visits: the baseline visit, visit 2 (day 4 or 5), and visit 3 (day 7±1). Participants recorded the times of medication instillation in a patient diary. The primary end points were clinical resolution and bacterial eradication of the baseline bacterial infection at visit 2 in patients with culture-confirmed bacterial conjunctivitis. Secondary end points were clinical resolution and bacterial eradication of the baseline bacterial infection at visit 3, individual clinical outcomes (ocular conjunctival discharge and bulbar conjunctival injection) at the follow-up visits, and microbial and clinical outcomes for overall bacterial species and individual gram-positive and gram-negative bacterial species. Tolerability assessments included ocular adverse events (AEs), changes in visual acuity, biomicroscopy and ophthalmoscopy findings, and nonocular AEs.

Results: Of 202 patients randomized to treatment (mean [SD] age, 25.2 [24.3] years; 56.9% female; 76.7% white), 109 had culture-confirmed bacterial conjunctivitis (53 besifloxacin ophthalmic suspension, 56 vehicle). At visit 2, the besifloxacin ophthalmic suspension group had significantly greater rates of clinical resolution compared with the vehicle group (37/53 [69.8%] vs 21/56 [37.5%], respectively; P < 0.001), as well as significantly greater rates of bacterial eradication (46/53 [86.8%] vs 32/56 [57.1%]; P < 0.001). At visit 3, rates of bacterial eradication were also significantly greater in the besifloxacin ophthalmic suspension group compared with the vehicle group (46/53 [86.8%] vs 39/56 [69.6%]; P = 0.038). Results for the individual clinical outcomes and microbial and clinical outcomes by gram-positive and gram-negative species were consistent with the primary efficacy outcomes. The incidence of ocular AEs did not differ significantly between treatment groups (4/94 [4.3%] vs 8/98 [8.2%]). Ocular AEs in all treated eyes in the respective groups included bacterial conjunctivitis (3/157 [1.9%] and 5/154 [3.2%]), conjunctivitis (3/157 [1.9%] and 4/154 [2.6%]), and allergic conjunctivitis (2/157 [1.3%] and 1/154 [0.6%]). These events were of mild or moderate severity. Changes in visual acuity and biomicroscopy and ophthalmoscopy findings were comparable between groups. There were few nonocular AEs (2/94 [2.1%] vs 3/98 [3.1%]; P = NS), none of them considered treatment related.
Conclusion: In these adults and children with bacterial conjunctivitis, treatment with besifloxacin ophthalmic suspension 0.6% administered twice daily for 3 days was effective and well tolerated.