

# WYOMING PDLAC THERAPEUTIC CLASS REVIEW

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## OPHTHALMIC ANTIBIOTICS

This publication is a result of the collaboration of the Goold Health Systems, Inc. Clinical Workgroup and represents the opinion of these authors based on a review of the literature available at the time it was written. It is intended for the sole purpose of providing information to committee members in order to compare medications within a specified subset of clinical parameters. It is not intended to provide specific clinical advice for any condition, or to be an exhaustive review of all potential aspects of pharmacotherapies for any given condition. Medical evidence is rapidly changing, and no representation is made regarding the use of this material beyond the stated purpose.

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## SYNOPSIS

Care must be taken with any patient who presents with a “red eye,” as there are numerous conditions that can simulate conjunctivitis. Most cases of conjunctivitis are associated with fairly painless discharge and irritation, essentially normal vision, a normally reactive pupil, normal intraocular pressure, an essentially clear cornea, and generally diffuse conjunctival injection. Conjunctivitis may be caused by viruses (most common), bacteria (second most common), chlamydia (third most common), parasites, fungi (rare), and antigens.

Ophthalmic antibiotics are medications used to treat bacterial infections in the eye. The actual incidence of bacterial conjunctivitis is unknown; many cases of conjunctivitis are treated as if they were caused by bacterial organisms, but it is not a common practice to culture the site. Eye infections are characterized by a rapid onset of unilateral lid edema, conjunctival injection, and a mucopurulent discharge, followed by involvement of the opposite eye within 1 to 2 days. *Staphylococcus* and *Corynebacterium* species are the most common organisms to colonize the lids and conjunctiva; consequently, they are prominent causes of infectious conjunctivitis. Although almost any bacterial organism can cause conjunctivitis given the appropriate set of conditions, the most common ones are *Staphylococcus* species, *Streptococcus pneumoniae*, *Haemophilus* species, *Moraxella*, *Corynebacterium diphtheriae*, *Neisseria* species, and enteric gram-negative rods. Chlamydia classically causes chronic conjunctivitis.

Although acute bacterial conjunctivitis often resolves spontaneously in 2-5 days, treatment with topical antibiotics is usually prescribed to reduce the duration and intensity of symptoms, as well as the potential for person-to-person spread. Treatment with a topical broad-spectrum agent is necessary for 7 to 10 days. Appropriate agents may be selected or altered based on laboratory results.<sup>1</sup>

The use of antibiotic/steroid combination products for the treatment of conjunctivitis is controversial. Although these combination products have FDA approval for the treatment of these infections, practice guidelines recommend that they *not* be used in the treatment of presumed infective conjunctivitis; steroids can disrupt the normal defense mechanisms of the eye, allowing existing viral or fungal infections to worsen.<sup>2</sup>

The drugs included in this therapeutic class review include: azithromycin (AzaSite®), bacitracin, bacitracin and polymyxin B (Polysporin®), bacitracin/neomycin/polymyxin B (Neosporin® Ointment), ciprofloxacin (Ciloxan®), erythromycin, gatifloxacin (Zymar®), gentamicin (Garamycin®), levofloxacin (Iquix®, Quixin®), moxifloxacin (Vigamox®), neomycin/polymyxin B/gramicidin (Neosporin® solution), ofloxacin (Ocuflox®), sulfacetamide (Bleph-10®), tobramycin (Tobrex®), and trimethoprim and polymyxin B (Polytrim®).

## FDA APPROVED INDICATIONS<sup>8-29, 36</sup>

The indications for treatment of bacterial infections or corneal ulcers listed in the table below are for those caused by susceptible strains, unless otherwise noted.

Drug	Bacterial conjunctivitis	Superficial ocular infections <sup>1</sup>	Corneal ulcer	Steroid-responsive inflammation w/bacterial infection
azithromycin (AzaSite®)	√			
bacitracin		√		
bacitracin and polymyxin B (Polysporin®)		√		
bacitracin, neomycin, and polymyxin B (Neosporin® ointment)		√		
bacitracin, neomycin, polymyxin B, hydrocortisone (Cortisporin®)				√
ciprofloxacin sol (Ciloxan®)		√		
ciprofloxacin ointment (Ciloxan®)	√			
erythromycin <sup>2</sup>		√		
gatifloxacin (Zymar®)	√			
gentamicin (Garamycin®)		√		
levofloxacin (Iquix®)			√	
levofloxacin (Quixin®)	√			
moxifloxacin (Vigamox®)	√			
neomycin, polymyxin B, & dexamethasone (Maxitrol®)				√

Drug	Bacterial conjunctivitis	Superficial ocular infections <sup>1</sup>	Corneal ulcer	Steroid-responsive inflammation w/bacterial infection
neomycin, polymyxin B, & gramicidin (Neosporin® solution)		√		
neomycin, polymyxin B, & hydrocortisone (Cortisporin®)				√
ofloxacin (Ocuflox®)		√		
sulfacetamide <sup>3</sup> (Bleph-10®)		√		
tobramycin (Tobrex®)		√		
tobramycin/dexamethasone (TobraDex®)				√
trimethoprim/polymyxin B (Polytrim®)	√			

<sup>1</sup> Infections involving the conjunctiva and/or cornea such as conjunctivitis, keratitis, keratoconjunctivitis, blepharitis, and blepharoconjunctivitis, corneal ulcers, acute meibomianitis, and dacryocystitis

<sup>2</sup> Also indicated for prophylaxis of ophthalmia neonatorum due to *N. gonorrhoeae* or *C. trachomatis*

<sup>3</sup> Also indicated as adjunctive treatment for trachoma with systemic sulfonamides

## DOSAGE FORMS, DOSE, AND MANUFACTURER<sup>8-29</sup>

All drops should be instilled into the affected eye(s) unless specifically noted. Please note that the brand name for erythromycin and bacitracin are no longer available.

Drug	Dosage Forms	Dose	Manufacturer
azithromycin (AzaSite®)	<u>1% solution:</u> 5 ml	1 drop BID x2 days, 8-12 hours apart, then 1 drop QD X5 days.	Inspire Pharmaceuticals
bacitracin	<u>Ointment:</u> 3.5 g	Apply 1 to 3 times daily.	Various generic manufacturers.
bacitracin and polymyxin B (Polysporin®)	<u>Ointment:</u> 3.5 g	Apply every 3- 4 hrs for 7-10 days.	Various generic manufacturers. (Monarch Pharm.)

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Drug	Dosage Forms	Dose	Manufacturer
<b>bacitracin, neomycin, and polymyxin B (Neosporin® OP)</b>	<u>Ointment:</u> 3.5 g	Apply every 3- 4 hours for 7- 10 days.	Various generic manufacturers. (Monarch Pharm.)
<b>ciprofloxacin (Ciloxan®)</b>	<u>0.3% solution:</u> 2.5ml, 5ml, 10 ml  <u>0.3% ointment:</u> (3.5 gm)	<b>Conjunctivitis:</b> <i>Ophthalmic soln:</i> 1-2 drops Q2hrs while awake X2 days then 1-2 drops every 4 hrs X5 days. <i>Ophthalmic oint:</i> Apply a 1/2" ribbon into the conjunctival sac TID X2 days then BID X5 days.  <b>Corneal ulcer:</b> <i>Ophthalmic soln:</i> Day 1: 2 drops every 15 min for 6 hrs, then 2 drops every 30 min. Day 2: 2 drops hourly. Day 3-14: 2 drops every 4 hrs. Treatment may continue after day 14 if re-epithelialization has not occurred.	Various generic manufacturers <sup>1</sup> (Alcon)
<b>erythromycin</b>	<u>0.5% ointment:</u> 3.5 gm	<i>Superficial ocular infections:</i> Apply up to 6x daily. <i>Neonatal prophylaxis:</i> Apply QD	Various generic manufacturers
<b>gatifloxacin (Zymar®)</b>	<u>0.3% solution:</u> 6ml, 10 ml	1 drop every 2 hours while awake (max 8X daily) on days 1- 2, then 1 drop QID on days 3-7.	Allergan
<b>gentamicin (Garamycin®)</b>	<u>0.1% ointment:</u> 3.5gm <u>0.3% solution:</u> 5ml, 15ml	Apply 2 to 3 times a day.	Various generic manufacturers. (H.J. Harkins Comp.)
<b>levofloxacin (Iquix®)</b>	<u>1.5% solution:</u> 5 ml	1-2 drops every 30 min-2 hrs while awake and every 4-6 hrs at bedtime days 1-3, then 1-2 drops every 1-4 hrs while awake	Santen
<b>levofloxacin (Quixin®)</b>	<u>0.5 % solution:</u> 5 ml	1-2 drops every 2 hrs while awake, up to 8 times daily days 1-2, then 1-2 drops every 4hrs up to QID days 3-7	Santen
<b>moxifloxacin (Vigamox®)</b>	<u>0.5% solution:</u> 3 ml	1 drop TID for 7 days.	Alcon
<b>neomycin, polymyxin B, and gramicidin (Neosporin®)</b>	<u>Solution:</u> 10 ml	1-2 drops 4 to 6 times per day or more frequently as required for severe infections.	Various generic manufacturers. (Monarch Pharm.)

Drug	Dosage Forms	Dose	Manufacturer
<b>ofloxacin (Ocuflox®)</b>	<u>0.3% solution:</u> 5ml, 10 ml	<b>Conjunctivitis:</b> 1-2 drops every 2-4 hours for the first 2 days, then use QID for 5 days. <b>Corneal ulcer:</b> Day 1-2: 1-2 drops every 30 min while awake and every 4-6 hours at bedtime. Days 3-8: 1-2 drops every hour while awake. Then 1-2 drops QID until clinical cure.	Various generic manufacturers. (Allergan)
<b>sulfacetamide (Bleph-10®)</b>	<u>10%, 15%, and 30% solution:</u> 5ml, 15 ml	<b>Ointment:</b> Apply to lower conjunctival sac QD-QID and HS <b>Solution:</b> 1-2 drops up to every 2-3 hrs in lower conjunctival sac during waking hours and less frequently at night for 7-10 days <b>Trachoma:</b> 2 drops in the conjunctival sac every 2 hrs; use in conjunction with systemic therapy	Various generic manufacturers. (Allergan)
<b>tobramycin (Tobrex®)</b>	<u>0.3% ointment:</u> 3.5 gm <u>0.3% solution:</u> 5 ml	<b>Ointment:</b> ½ inch ribbon BID-TID. In severe infections, ½ in. every 3-4 hrs until improvement <b>Solution:</b> 1-2 drops every 4 hrs. In severe infections, 2 drops every hr until improvement	Various generic manufacturers <sup>1</sup> (Alcon)
<b>trimethoprim and polymyxin B (Polytrim®)</b>	<u>1mg/10000U per ml solution:</u> 5ml, 10 ml	1 drop every 3 hrs (max of 6 doses) for 7- 10 days	Various generic manufacturers (Allergan)

<sup>1</sup> Solution only

## PHARMACOLOGY <sup>8-29</sup>

Quinolone antibiotics (e.g. ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin) exert their antibacterial action through inhibition of topoisomerase II and topoisomerase IV. Bacitracin interferes with bacterial cell wall synthesis. Polymyxin B increases the permeability of the bacterial cell membrane. Azithromycin and erythromycin are macrolide antibiotics that act by inhibiting bacterial protein synthesis, whereas gentamicin and neomycin are aminoglycoside antibiotics that act in the same manner. Trimethoprim blocks the production of tetrahydrofolic acid, which selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

## PHARMACOKINETICS <sup>8-29</sup>

Ophthalmic antibiotics are used topically in the eye to treat bacterial infection. Information concerning the pharmacokinetics of ophthalmic antibiotics is very limited. Several of these antibiotics are also used for systemic administration. Pharmacokinetic parameters determined after systemic use cannot be applied to topical use in the eye. Serum concentrations were determined for a few products and the resultant concentrations were significantly less than the serum concentrations achieved after systemic administration.

## CLINICAL TRIALS

Many of these products received FDA approval over 30 years ago. Clinical trials performed to obtain FDA approval confirmed all the medications in this therapeutic class to be superior in efficacy, as well as showing safety of the drug, when compared to placebo.

Multiple randomized controlled trials comparing topical antibiotics have generally found no statistically significant differences between antibiotics in terms of clinical or microbiologic cure in patients with suspected or proven conjunctivitis.<sup>3</sup> A systematic review of randomized controlled trials (RCTs) of topical antibiotics vs placebo in patients with culture-positive bacterial conjunctivitis found that all the active treatments studied (ciprofloxacin, polymyxin B sulfate-bacitracin, and ofloxacin) were significantly more effective than placebo in terms of clinical and microbiologic cure rates at 2-10 days.<sup>4</sup> A Cochrane Review in 2006 included trials involving polymyxin-bacitracin, ciprofloxacin 0.3%, and norfloxacin 0.3% for the treatment of acute bacterial conjunctivitis. Results of this study also indicated that topical antibiotics were advantageous in terms of earlier clinical and microbiological remission when compared to placebo, but overall the results were marginal in this self-limiting condition.<sup>31</sup>

In keeping with these general findings, two RCTs of topical ciprofloxacin vs topical tobramycin and one RCT of topical gentamicin vs topical trimethoprim-polymyxin B sulphate vs sulfacetamide found no difference in clinical or microbiological cure rates after 7 days.<sup>5-7</sup>

The table below discusses further comparator trials for ophthalmic antibiotics.

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Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
Protzko et al <sup>33</sup> 2007	Prospective, randomized, active-controlled, double-masked, phase 3 trial  azithromycin 1% vs tobramycin 0.3%	N=743  5 days	Subjects with clinical diagnosis of bacterial conjunctivitis	Compared safety and tolerability of the two treatment arms	-Both studies were well tolerated. Eye irritation (1.9%), worsening bacterial conjunctivitis (1.1%), and conjunctival hyperemia (1.1%) were most frequently observed with azithromycin.  -Microbial eradication rates, as well as bacterial infection recurrence were equivalent with both treatment groups.	-Both treatments were equally effective and safe for the treatment of bacterial conjunctivitis.
Granet et al <sup>34</sup> 2008	Multicenter, randomized trial  polymyxin/ trimethoprim (P/T) vs moxifloxacin 0.5%	N=84  7 days	Subjects younger than 18 with a clinical diagnosis of bacterial conjunctivitis	Relief of all signs and symptoms of bacterial conjunctivitis	-81% of patients in the moxifloxacin treatment group had complete resolution of ocular signs and symptoms as compared with 44% with complete resolution in the P/T group (p=0.001) at the 48-hour visit.  -There were not any adverse events reported.	-While both P/T and moxifloxacin were safe treatments for bacterial conjunctivitis, it was shown that moxifloxacin resolved the infection statistically significantly faster than P/T.
Gross et al <sup>35</sup> 1997	Double-blind, randomized, controlled study  ciprofloxacin 0.3% solution vs tobramycin solution	N=257  7 days	Pediatric patients aged from less than 1 year of age to 12 years diagnosed with bacterial conjunctivitis	Compared safety and tolerability of the two treatment arms in pediatric population	-90.1% of the ciprofloxacin group showed microbial eradication compared with 84.3% of the tobramycin group (p=0.29).  -87% of the ciprofloxacin group were deemed clinically cured on day 7 by physicians compared with 89.9% of the tobramycin group (p>0.5%).  -Serious side effects were not reported with either treatment group.	-Both ciprofloxacin and tobramycin were safe and effective treatments for bacterial conjunctivitis in the pediatric population.  - Ciprofloxacin and tobramycin were equally efficacious and comparable treatments.

**CONTRAINDICATIONS** 8-29

All medications in this therapeutic class carry a contraindication of hypersensitivity to their active ingredient or to any component of the compound. All of the antibiotics in the quinolone family carry a contraindication for use if there is a history of hypersensitivity to other fluoroquinolones.

**SPECIAL POPULATIONS** 8-29

There are several medications in this therapeutic class in which safety and efficacy have not been determined for use in the pediatric population. There is currently no information regarding dosage change for those with renal or hepatic impairment.

<b>Drug</b>	<b>Pediatrics</b>	<b>Pregnancy Category</b>
<b>azithromycin (AzaSite®)</b>	> 1 yr	B
<b>bacitracin</b>	Not specified	C
<b>bacitracin and polymyxin B (Polysporin®)</b>	No	C
<b>bacitracin, neomycin, and polymyxin B (Neosporin® OP)</b>	No	C
<b>ciprofloxacin (Ciloxan®)</b>	<i>Solution:</i> > 1 yr <i>Ointment:</i> > 2 yrs	C
<b>erythromycin</b>	Indicated for use in neonates.	B
<b>gatifloxacin (Zymar®)</b>	> 1 yr	C
<b>gentamicin (Garamycin®)</b>	Not established for neonates.	C
<b>levofloxacin (Iquix®)</b>	> 6 yr	C
<b>levofloxacin (Quixin®)</b>	> 1 yr	C
<b>moxifloxacin (Vigamox®)</b>	> 1 yr	C

Drug	Pediatrics	Pregnancy Category
<b>neomycin, polymyxin B, and gramicidin (Neosporin®)</b>	Not specified	C
<b>ofloxacin (Ocuflox®)</b>	> 1 yr	C
<b>sulfacetamide (Bleph-10®)</b>	> 2 months	C
<b>tobramycin (Tobrex®)</b>	> 2 months	B
<b>trimethoprim and polymyxin B (Polytrim®)</b>	> 2 months	C

## ADVERSE DRUG REACTIONS <sup>8-29</sup>

All bacitracin, erythromycin, gentamicin, and tobramycin products carry an incidence of hypersensitivity reactions, including itching, reddening, and edema of the conjunctiva and eyelid. AzaSite carries a 1-2% incidence of eye irritation. When Ciloxan® solution was being used to treat corneal ulcer, approximately 17% of patients had white crystalline precipitates. Sulfacetamide can also cause burning/stinging and conjunctivitis.

Other than those mentioned, the specific incidence of adverse reactions were not available.

Ocular Adverse Reaction	ciprofloxacin <sup>1</sup> (Ciloxan®)	gatifloxacin (Zymar®)	levofloxacin (Iquix®)	levofloxacin (Quixin®)	moxifloxacin (Vigamox®)	ofloxacin (Ocuflox®)
Conjunctival irritation		√				
Conjunctivitis					√	√
Decreased/blurred vision		√	√	√	√	√
Dry eye		√			√	√
Foreign body sensation	√			√		√
Increased lacrimation		√				

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Ocular Adverse Reaction	ciprofloxacin <sup>1</sup> (Ciloxan®)	gatifloxacin (Zymar®)	levofloxacin (Iquix®)	levofloxacin (Quixin®)	moxifloxacin (Vigamox®)	ofloxacin (Ocuflox®)
Instillation site irritation	√		√			
Keratitis		√			√	√
Ocular burning				√		
Ocular discomfort/pain		√	1-2%	√	√	√
Ocular infection			√			
Photophobia				√		√
Red eye		√				√
Tearing					1-6%	√

<sup>1</sup>ciprofloxacin solution  
√-% incidence not provided

The table below describes those medications in this class review with reported non-ocular adverse events.

Drug	Non-Ocular Events
azithromycin (AzaSite®)	Nasal congestion, sinusitis (< 1%)
gatifloxacin (Zymar®)	Headache, taste disturbance (1-4%).
gentamicin (Garamycin®)	Thrombocytopenia purpura, hallucinations.
levofloxacin (Iquix®)	Headache, taste disturbance (8-10%). Diarrhea, dyspepsia, fever, infection nausea, and throat irritation (1-2%).
levofloxacin (Quixin®)	Fever, headache, pharyngitis.
moxifloxacin (Vigamox®)	Fever, ↑ cough, infection, otitis media, pharyngitis, rash, and rhinitis (1-4%).
ofloxacin (Ocuflox®)	Dizziness, nausea

## DRUG-DRUG INTERACTIONS <sup>8-29</sup>

There is currently no drug-drug interactions specified or reported in this therapeutic category.

## SUMMARY

Although acute bacterial conjunctivitis is often self-limiting, the use of antibiotics is associated with significantly improved rates of early clinical remission, and early and late microbiological remission. Topical broad-spectrum antibiotics are extremely effective in the treatment of bacterial conjunctivitis. Redness and discharge are reduced within 48 hours and resolve within a week in most cases. The prevailing approach to the management of acute bacterial conjunctivitis remains empiric treatment with a topical preparation. The American Academy of Ophthalmology treatment guidelines for bacterial conjunctivitis recommends that treatment selection should be based upon what is the most convenient or is the least expensive option.<sup>32</sup>

Most red eye is viral in nature and may not require antimicrobial therapy. If concern exists for a bacterial infection, there is no clear evidence that one agent is more effective than another. While the quinolones may have more in vitro activity against *Staphylococcal aureus*, the evidence of clinical superiority over less expensive drugs is lacking. There is also no clear clinical advantage of one of the newer agents over the others.

One approach is to utilize trimethoprim-polymyxin B (Polytrim<sup>®</sup>), bacitracin-polymyxin B (Polysporin<sup>®</sup>), or erythromycin ointment as first line therapy and reserve the quinolones for more serious cases, especially if suspected *Pseudomonas* (contact lens wearers) or corneal ulcers exist.<sup>30</sup>

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