Therapeutic Class Overview
Ophthalmic Antibiotics and Combinations

INTRODUCTION

- Blepharitis is a chronic inflammatory condition of the eyelids, often presenting with the symptoms of eye irritation and redness. Overgrowth of normal bacterial flora plays a role in the pathophysiology of blepharitis, with the most common causative organisms including *Staphylococcus* species, *Corynebacterium* species, and *Propionibacterium acnes*. The mainstay of the treatment of blepharitis is patient education regarding eyelid hygiene as well as the use of ophthalmic antibiotics. Of note, blepharitis is a chronic condition without definitive cure; therefore, satisfactory results require a long-term commitment to treatment and appropriate expectations. Ophthalmic corticosteroids may also be used acutely to treat exacerbations (*American Academy of Ophthalmology [AAO] 2013*).
- Conjunctivitis occurs worldwide and affects all ages and social strata. This infection rarely causes permanent visual loss or structural damage, and mild cases may be self-limited, as many cases will resolve without treatment in immunocompetent individuals. The most common causative pathogens seen with bacterial conjunctivitis include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. The selection of an ophthalmic antibiotic is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis (*AAO 2013; American Optometric Association [AOA] 2002*).
- Severe bacterial conjunctivitis is characterized by purulent discharge, pain, and marked eye inflammation. In these cases, cultures and slides for gram staining should be obtained, and the results of these laboratory tests should guide the choice of the antibiotic. Methicillin-resistant *S. aureus* has been isolated in patients with bacterial conjunctivitis with increasing frequency and may be resistant to many available ophthalmic antibiotics. In patients with conjunctivitis caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, systemic antibiotic therapy is necessary, and while not necessary, ophthalmic antibiotics are also typically used (*AAO 2013; AOA 2002*).
- Bacterial keratitis is characterized by an inflammation of the cornea and rarely occurs in the normal eye due to the cornea's natural resistance to infection. However, several predisposing factors such as contact lens wear, trauma, corneal surgery, ocular surface disease, systemic disease, and immunosuppression may alter the defense mechanisms of the ocular surface and allow for infection of the cornea. Due to corneal scarring or topographic irregularity, many forms of this infection result in visual loss. Untreated or severe bacterial keratitis can result in corneal perforation and may develop into endophthalmitis and result in the loss of the eye. The most common causative organisms of bacterial keratitis include *Staphylococci* and gram-negative rods, of which the most frequent organisms identified are *Pseudomonas* species. Ophthalmic antibiotics are the preferred method of treatment in many cases, and antibiotic ointments may be useful at bedtime in less severe cases or as adjunctive therapy. In addition, broad-spectrum ophthalmic antibiotics are used initially as empiric treatment. In severe cases, patients should be followed daily until stabilization or clinical improvement is documented (*AAO 2013*).
- Though not Food and Drug Administration (FDA)-approved, ophthalmic antibiotics are routinely used to prevent postoperative infections after eye surgeries such as refractive surgeries and cataract removal, while ophthalmic corticosteroids may also be used to reduce inflammation associated with surgeries (*AAO 2016; AAO 2013; AOA 2004*).
- Medispan class: Ophthalmic Antibiotics, Ophthalmic Anti-infective Combinations, and Ophthalmic Sulfonamides.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aminoglycosides	
Gentak (gentamicin) †	✔
Tobrex (tobramycin) †	✔ *
Macrolides	
Azasite (azithromycin)	-
erythromycin	✔
Other	
bacitracin	✔
Bleph-10 (sulfacetamide sodium) §	✔
Quinolones	
Besivance (besifloxacin)	-
Ciloxan (ciprofloxacin)	✔ *
levofloxacin	✔
Moxeza, Vigamox (moxifloxacin)	✔ ‖
Ocuflox (ofloxacin)	✔
Zymaxid (gatifloxacin)	✔
Combinations	
bacitracin/neomycin/polymyxin	✔
bacitracin/polymyxin	✔
Neosporin (gramicidin/neomycin/polymyxin)	✔
Polytrim (polymyxin/trimethoprim)	✔

*solution only
† Gentak is a branded generic of gentamicin ophthalmic ointment; Genoptic brand of gentamicin sulfate solution has been discontinued; generic is available. AK-tob brand of tobramycin has been discontinued.
§ Brand name Bleph-10 is available in solution only; generics are available for solution and ointment. Cetamide brand of sulfacetamide sodium has been discontinued.
‖Multiple generic versions of Vigamox are available.

(*Drugs@FDA, 2018; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2018; Drug Facts and Comparisons, 2018; Clinical Pharmacology, 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aminoglycosides		Macrolides		Other		Quinolones							Combinations			
	gentamicin	tobramycin	Azasite	erythromycin	bacitracin	sulfacetamide	ciprofloxacin	levofloxacin	ofloxacin	Besivance	Moxeza	Vigamox	Zymaxid	bacitracin/neomycin/polymyxin	bacitracin/polymyxin	gramicidin/neomycin/polymyxin	polymyxin/trimethoprim
Treatment of bacterial conjunctivitis			✔				✔	✔	✔	✔	✔	✔	✔				
Treatment of corneal ulcers							✔ †		✔								
Treatment of external infections of the eye and its adnexa caused by susceptible bacteria		✔												✔		✔	
Treatment of superficial ocular infections involving the conjunctiva and/or cornea				✔	✔										✔		
Prophylaxis of ophthalmia neonatorum due to *N. gonorrhoeae* or *C. trachomatis*				✔ §													
Treatment of ocular bacterial infections including conjunctivitis, keratitis, keratoconjunctivitis, corneal ulcers, blepharitis, blepharoconjunctivitis, acute meibomianitis, and dacryocystitis	✔																
Treatment of surface ocular infections, including acute bacterial conjunctivitis and blepharoconjunctivitis																	✔
Treatment of conjunctivitis and other superficial ocular infections						✔											
Adjunctive treatment with systemic treatment for trachoma						✔ †											

†solution only

§ The effectiveness of erythromycin in the prevention of ophthalmia caused by penicillinase-producing *N. gonorrhoeae* is not established.

(*Prescribing information: Azasite, 2017; bacitracin, 2013; bacitracin/neomycin/polymyxin, 2016; bacitracin/polymyxin, 2013; Besivance, 2018; Bleph-10, 2017; Ciloxan solution, 2017; Ciloxan ointment, 2017; erythromycin, 2017; Gentak, 2016; gentamicin, 2016; levofloxacin, 2017; Moxeza, 2017; Neosporin, 2016; Ocuflox, 2017; polymyxin/trimethoprim, 2018; Polytrim, 2004; sulfacetamide ointment, 2013; sulfacetamide solution, 2017; Tobrex ointment, 2018; Tobrex solution, 2018; Vigamox, 2017; Zymaxid, 2016*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated that ophthalmic antibiotics are effective in treating and providing relief of bacterial conjunctivitis in pediatric and adult patients (*Abelson et al 2007; Abelson et al 2008; Bremond-Gignac et al 2014; Cochereau et al 2007; DeLeon et al 2012; Gross et al 1997; Hwang et al 2003; Karpecki et al 2009; Kernt et al 2005; McDonald et al, 2009; Schwab et al 2003; Sheikh et al 2012; Silver et al 2005; Silverstein et al 2011; Silverstein et al, 2012; Tauber et al 2011; Tepedino et al 2009; Williams et al 2012*). Several studies comparing ophthalmic antibiotics such as azithromycin, besifloxacin, levofloxacin, and moxifloxacin to placebo have concluded that these medications resulted in significantly higher clinical resolution rates at days 1 through 5 (*Abelson et al 2008; DeLeon et al 2012; Hwang et al 2003; Karpecki et al 2009; Silverstein et al 2011; Tauber et al 2011; Tepedino et al 2009*).
- In a trial, there was no difference in clinical cure rate between treatment with ophthalmic polymyxin B/trimethoprim and ophthalmic moxifloxacin (p = 0.59) (*Williams et al 2012*). In a 5-day trial, a higher percentage of patients receiving levofloxacin had microbial eradication at the final visit compared to patients receiving ofloxacin (p = 0.034); however, clinical cure rates were similar between the 2 treatments (p value not reported) (*Schwab 2003*).
- Most other studies have shown no significant difference between ophthalmic antibiotic treatments with regard to bacterial eradication, clinical resolution, clinical response, efficacy, microbial eradication, physician's judgment of resolution, severity rating, or symptom improvement (*Ableson et al 2007; Cochereau et al 2007, Gross et al 1997; McDonald et al 2009; Sanfilippo et al 2017; Silver et al 2005*). While no difference was found between ophthalmic formulations of azithromycin and tobramycin with regard to clinical resolution and bacterial eradication, ophthalmic azithromycin produced the same clinical outcome with 65% fewer drops (*Abelson et al 2007*). In all studies, most adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events included burning, ocular discomfort, stinging, and tearing (*Abelson et al 2007; Cochereau et al 2007; Gross et al 1997; McDonald et al 2009; Schwab et al 2003; Silver et al 2005; Williams et al 2012*).
- A number of studies consisted of patients with multiple diagnoses such as blepharitis, blepharoconjunctivitis, bacterial conjunctivitis, keratoconjunctivitis, or symptoms of surface ocular infections. These studies found that the ophthalmic formulations of gentamicin, levofloxacin, ofloxacin, and tobramycin solution were efficacious in resolving or curing multiple ocular infections (*Gwon 1992 Sep; Gwon 1992 Dec; Kanda et al 2012*). No significant differences were observed in any study with regard to cure rates, decline in bacterial counts, bacterial eradication or reduction of bacteria, microbial improvement, or overall improvement. In one study, ophthalmic ofloxacin was shown to significantly decrease the cumulative summary score on days 3 through 5 in patients with conjunctival hyperemia, eyelid crusting or discharge, and positive bacterial culture when compared to ophthalmic tobramycin (p < 0.05); however, by day 11, there were no significant differences between the 2 treatments with regard to clinical, microbial, and overall improvement rates (*Gwon 1992 Sep*). In studies of patients with multiple diagnoses, the most commonly reported adverse events were similar between treatment groups. The most common adverse events included burning, mild discomfort, and stinging on instillation.
- In one study evaluating the treatment of ophthalmia neonatorum, conjunctivitis in newborn babies principally caused by *N. gonorrhoeae*, prophylaxis with ophthalmic erythromycin ointment was found to be most effective prior to the infant's second week of life. The efficacy of ophthalmic erythromycin prophylaxis from days 0 to 14 was statistically significant when compared to no prophylaxis; however, the efficacy was not significant from days 15 to 60 (14 vs 9%; p = 0.05 and 7 vs 8%; p = 0.92, respectively) (*Bell et al 1993*). In another study, ophthalmic erythromycin prophylaxis resulted in significantly fewer reports of conjunctival redness and tearing or serious or purulent discharge during the first 24 hours to 2 weeks of life when compared to no prophylaxis (18.4 vs 22.4%; p = 0.03) (*Ali et al 2007*).
- In a study involving patients undergoing cataract extraction by either manual extraction or phacoemulsification with intraocular lens implantation, ophthalmic tobramycin/dexamethasone was non-inferior to ophthalmic neomycin/polymyxin B/dexamethasone concerning inflammation scores at days 3, 8, 14, and 21. Inflammation scores in the ophthalmic tobramycin/dexamethasone group were significantly lower than scores seen in the ophthalmic neomycin/polymyxin B/gramicidin group at days 8, 14, and 21 (p < 0.05 for all), and scores in the ophthalmic

neomycin/polymyxin B/dexamethasone group were significantly lower than those seen in the ophthalmic neomycin/polymyxin B/gramicidin group at day 8 ($p < 0.05$) (*Notivol et al 2004*).

CLINICAL GUIDELINES

- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin, and the guidelines note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis (*AAO 2013*).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with an ophthalmic fluoroquinolone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin than other fluoroquinolones (*AAO 2013*).
- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment, if needed (*AAO 2013; AOA 2002*).

SAFETY SUMMARY

- Contraindication to use of these products is hypersensitivity to any component of the product.
- Warnings/precautions include the following: 1) do not wear contact lenses while infected; 2) prolonged use may result in overgrowth of non-susceptible organisms, including fungi; and 3) cutaneous sensitization may occur with products containing neomycin.
- The most frequent adverse effects were burning, stinging, and irritation upon instillation, redness, blurred vision, itching, swelling, tearing, eye pain, and photophobia. Non-ocular reactions can occur and include headache, pharyngitis, dizziness, and allergic reactions. Ciloxan (ciprofloxacin) had a reported incidence of 17% for white crystalline precipitates in corneal ulcer studies.
- These agents are minimally absorbed; therefore, drug interactions are not likely to occur.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Gentak (gentamicin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Ointment**: 2 or 3 times a day **Solution**: every 4 hours *Severe infections:* dosage may be increased to as much as every hour.	Safety and efficacy in neonates have not been established.
Tobrex (tobramycin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Ointment**: *Mild to moderate disease*: 2 or 3 times a day *Severe infections*: every 3 to 4 hours until improvement, following which treatment should be reduced prior to discontinuation. **Solution**: *Mild to moderate disease*: every 4 hours *Severe infections*: hourly until improvement, following which treatment should be reduced prior to discontinuation	Safety and efficacy have not been established in infants < 2 months of age.
Azasite (azithromycin)	Ophthalmic solution: 1%	Twice daily, 8 to 12 hours apart for the first 2 days, then once daily for the next 5 days	Safety and efficacy have not been established in children < 1 year of age
erythromycin	Ophthalmic ointment: 0.5%	**Superficial infections**: Apply directly to the infected structure up	For neonates: The ointment should not be flushed from the eye following instillation

Drug	Available Formulations	Usual Recommended Frequency	Comments
		to 6 times daily, depending on the severity of the infection. **Prophylaxis of neonatal gonococcal or chlamydial conjunctivitis:** apply into each lower conjunctival sac.	
bacitracin	Ophthalmic ointment: 500 units/gram	Apply directly into the conjunctival sac 1 to 3 times daily	No data in pediatric patients
Bleph-10 (sulfacetamide sodium)	Ophthalmic ointment: 10% Ophthalmic solution: 10%	**Ointment**: every 3 to 4 hours and at bedtime for 7 to 10 days **Solution**: every 2 to 3 hours for 7 to 10 days *Trachoma*: every 2 hours; must also use systemic administration	Safety and efficacy have not been established in infants < 2 months of age.
Besivance (besifloxacin)	Ophthalmic suspension: 0.6%	Three times daily, 4 to 12 hours apart for 7 days	Safety and efficacy have not been established in children < 1 year.
Ciloxan (ciprofloxacin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Corneal ulcers**: *Solution*: every 15 minutes for the first 6 hours, every 30 minutes for the remainder of the first day. Second day: every hour Third through 14th day: every 4 hours **Conjunctivitis**: *Ointment*: 3 times daily for first 2 days, then twice daily for the next 5 days *Solution*: every 2 hours while awake for 2 days, then every 4 hours while awake for next 5 days	**Ointment**: Safety and efficacy have not been established in children < 2 years of age. **Solution**: Safety and efficacy have been established in all ages.
levofloxacin	Ophthalmic solution: 0.5%	Every 2 hours while awake, up to 8 times per day on days 1 and 2, then every 4 hours while awake, up to 4 times per day for days 3 to 7	Safety and efficacy have not been established in children < 1 year of age
Moxeza, Vigamox (moxifloxacin)	Ophthalmic solution: 0.5% (Moxeza - twice daily formulation), 0.5% (Vigamox - 3 times daily formulation)	**Moxeza**: twice daily for 7 days **Vigamox**: 3 times daily for 7 days	**Moxeza**: Safety and efficacy have not been established in infants < 4 months of age. **Vigamox**: Safety and efficacy have been established in all ages.
Ocuflox (ofloxacin)	Ophthalmic solution: 0.3%	**Conjunctivitis**: every 2 to 4 hours days 1 and 2, then 4 times daily for days 3 through 7 **Corneal ulcers:** *Days 1 and 2*: every 30 minutes, while awake *Days 3 through 7 to 9*: hourly, while awake *Days 7 to 9 through treatment completion*: 4 times daily	Safety and efficacy have not been established in children < 1 year of age.

Drug	Available Formulations	Usual Recommended Frequency	Comments
Zymaxid (gatifloxacin)	Ophthalmic solution: 0.5%	Every 2 hours while awake up to 8 times on day 1, then 2 to 4 times per day while awake on days 2 through 7	Safety and efficacy have not been established in children < 1 year of age.
bacitracin/ neomycin/ polymyxin	Ophthalmic ointment: bacitracin zinc 400 units, neomycin 3.5 mg, polymyxin B sulfate 10,000 units	Every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection	Safety and efficacy have not been established in pediatric patients
bacitracin/ polymyxin	Ophthalmic ointment: bacitracin zinc 500 units, polymyxin B sulfate 10,000 units	Every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection	No data in pediatric patients
Neosporin (gramicidin/ neomycin/ polymyxin)	Ophthalmic solution: neomycin sulfate 1.75 mg, polymyxin B sulfate 10,000 units, gramicidin 0.025 mg	Every 4 hours for 7 to 10 days *Severe infections*: may increase to every hour	Safety and efficacy have not been established in pediatric patients.
Polytrim (polymyxin/ trimethoprim)	Ophthalmic solution: polymyxin B sulfate 10,000 units, trimethoprim 1 mg	*Mild to moderate infections*: Every 3 hours (maximum of 6 doses per day) for a period of 7 to 10 days	Safety and efficacy have not been established in iinfants < 2 months of age.

See the current prescribing information for full details

CONCLUSION

- Ophthalmic antibiotics are used to treat ophthalmic infections, including blepharitis, conjunctivitis, and keratitis as well as several others. Classes of ophthalmic antibiotics include aminoglycosides, macrolides, quinolones, and other miscellaneous and combination products. For all FDA-approved indications, a generic ophthalmic antibiotic is available.
- In comparative clinical trials, no one ophthalmic antibiotic has been shown to be more effective than another in bacterial eradication, clinical resolution, clinical response, or symptom improvement.
- In clinical studies, adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events reported include burning, ocular discomfort, stinging, and tearing.
- Ophthalmic antibiotics are not intended to be used for prolonged periods of time in order to avoid overgrowth of non-susceptible organisms and reduce the risk of resistance. Should super-infection occur, the ophthalmic antibiotic should be discontinued, and an alternative therapy should be initiated.
- Guidelines published by the AAO recommend that blepharitis be treated with ophthalmic bacitracin or ophthalmic erythromycin, and the guidelines note that macrolide antibiotics may have anti-inflammatory activity with regard to the treatment of blepharitis (*AAO 2013*).
- Guidelines state that keratitis should be treated with a broad-spectrum ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with an ophthalmic fluoroquinolone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin than other fluoroquinolones (*AAO 2013*).
- For the treatment of bacterial conjunctivitis, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment, if needed (*AAO 2013; AOA 2002*).

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