Ophthalmic Antibiotics
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indication(s)	Age Range
Aminoglycosides			
gentamicin solution/ointment[1]	generic	Superficial ocular infections involving the conjunctiva or cornea	all ages except neonates
tobramycin ointment (Tobrex®)[2]	Alcon/Novartis	Treatment of external infections of the eye and its adnexa	≥ 2 months
tobramycin solution (Tobrex®)[3]	generic, Alcon/Novartis	Superficial ocular infections involving the conjunctiva or cornea	≥ 2 months
Fluoroquinolones*			
besifloxacin (Besivance®)[4]	Valeant	Bacterial conjunctivitis	≥ 1 year
ciprofloxacin solution (Ciloxan®)[5]	generic, Alcon/Novartis	Bacterial conjunctivitis Corneal ulcers	≥ 1 year
ciprofloxacin ointment (Ciloxan®)[6]	Alcon/Novartis	Bacterial conjunctivitis	≥ 2 years
gatifloxacin 0.5% (Zymaxid®)[7]	generic, Allergan	Bacterial conjunctivitis	≥ 1 year
levofloxacin 0.5%[8]	generic	Bacterial conjunctivitis	≥ 1 year
moxifloxacin 0.5% (Moxeza®)[9]	Alcon/Novartis	Bacterial conjunctivitis	≥ 4 months
moxifloxacin 0.5% (Vigamox®)[10]	generic, Alcon/Novartis	Bacterial conjunctivitis	neonates to adults
ofloxacin (Ocuflox®)[11]	generic, Allergan	Bacterial conjunctivitis Corneal ulcers	≥ 1 year
Macrolides			
azithromycin (AzaSite®)[12]	Akorn	Bacterial conjunctivitis	≥ 1 year
erythromycin[13]	generic	Superficial ocular infections involving the conjunctiva or cornea For ophthalmia neonatorum due *to Chlamydia trachomatis* and prophylaxis of ophthalmia neonatorum due *to Neisseria gonorrhoeae*	newborn infants to adults
Other			
bacitracin[14]	generic	Superficial ocular infections involving the conjunctiva or cornea	not specified
bacitracin/polymyxin B[15,16]	generic	Superficial ocular infections involving the conjunctiva or cornea	not specified
natamycin (Natacyn®)[17]	Alcon/Novartis	Fungal blepharitis, conjunctivitis, and keratitis	adults

* Zymar® (gatifloxacin 0.3%) by Allergan was discontinued in 2011. In 2017, its United States (U.S.) labeling was updated indicating safety and efficacy for bacterial conjunctivitis has been demonstrated in all ages including neonates.[18]

FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indication(s)	Age Range
Other *(continued)*			
neomycin/polymyxin B/ bacitracin[19,20]	generic	Bacterial conjunctivitis Superficial ocular infections	adults
neomycin/polymyxin B/ gramicidin[21,22]	generic	Bacterial conjunctivitis Superficial ocular infections	adults
polymyxin B/trimethoprim (Polytrim®)[23,24]	generic, Allergan	Bacterial conjunctivitis Blepharoconjunctivitis Superficial ocular infections	≥ 2 months
sulfacetamide (Bleph®-10)[25]	generic, Allergan	Bacterial conjunctivitis Superficial ocular infections Adjunctive therapy with systemic sulfonamide therapy for trachoma	≥ 2 months

OVERVIEW

Conjunctivitis can be bacterial, viral, or noninfectious (e.g., allergic or nonallergic). Viral or noninfectious conjunctivitis are often self-limiting. Therapy may reduce symptoms but does not affect the clinical course of viral conjunctivitis. Although bacterial conjunctivitis can also be a self-limiting condition, topical antibiotics may be applied as a solution, suspension, or ointment for several days, and topical antibiotics, in many cases, may shorten the clinical course, as well as reduce spread of infection.[26,27] Bacterial conjunctivitis is commonly caused by *Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus*, and *Moraxella catarrhalis*. These pathogens, particularly *H. influenza* and *S. pneumoniae,* are more common in children, whereas *S. aureus* and *H. influenza* are more common in adults.[28,29] A variety of antimicrobial agents are available for the treatment of conjunctivitis and other superficial ocular infections. More serious conditions, such as corneal ulcers and other infections that potentially threaten vision, may require broad-spectrum antibiotics.[30]

This review focuses on antibiotics for ophthalmic use; it does not include a review of intraocularly administered products (moxifloxacin and vancomycin).

PHARMACOLOGY[31]

Aminoglycosides (gentamicin, neomycin, tobramycin) inhibit protein synthesis by binding to the 30S ribosomal subunit.

Bacitracin inhibits bacterial growth through prevention of cell wall subunits being added to the peptidoglycan chain. Bacitracin is bactericidal.

Fluoroquinolones (besifloxacin [Besivance], ciprofloxacin [Ciloxan], gatifloxacin [Zymaxid], levofloxacin, moxifloxacin [Moxeza, Vigamox], and ofloxacin [Ocuflox]) inhibit DNA gyrase (topoisomerase II) and topoisomerase IV. DNA gyrase is an essential enzyme involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. Fluoroquinolones with an 8-methoxy substitution, such as gatifloxacin and moxifloxacin, have enhanced antimicrobial activities that may limit the selection of resistant mutants in pathogens.[32] Ciprofloxacin (Ciloxan) and ofloxacin (Ocuflox) are considered second-generation fluoroquinolones, with levofloxacin being a third-generation

fluoroquinolone. The fourth-generation fluoroquinolones include gatifloxacin and moxifloxacin. Besifloxacin has an N-cyclopropyl group, which confers a broad spectrum similar to gatifloxacin and moxifloxacin, and an 8-chloro substituent, which may improve potency against bacterial DNA gyrase and topoisomerase IV.[33] Minimum inhibitory concentrations to inhibit growth of 90% of organisms (MIC_{90}) for besifloxacin are similar to those of moxifloxacin.

Azithromycin binds to the 50S ribosomal subunit of susceptible microorganisms and interferes with microbial protein synthesis.[34] In AzaSite, azithromycin is formulated in the mucoadhesive deliery system, DuraSite®; this formulation showed increased bioavailability of azithromycin in rabbit ocular tissue. However, this same effect has not been demonstrated in humans. Erythromycin, another macrolide, also binds to the 50S subunit of the ribosome, causing inhibition of protein synthesis.

Gramicidin has bactericidal action on gram-positive organisms. Gramicidin increases bacterial cell permeability to inorganic cations by forming a network of channels through the lipid bilayer of the membrane.

Natamycin (Natacyn) is a tetraene polyene antifungal antibiotic derived from *Streptomyces natalensis*. It binds to the sterol moiety of the fungal cell membrane. The polyenesterol complex alters the permeability of the membrane to produce depletion of essential cellular constituents. Natamycin is predominantly fungicidal, but its effect is dose-related.

Polymyxin B is bactericidal for a variety of gram-negative organisms. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.

Sulfacetamide is a synthetic sulfonamide antibiotic and inhibits bacterial dihydrofolate synthetase, an enzyme responsible for the conversion of para-aminobenzoic acid (PABA) into folic acid. Folic acid is essential for bacteria for the transport of one-carbon fragments from one molecule to another and is crucial during the synthesis of thymidine, purines, and certain amino acids.

Trimethoprim interferes with folate synthesis by blocking the production of tetrahydrofolic acid from dihydrofolic acid. Trimethoprim reversibly inhibits dihydrofolate reductase.

Antibacterial Activity

In vitro tests of ophthalmic antibiotics, in general, among isolates tested, moxifloxacin was the most potent fluoroquinolone for gram-positive bacteria (p=0.05) including *Staphylococcus aureus,* coagulase-negative *Staphylococci*, and *Streptococcus viridans,* followed by gatifloxicin (coagulase-negative *Staphylococci* and *Streptococcus viridans*).[35] Ciprofloxacin, moxifloxacin, gatifloxacin, and levofloxacin demonstrated equivalent potencies to gram-negative bacteria.[36,37,38] Another study demonstrated the overall relative *in vitro* efficacy for gram-positive organisms as follows (descending order): chloramphenicol, ciprofloxacin, ofloxacin, norfloxacin, bacitracin, tetracycline, neomycin, erythromycin, tobramycin, and gentamicin.[39]

Streptococcal isolates were collected from patients with keratitis and endophthalmitis between 1990 and 2001.[40] Levofloxacin, ofloxacin, and ciprofloxacin were compared for the *in vitro* MICs against the 65 isolates using E-test methodology. Levofloxacin was more active than ofloxacin and ciprofloxacin against the *S. pneumoniae* isolates with MIC values of 1.5, 6, and 3 mcg/mL, respectively. Levofloxacin was also the most active against the *S. viridans* isolates compared to ofloxacin and ciprofloxacin. Of the penicillin-intermediate or -resistant strains of *S. pneumoniae* (63% of isolates), levofloxacin covered 100% of the isolates compared to only 33.8% and 29.2% for ofloxacin and ciprofloxacin, respectively.

Ciprofloxacin and levofloxacin MICs were compared in 1,230 *S. aureus* isolates from patients with keratitis and conjunctivitis from 2 time periods: 1990 to 1995 and 1996 to 2001.[41] MICs were evaluated in the methicillin-sensitive and methicillin-resistant *S. aureus* strains. The resistance rate of *S. aureus* among the methicillin-resistant *S. aureus* (MRSA) isolates to ciprofloxacin rose from 55.8% to 83.7%; the resistance rate for methicillin-sensitive *S. aureus* (MSSA) isolates to ciprofloxacin increased from 2% to 5%. In data from January 2000 to December 2001, the resistance rate for MSSA was 4.7% versus 11.9% for levofloxacin and ciprofloxacin, respectively (p=0.05). For MRSA isolates, the resistance rate has also been reported at 82.1% versus 95.7% for levofloxacin and ciprofloxacin, respectively (p=0.04). Vancomycin resistance was not identified in this collection of *S. aureus* isolates.

Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) has been the presumed infectious agent for a variety of ophthalmic infections.[42] In a small report of 9 cases, CA-MRSA varied in susceptibility to ciprofloxacin, whereas the 9 isolates were all sensitive to gentamicin.

Isolates from bacterial conjunctivitis from a phase 3 trial were examined for *in vitro* resistance to azithromycin and moxifloxacin.[43] The most common isolates collected were *Haemophilus influenzae* (40.6%), *Staphylococcus epidermidis* (19.3%), *Propionibacterium acnes* (17.3%), *S. pneumoniae* (16.8%), and *S. aureus* (0.06%). The MIC values for all these organisms were well below established resistance breakpoints for moxifloxacin, indicating no bacterial resistance. The MIC value for *H. influenzae* was 3-fold higher than the resistance breakpoint for azithromycin, ≥ 128-fold higher for *S. epidermidis*, 16-fold higher for *S. pneumoniae,* and ≥ 128-fold higher for *S. aureus*, indicating moderate to very high bacterial resistance to azithromycin.

The Ocular Tracking Resistance in US Today (TRUST) annually evaluated *in vitro* antimicrobial susceptibility of *S. aureus*, *S. pneumoniae*, and *H. influenzae* to ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, penicillin, azithromycin, tobramycin, trimethoprim, and polymyxin B in national samples of ocular isolates evaluated annually from 2006 to 2008 (TRUST 1, TRUST 2, TRUST 3).[44] Prospectively collected ocular isolates (n=278) from 35 institutions and archived ocular isolates (n=1,116) from 34 institutions were tested. Mean minimum inhibitory concentrations that would inhibit growth of 90% of the tested isolates (MIC_{90}) were interpreted as susceptible, intermediate, or resistant according to standardized breakpoints for systemic treatment. Methicillin susceptible *S. aureus* (MSSA) or methicillin resistant *S. aureus* (MRSA) susceptibility patterns were virtually identical among the fluoroquinolones; MSSA susceptibility was 79.9% to 81.1%, and MRSA susceptibility was 15.2%. Trimethoprim was the only agent tested with high activity against MRSA. All *S. pneumoniae* isolates were susceptible to gatifloxacin, levofloxacin, and moxifloxacin; 89.8% were susceptible to ciprofloxacin. *H. influenzae* isolates were 100% susceptible to all tested agents except trimethoprim. Ocular TRUST 1 data were consistent with the 8-year longitudinal sample of archived ocular isolates. The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) surveillance study assessed 3,237 *S. aureus*, coagulase-negative staphylococci (CoNS), *S. pneumoniae*, *H. influenzae*, and *Pseudomonas aeruginosa* ocular isolates collected from 2009 to 2015 at 72 centers in the U.S.[45] Methicillin resistance was found among 42.2% of *S. aureus* isolates and 49.7% of CoNS isolates, and methicillin resistant isolates had a high probability of concurrent resistance to aminoglycosides, fluoroquinolones, or macrolides. Resistance among *S. pneumoniae* isolates was highest for azithromycin. Staphylococcal isolates from elderly patients and patients from the southern U.S. were more likely to be methicillin resistant. Notably, methicillin resistance among staphylococci did not increase during the study period. A subsequent ARMOR analysis that included 1,198 isolates (*S. aureus,* CoNS, *H. influenzae, S. pneumoniae, P. aeruginosa*) obtained from the conjunctiva only collected from

57 sites across the US from 2009 to 2016 showed little variation in *in vitro* resistance compared to the 2009-2015 comprehensive ocular isolate data.[46] These newer data indicate that antibiotic resistance remained high but did not increase among conjunctival-obtained isolates collected during 2009 to 2016. Further, for certain antibiotic/pathogen combinations, there was a trend toward decreased resistance, including a decrease in oxacillin resistance among *S. aureus*.

Natamycin is not effective *in vitro* against gram-positive or gram-negative bacteria.[47] It has *in vitro* activity against a variety of yeast and filamentous fungi including *Candida, Aspergillus, Cephalosporium, Fusarium,* and *Penicillium*.

PHARMACOKINETICS

Ophthalmic ointments have the longest contact time between the drug and the ocular tissues; however, ointments can impede delivery of other ophthalmic drugs by serving as a physical barrier. Ointments are useful in children as they decrease the loss of drug by tears. Ophthalmic ointments are useful in children, patients with poor compliance, and in patients with difficulty administering drops. However, ointments blur vision for a short period after the dose is administered. This should be taken into consideration for patients who need to perform tasks which require clear vision immediately after dosing. Ophthalmic suspensions mix with tears less rapidly and remain in the cul-de-sac longer than solutions.

Azithromycin (AzaSite) and besifloxacin (Besivance) contain DuraSite® which is a mucoadhesive delivery system.[48,49]

Plasma concentrations of besifloxacin were measured in adult patients with suspected bacterial conjunctivitis who received besifloxacin bilaterally 3 times a day (16 doses total). Following the first and last dose, the maximum plasma besifloxacin concentration in each patient was < 1.3 ng/mL. The mean besifloxacin Cmax was 0.37 ng/mL on day 1 and 0.43 ng/mL on day 6. The average elimination half-life of besifloxacin in plasma following multiple dosing was estimated to be 7 hours.[50]

Moxifloxacin (Moxeza, Vigamox) does not contain a preservative.[51,52] The other ophthalmic solutions may contain benzalkonium chloride (BAK) or thimerosal as a preservative.

Ocular Penetration

Several studies have been published regarding the corneal penetration of fluoroquinolone products as measured in the aqueous humor during surgery. The dosing regimens used to determine ocular penetration are not those approved by the FDA. While comparative penetrations and resultant antibiotic concentrations are important, the study endpoints do not represent clinical outcomes nor do these studies provide insight into aqueous humor concentrations achieved with FDA-approved regimens.

besifloxacin, moxifloxacin, and gatifloxacin

In a randomized open-label controlled clinical trial, 105 patients were enrolled to determine the concentrations of besifloxacin, moxifloxacin, and gatifloxacin in human aqueous humor after topical instillation of commercially-available besifloxacin ophthalmic suspension 0.6%, moxifloxacin ophthalmic solution 0.5%, and gatifloxacin ophthalmic solution 0.3%. Samples were then taken to assess the concentrations of each drug relative to the minimum inhibitory concentration for 90% of strains (MIC_{90}) for each drug against bacterial pathogens identified in recent cases of postoperative

endophthalmitis.[53] Aqueous humor samples were analyzed for 103 of those patients, age 18 years and older, having uncomplicated cataract surgery. The aqueous humor drug concentrations were compared 60 minutes ± 5 minutes after instillation of 1 topical drop to patients. The mean aqueous humor concentrations were 0.13 mcg/mL ± 0.58 (standard deviation [SD]) for besifloxacin, 0.67 ± 0.5 mcg/mL for moxifloxacin and 0.13 ± 0.08 mcg/mL for gatifloxacin. Both besifloxacin and moxifloxacin achieved aqueous humor concentrations equal to or slightly higher than their respective MIC_{90} for methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* and *Staphylococcus epidermidis*; none of the fluoroquinolones achieved concentrations above their MIC_{90} for ciprofloxacin-resistant strains of *S. aureus* and *S. epidermidis*.

ciprofloxacin (Ciloxan), gatifloxacin, and moxifloxacin (Vigamox)

Fifty-two patients scheduled to undergo cataract extraction were enrolled in a double-blind study to compare the aqueous humor penetration of gatifloxacin 0.3%, moxifloxacin 0.5%, and ciprofloxacin 0.3%.[54] Patients were randomized to 1 of the 3 drugs and were to administer the drug 4 times daily for 3 days prior to surgery. Just prior to surgery, each patient received the randomized antibiotic every 15 minutes for 3 doses ending 1 hour pre-operatively. Mean aqueous concentrations were 0.63 mcg/mL for gatifloxacin, 1.31 mcg/mL for moxifloxacin, and 0.15 mcg/mL for ciprofloxacin at the time of surgery. Moxifloxacin and gatifloxacin achieved significantly greater levels in the aqueous humor than ciprofloxacin ($p<0.001$, $p<0.005$, respectively), and mean moxifloxacin levels were significantly greater than mean gatifloxacin levels ($p<0.05$).

levofloxacin 0.5% solution and ofloxacin (Ocuflox)

In a similarly designed investigator-masked study, levofloxacin 0.5% and ofloxacin 0.3% were compared for concentrations in the aqueous humor in 69 patients undergoing cataract surgery.[55] Patients received 4 drops of either levofloxacin 0.5% or ofloxacin 0.3% eyedrops within 1 hour (60 minutes, 45 minutes, 30 minutes, and 15 minutes) of elective cataract surgery. The mean concentration of levofloxacin (1.1399 mcg/mL) was significantly higher than ofloxacin (0.6217 mcg/mL) at the beginning of the operation ($p=0.0008$).

moxifloxacin (Vigamox) and ofloxacin (Ocuflox)

A randomized, double-blind study enrolled 27 patients undergoing vitrectomy. Patients were randomized to ofloxacin 0.3% or moxifloxacin 0.5% given every 10 minutes for 1 hour prior to surgery.[56] Aqueous and vitreous samples were obtained and analyzed by HPLC. Moxifloxacin aqueous (1.576 mcg/mL) and vitreous (0.225 mcg/mL) levels were significantly higher than ofloxacin aqueous (0.816 mcg/mL, $p=0.0009$) and vitreous levels (0.184 mcg/mL, $p=0.0054$). Moxifloxacin concentrations exceeded the MIC_{90} values for a wide variety of pathogens. This study was supported by the manufacturer of moxifloxacin.

moxifloxacin (Vigamox) and besifloxacin (Besivance)

In a prospective, randomized, double-blind trial, moxifloxacin 0.5% solution and besifloxacin 0.6% suspension were compared in 50 patients undergoing routine cataract surgery.[57] The randomized product was administered every 10 minutes for a total of 4 doses beginning 1 hour before surgery. Aqueous humor concentrations was detectable in all moxifloxacin (n=23) samples and in 40% of the besifloxacin samples (n=25) ($p<0.0001$). The mean aqueous concentration of moxifloxacin samples was

50-fold higher than in the besifloxacin samples (1.618 mcg/mL versus 0.0319 mcg/mL, respectively) when all samples were included (p<0.0001).

CONTRAINDICATIONS/WARNINGS[58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73]

These agents are for topical ophthalmic use only.

Hypersensitivity is considered a contraindication for use for all agents. Fatalities have occurred due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sulfacetamide (Bleph-10) is contraindicated in patients with hypersensitivity to sulfonamides or to any ingredient in the product.

Patients should not wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Bacitracin ophthalmic ointment should not be used for deep-seated ocular infections or for infections that are likely to become systemic.

DRUG INTERACTIONS[74,75,76,77,78,79,80,81,82,83,84,85,86]

Specific drug interaction studies have not been performed with the ophthalmic preparations.

ADVERSE EFFECTS[87,88,89,90,91,92,93,94,95,96]

Drug	Discomfort/ Pain	Eyelid edema	Foreign body sensation	Itching	Conjunctival hyperemia	Transient burning
Fluoroquinolones						
besifloxacin (Besivance)	1-2	nr	nr	1–2	2	nr
ciprofloxacin solution	most reported	< 1	< 10	< 10	< 10	most reported
ciprofloxacin ointment (Ciloxan)	2	< 1	< 1	< 1	< 1	nr
gatifloxacin 0.5% (Zymaxid)	≥ 1	< 1	nr	nr	≥ 1	nr
levofloxacin 0.5%	1–3	< 1	1–3	< 1	nr	1–3
moxifloxacin 0.5% (Moxeza)	nr	nr	nr	nr	1–2	nr
moxifloxacin (Vigamox)	1–6	nr	nr	1-6	1–6	nr
ofloxacin (Ocuflox)	most reported	reported	reported	reported	reported	most reported
Macrolides						
azithromycin (AzaSite)	1–2	nr	nr	< 1	nr	< 1
erythromycin	reported	nr	nr	reported	nr	reported

Adverse effects data are reported from product information as percentage occurrence and therefore cannot be considered comparative or all inclusive. nr = not reported.

Overall, most adverse effects are related to local irritation upon instillation. Occasionally, allergic sensitization reactions, such as itching, swelling, and conjunctival erythema, occur. Serious hypersensitivity reactions, including anaphylaxis, have rarely been reported. Secondary fungal and viral infections have been reported. Headache was reported in 1% to 2% of patients taking besifloxacin (Besivance). Taste disturbance was reported in < 10% and < 1% in patients taking ciprofloxacin solution and ointment, respectively.

Aminoglycosides (gentamicin, tobramycin) have the following adverse effects: localized ocular toxicity and hypersensitivity, lid itching, lid swelling, conjunctival erythema (< 3% with tobramycin), bacterial/fungal corneal ulcers, nonspecific conjunctivitis, conjunctival epithelial defects, and conjunctival hyperemia.[97]

In clinical trials, tobramycin (Tobrex) ophthalmic ointment produced significantly fewer adverse reactions (3.7%) than did gentamicin ophthalmic ointment (10.6%).[98]

Ocular irritation accompanied by stinging and burning has been reported with sulfacetamide solution.[99]

The following were reported for natamycin (Natacyn): ocular irritation, change in vision, corneal opacity, eye discomfort/pain/edema, eye hyperemia, foreign body sensation, paresthesia, and tearing.[100]

SPECIAL POPULATIONS[101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118]

Pediatrics

Ophthalmic tobramycin ointment and solution may be used in patients 2 months and older. Ophthalmic gentamicin is used in pediatrics but not in neonates.

All fluoroquinolones, excluding ciprofloxacin ointment (Ciloxan), have been studied in children as young as 1 year. Ciprofloxacin ointment has been studied in children 2 years and older. The safety and effectiveness of moxifloxacin (Moxeza) 0.5% solution was studied in patients as young as 4 months. Moxifloxacin 0.5% (Vigamox) has been studied in all ages and children from birth to 31 days of age demonstrated a clinical cure rate of 80%. The macrolides, azithromycin (AzaSite) and erythromycin, may be utilized in pediatrics at least 1 year of age and infants to adults, respectively. The age for ophthalmic bacitracin and bacitracin/polymyxin B is not specified. Neomycin/polymyxin B/bacitracin and neomycin/polymyxin B/gramicidin are not indicated for pediatrics.

Polymyxin B/trimethoprim (Polytrim) and sulfacetamide are indicated in pediatrics 2 months and older. Safety and effectiveness of sulfacetamide (Bleph-10) has not been shown in infants ages 2 months or less.

Pregnancy

Azithromycin (AzaSite), erythromycin ophthalmic ointment, and tobramycin solution and ointment are Pregnancy Category B. All other agents in this class currently assigned a Pregnancy Category are Pregnancy Category C. As labeling for products are updated, assigned Pregnancy Categories have been replaced with descriptive text in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). While previously assigned Pregnancy Category C, the labeling for gatifloxacin (Zymaxid) now states that there are no available data on use in pregnant women to inform of a drug-related risk to the fetus.

Labeling for ofloxacin (Ocuflox) states that there are no adequate and well-controlled studies in pregnant women.

Renal and Hepatic Impairment

Due to the topical application of these agents, it is not expected that any dosage adjustments are required for renal or hepatic impairment.

DOSAGES[119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137]

Drug	Dosage for Blepharitis or Conjunctivitis	Dropper Dosage for Corneal Ulcers	Availability
Aminoglycosides			
gentamicin ointment	½ inch 2 to 3 times a day	--	0.3% ointment 3.5 g tube (generic product by Akorn under trade name Gentak®)
gentamicin solution	1 to 2 drops every 4 hours, up to 2 drops every hour for severe infections	--	0.3% solution 5 mL, 15 mL
tobramycin ointment (Tobrex)	½ inch every 3 to 4 hours up to 2 to 3 times a day dosing based on severity of infection	--	0.3% ointment 3.5 g tube
tobramycin solution (Tobrex)	1 to 2 drops every 4 hours; in severe infections, 2 drops hourly until improvement, then taper	--	0.3% solution 5 mL
Fluoroquinolones			
besifloxacin (Besivance)	1 drop 3 times daily 4 to 12 hours apart for 7 days	--	0.6% suspension 5 mL
ciprofloxacin solution (Ciloxan)	1 to 2 drops every 2 hours while awake for 2 days, then 1 to 2 drops every 4 hours while awake for 5 days	Day 1: 2 drops every 15 minutes for 6 hours, then every 30 minutes Day 2: 2 drops every hour Days 3–14: 2 drops every 4 hours	0.3% solution 2.5 mL, 5 mL, 10 mL
ciprofloxacin ointment (Ciloxan)	½ inch 3 times a day for 2 days, then ½ inch twice daily for 5 days	--	3 mg/g ointment 3.5 g tube
gatifloxacin 0.5% (Zymaxid)	Day 1: 1 drop every 2 hours (up to 8 times) while awake; Days 2–7: 1 drop given 2 to 4 times a day while awake	--	0.5% solution 2.5 mL
levofloxacin	Days 1–2: 1 to 2 drops every 2 hours (up to 8 times) while awake; Days 3–7: 1 to 2 drops every 4 hours while awake (up to 4 times)	--	0.5% solution 5 mL
moxifloxacin 0.5% (Moxeza)	1 drop 2 times daily for 7 days	--	0.5% solution 3 mL
moxifloxacin 0.5% (Vigamox)	1 drop 3 times a day for 7 days	--	0.5% solution 3 mL

Dosages (continued)

Drug	Dosage for Blepharitis or Conjunctivitis	Dropper Dosage for Corneal Ulcers	Availability
Fluoroquinolones *(continued)*			
ofloxacin 0.3% (Ocuflox)	1 to 2 drops every 2 to 4 hours for 2 days; then 1 to 2 drops 4 times daily for 5 days	Days 1–2: 1 to 2 drops every 30 minutes, while awake; awaken at approximately 4 and 6 hours after retiring and instill 1 to 2 drops Days 3 through 7 to 9: 1 to 2 drops hourly while awake Days 7 to 9 through treatment completion: 1 to 2 drops 4 times daily	0.3% solution 5 mL, 10 mL
Macrolides			
azithromycin (AzaSite)	1 drop in the affected eye(s) twice daily (8 to 12 hours apart) for the first 2 days then 1 drop daily for the next 5 days	--	1% solution 2.5 mL
erythromycin	½ inch to affected eye(s) up to 6 times daily	--	0.5% ointment 3.5 g tube
Other			
bacitracin	½ inch every 3 to 4 hours for 7 to 10 days	--	500 units/g ointment 3.5 g tube
bacitracin/ polymyxin B	Thin film every 3 to 4 hours for 7 to 10 days	--	500 units-10,000 units/g ointment 3.5 g tube
natamycin (Natacyn)	1 drop every 1 to 2 hours, reduced to 6 to 8 times daily after the first 3 to 4 days	--	5% suspension 15 mL
neomycin/ polymyxin B/ bacitracin	½ inch every 3 to 4 hours for 7 to 10 days depending on severity of infection	--	3.5 mg/g-10,000 units/g-400 units/g ointment 3.5 g tube
neomycin/ polymyxin B/ gramicidin	1 to 2 drops every 4 hours for 7 to 10 days; up to 2 drops every hour for severe infections	--	1.75 mg/mL-10,000 units/mL-0.025 mg/mL solution 10 mL
polymyxin B/ trimethoprim (Polytrim)	1 drop every 3 hours up to 6 doses daily for 7 to 10 days	--	10,000 units/mL-1 mg/mL solution 10 mL
sulfacetamide	½ inch 4 times daily and bedtime for 7 to 10 days The ointment may be used adjunctively with sulfacetamide solution	--	10% ointment 3.5 g tube
sulfacetamide (Bleph-10)	1 to 2 drops every 2 to 3 hours initially, while awake; less frequently at night for 7 to 10 days Dosing dependant on severity of infection	--	10% solution 5 mL, 15 mL (15 mL generic only)

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the ophthalmic use of all drugs in this class. Due to changing susceptibility patterns, only trials from the last nine years are included. Randomized controlled comparative trials for ophthalmic FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. In studies evaluating minor infections, such as acute bacterial conjunctivitis, a large portion of patients are lost to follow-up. Very little comparative data of good quality from the United States have been published.

There are currently no published, comparative trials in relevant populations of gentamicin solution or ointment, tobramycin ointment (Tobrex), ciprofloxacin ointment or solution (Ciloxan), gatifloxacin (Zymaxid), moxifloxacin (Moxeza), erythromycin, bacitracin, bacitracin/polymyxin B, natamycin (Natacyn), neomycin/polymyxin B/bacitracin, neomycin/polymyxin B/gramicidin, and sulfacetamide ointment or solution (Bleph-10).

levofloxacin and ofloxacin (Ocuflox)

In an analysis of 167 patients (ages 1 to 16 years), either levofloxacin 0.5% or ofloxacin 0.3% were instilled every 2 hours on days 1 and 2 and every 4 hours on days 3 through 5 for the treatment of bacterial conjunctivitis.[138] There was also a placebo comparison group in this study. This analysis was taken from 2 randomized, double-blind, multicenter studies in patients with bacterial conjunctivitis. Signs and symptoms were collected, as well as conjunctival cultures. At endpoint (mean of 6.5 days), levofloxacin demonstrated greater microbial eradication than ofloxacin in children ages 2 to 11 years: 87% for levofloxacin versus 62% for ofloxacin ($p \leq 0.032$) and 88% for levofloxacin versus 24% for placebo ($p < 0.001$). No differences in microbial eradication rates were observed in other age subgroups.

azithromycin (AzaSite) and tobramycin (Tobrex)

A prospective, randomized, active-controlled, double-masked, phase 3 trial was conducted over a 14-month period at 47 sites.[139] Patients with a clinical diagnosis of bacterial conjunctivitis were randomly assigned to receive either azithromycin 1% ophthalmic solution (n=365) or tobramycin ophthalmic solution 0.3% (n=378). Both groups received masked medication 4 times daily for 5 days, but participants received an active dose of azithromycin only twice daily for the first 2 days then daily on days 3 to 5. Conjunctival cultures were taken, and ocular signs and symptoms were evaluated at baseline and at 2 follow-up visits. A total of 743 patients were randomized; 710 completed the trial. Rates of microbial eradication and bacterial infection recurrence were the same in both groups. The

most frequently observed ocular adverse events in the azithromycin group were eye irritation (1.9%), conjunctival hyperemia (1.1%), and worsening bacterial conjunctivitis (1.1%). These rates compared favorably with those obtained with tobramycin.

polymyxin B/trimethoprim (Polytrim) and moxifloxacin (Vigamox)

A multicenter study randomized 56 patients younger than 18 years with a clinical diagnosis of bacterial conjunctivitis to 1 drop of polymyxin B/trimethoprim 4 times daily for 7 days or 1 drop of moxifloxacin 0.5% 3 times daily for 7 days.[140] At the 48-hour visit, complete resolution of ocular signs and symptoms was observed in 81% and 44% of patients treated with moxifloxacin versus polymyxin B/trimethoprim, respectively (p=0.001). The majority of patients were cured and symptom-free by 48 hours. In this study, moxifloxacin was significantly more efficacious than polymyxin B/trimethoprim in the speed of clinical efficacy. No adverse events were reported. This study was sponsored by the manufacturer of moxifloxacin.

besifloxacin (Besivance) and moxifloxacin (Vigamox)

Besifloxacin ophthalmic suspension 0.6% 3 times daily was compared to moxifloxacin ophthalmic solution 0.5% 3 times daily for the treatment of bacterial conjunctivitis in a randomized, double-masked, parallel-group, active-controlled, multicenter, noninferiority study of 1,116 patients (533 with culture-confirmed bacterial conjunctivitis) ages 1 year and older.[141] Besifloxacin was noninferior to moxifloxacin for clinical resolution on day 5 (58.3% versus 59.4%, respectively; 95% confidence interval [CI], -9.48% to 7.29%) and day 8 (84.5% versus 84%, respectively, 95% CI, -5.6% to 6.75%). Besifloxacin was also noninferior to moxifloxacin for microbial eradication on day 5 (93.3% versus 91.1%, respectively, 95% CI, -2.44% to 6.74%) and day 8 (87.3% versus 84.7%; 95% CI, -3.32% to 8.53%). There was no statistically significant difference between the 2 treatment groups for either efficacy endpoints on days 5 or 8 (p>0.05). Both treatments were well tolerated. Although total ocular adverse events were similar between treatments (12% and 14% with besifloxacin and moxifloxacin, respectively), eye irritation occurred more frequently in the moxifloxacin group (0.3% for besifloxacin compared to 1.4% for moxifloxacin; p=0.0201).

Anti-Infective Efficacy Rates for Bacterial Conjunctivitis[142,143,144,145,146,147,148,149,150,151,152]

Drug	Clinical Cure (%)	Bacterial Eradication (%)
Fluoroquinolones		
besifloxacin 0.6% (Besivance)	45	91
ciprofloxacin ointment (Ciloxan)	75	80
ciprofloxacin 0.3% solution (Ciloxan)	52	70–80
gatifloxacin 0.3%	77	92
gatifloxacin 0.5% (Zymaxid)	58	90
levofloxacin 0.5%	79	90
moxifloxacin 0.5% (Moxeza)	63	75
moxifloxacin 0.5% (Vigamox)	59.4-69	84–94
ofloxacin 0.3% (Ocuflox)	86	65
Macrolides		
azithromycin solution 1% (AzaSite)	63	88

Data are collected from product information and, therefore, cannot be considered comparative.

Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

Efficacy data for erythromycin ophthalmic ointment in the treatment of bacterial conjunctivitis is not available in current literature.

META-ANALYSIS

For acute bacterial conjunctivitis, there appears to be a lack of good quality literature comparing antibiotics of any type compared to placebo. The Cochrane Eyes and Vision Group did a systematic review of all randomized controlled trials of any type of antibiotic treatment versus placebo for acute bacterial conjunctivitis.[153,154,155,156,157] Topical and systemic antibiotics were included, as well as combination products that included antibiotics. Six trials were identified; however, 3 were excluded from evaluation. In the 2005 and 2006 updates, 2 more studies were identified. In the 2012 update, an additional 6 studies were identified of which 2 were assessed as high quality. The meta-analysis found that antibiotics are associated with beneficial effects on early (days 2 through 5) clinical and microbiological remission rates; however, after day 6, the benefit of antibiotics is reduced but persistent.

SUMMARY

While acute bacterial conjunctivitis is often self-limiting, empiric therapy with ophthalmic antibiotics is a common practice. Serious vision-threatening infections require the empirical use of broad-spectrum antibiotics. Treatment with antibiotics typically leads to significantly faster rates of clinical and microbiological remission.

A wide variety of ophthalmic antimicrobials are available, and many of these antibiotics exhibit a broad spectrum of activity. Many agents used to treat acute bacterial conjunctivitis are available as generic products including second generation fluoroquinolones and certain macrolides.

In *in vitro* studies, the fluoroquinolones, gatifloxacin (Zymaxid) and moxifloxacin (Moxeza, Vigamox), appear to provide better coverage for gram-positive and resistant organisms than levofloxacin, ciprofloxacin (Ciloxan), and ofloxacin (Ocuflox). Besifloxacin (Besivance), a relatively new ophthalmic fluoroquinolone indicated for the treatment of bacterial conjunctivitis, is reported to be noninferior to moxifloxacin (Vigamox) in clinical studies. Comparative clinical studies will need to be conducted to demonstrate this claim.

Comparative clinical data with azithromycin (AzaSite) and gatifloxacin (Zymaxid) are limited at this time.

Moxifloxacin 0.5% ophthalmic solution (Moxeza) is approved for twice daily dosing. Vigamox, also a moxifloxacin 0.5% solution, is administered 3 times a day. Besifloxacin (Besivance) is given 3 times a day, as well. Ciprofloxacin ointment is applied 3 times per day to start. All other products are dosed 4 times per day or more.

Moxifloxacin 0.5% (Vigamox) and erythromycin are approved from birth upwards.

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