Therapeutic Class Overview
Ophthalmic Fluoroquinolones

Therapeutic Class

- **Overview/Summary:** This review will focus on the ophthalmic fluoroquinolone antibiotics. These agents are used for the treatment of bacterial conjunctivitis and corneal ulcers caused by susceptible isolates.[1-8] Conjunctivitis occurs worldwide and affects all ages, social strata, and both genders. 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 pneumonia*, *Haemophilus influenza*, and *Moraxella catarrhalis*.[9] Major clinical features of bacterial conjunctivitis include redness and discharge in one eye, although it can be bilateral. Patients eye(s) will often be "stuck shut" in the morning. Purulent discharge continues throughout the day and is thick, globular and may be yellow, white or green in color, which may help distinguish between viral and allergic conjunctivitis which usually has watery discharge.[9] Fluoroquinolone antibiotics act via direct inhibition of bacterial DNA synthesis, preventing the action of DNA gyrase and topoisomerase IV, which blocks DNA replication and eventually leads to damage to bacterial DNA and cell death.[10] Currently, ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically.

  These ophthalmiac quinolones include besifloxacin, ciprofloxacin hydrochloride, gatifloxacin, levofloxacin, moxifloxacin hydrochloride, and ofloxacin. They are all indicated for the treatment of bacterial conjunctivitis.[1-8] In addition, ciprofloxacin solution and ofloxacin have the indication to treat corneal ulcers caused by susceptible isolates.[2,8] All medications are formulated as drops (either solution or suspension) with only ciprofloxacin hydrochloride being formulated as an ointment (Ciloxan®).[3] Although generally considered equally effective, differences in resistance exist, with fewer gram-positive cocci being resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones.[13] Frequency and duration of therapy varies depending on specific agents. Treatment for bacterial conjunctivitis with besifloxacin and moxifloxacin hydrochloride is usually dosed twice or three times daily, while the others are generally prescribed every two to four hours.[1-8] Most ophthalmic quinolones are indicated for use in patients one year of age or older, however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

Table 1. Current Medications Available in Therapeutic Class[1-8]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Besifloxacin ophthalmic (Besivance®)	Treatment of bacterial conjunctivitis	Ophthalmic suspension: 0.6% (5 mL)	-
Ciprofloxacin hydrochloride ophthalmic (Ciloxan®*)	Treatment of bacterial conjunctivitis; treatment of corneal ulcers (solution)	Ophthalmic ointment: 0.3% (3.5 g) Ophthalmic solution: 0.3% (2.5, 5, 10 mL)	✔ (solution)
Gatifloxacin ophthalmic (Zymaxid®*)	Treatment of bacterial conjunctivitis	Ophthalmic solution: 0.5% (2.5 mL)	✔
Levofloxacin ophthalmic	Treatment of bacterial conjunctivitis; treatment of corneal ulcers	Ophthalmic solution: 0.5% (5 mL)	✔
Moxifloxacin hydrochloride ophthalmic (Moxeza®, Vigamox®)	Treatment of bacterial conjunctivitis	Ophthalmic solution: 0.5% (3 mL)	-
Ofloxacin ophthalmic	Treatment of bacterial	Ophthalmic solution:	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
(Ocuflox®*)	conjunctivitis; treatment of corneal ulcers	0.3% (5, 10 mL)	

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated that ophthalmic fluoroquinolones are effective in treating and providing relief of conjunctivitis and corneal ulcers in pediatric and adult patients.[15-40]
- Several studies comparing ophthalmic fluoroquinolones to either placebo or vehicle have concluded that these medications resulted in significantly higher clinical resolution rates at days one through five.[15-20]
- Head-to-head trials evaluating the efficacy of ophthalmic antibiotics for the treatment of bacterial conjunctivitis have found that no one medication was inferior to another.[21-30]
- In one trial, significantly more patients in the ophthalmic moxifloxacin group had complete resolution of ocular signs and symptoms at 48 hours when compared to patients treated with ophthalmic polymyxin B sulfate/trimethoprim (P=0.001).[22] One study found levofloxacin 0.5% to have statistically greater microbial eradication in pediatric patients two to 11 years of age with bacterial conjunctivitis (P≤0.032) compared to ofloxacin 0.3% in, but not in any other pediatric age group..[26] In a seven 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 two treatments (P value not reported).[27] In a small meta-analysis, moxifloxacin was found to be associated with fewer drop-outs for treatment failure (P=0.002) compared to ofloxacin.[28]
- In patients with a diagnosis of corneal ulcer, ophthalmic ciprofloxacin hydrochloride was shown to be efficacious treatment options.[31,32] Specifically, in one trial of patients with a diagnosis of infectious keratitis ophthalmic ciprofloxacin had a shorter average time to healing as compared to ophthalmic cefazolin sodium fortified with gentamicin sulfate, although this was not found to be significant (P value not reported).[32]
- A number of studies consisted of patients with multiple diagnoses such as blepharitis, blepharoconjunctivitis, bacterial conjunctivitis and blepharitis, keratoconjunctivitis, or symptoms of surface ocular infections. These studies found that the ophthalmic formulations of ciprofloxacin, gentamicin sulfate, ofloxacin, tobramycin solution, and polymyxin B sulfate/trimethoprim were efficacious in resolving or curing multiple ocular infections. 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. [34-39]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. Therapy for severe conjunctivitis disease be based on culture and sensitivity, but if that is not available or if mild disease is present, empiric therapy is considered appropriate.[9,11-13]
    - The selection of an ophthalmic antibiotics for bacterial conjunctivitis is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis.[11]
    - Although effective, ophthalmic quinolones are generally regarded as second-line agents for routine bacterial conjunctivitis because of resistance and cost concerns.[9,11,12]
    - Ophthalmic quinolones are the considered the treatment of choice for corneal ulcers and for infections caused by pseudomonas.[9,13]
    - The recommended ophthalmic antibiotics for treatment of keratitis vary depending on organism identified. Empiric therapy is often utilized and includes ophthalmic quinolones[13]
    - Fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones[13]

  - Single-drug therapy using an ophthalmic fluoroquinolone has been shown to be as effective as combination therapy with ophthalmic antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics.[13]
- Other Key Facts:
  - Ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically.
  - Only ciprofloxacin hydrochloride is formulated as an ointment.[3]
  - Moxeza® (moxifloxacin) is dosed twice daily while besifloxacin and Vigamox® (moxifloxacin) are dosed three times a day. The remaining agents are dosed every two or every four hours while awake.[1-8]
  - Most ophthalmic quinolones are indicated for use in patients one year of age or older; however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

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Therapeutic Class Review
Ophthalmic Fluoroquinolones

Overview/Summary

This review will focus on the ophthalmic fluoroquinolone antibiotics, which are used for the treatment of bacterial conjunctivitis and corneal ulcers caused by susceptible isolates.[1-8] Conjunctivitis occurs worldwide and affects all ages, social strata, and both genders. 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 pneumonia*, *Haemophilus influenza*, and *Moraxella catarrhalis*.[9] Major clinical features of bacterial conjunctivitis include redness and discharge in one eye, although it can be bilateral. Patient's eye(s) will often be "stuck shut" in the morning. Purulent discharge continues throughout the day and is thick, globular and may be yellow, white or green in color, which may help distinguish between viral and allergic conjunctivitis which usually has watery discharge.[9] Fluoroquinolone antibiotics act via direct inhibition of bacterial DNA synthesis, preventing the action of DNA gyrase and topoisomerase IV, which blocks DNA replication and eventually leads to damage to bacterial DNA and cell death.[10] Current clinical guidelines recommend therapy for severe disease be based on culture and sensitivity, but if that is not available or if mild disease is present, empiric therapy is considered appropriate.[9,11-13] 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.[11] Although effective, quinolones are generally regarded as second-line agents for routine bacterial conjunctivitis because of resistance and cost concerns.[9,11,12] They are the considered the treatment of choice for corneal ulcers and for infections caused by *Pseudomonas* species.[9,13] Currently, ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically.

These ophthalmiac quinolones include besifloxacin, ciprofloxacin hydrochloride, gatifloxacin, levofloxacin, moxifloxacin hydrochloride, and ofloxacin. They are all indicated for the treatment of bacterial conjunctivitis.[1-8] In addition, ciprofloxacin solution and ofloxacin have the indication to treat corneal ulcers caused by susceptible isolates.[2,8] All medications are formulated as drops (either solution or suspension) with only ciprofloxacin hydrochloride being formulated as an ointment (Ciloxan®).[3] Although generally considered equally effective, differences in resistance exist, with fewer gram-positive cocci being resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones.[13] Treatment for bacterial conjunctivitis with besifloxacin and moxifloxacin hydrochloride is usually dosed twice or three times daily, while the others are generally prescribed every two to four hours.[1-8] Most ophthalmic quinolones are indicated for use in patients one year of age or older; however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

Medications

Table 1. Medications Included Within Class Review[1-8]

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Besifloxacin ophthalmic (Besivance®)	Quinolone antibiotic	-
Ciprofloxacin hydrochloride ophthalmic (Ciloxan®*)	Quinolone antibiotic	✔ (solution)
Gatifloxacin ophthalmic (Zymaxid®*)	Quinolone antibiotic	✔
Levofloxacin ophthalmic	Quinolone antibiotic	✔
Moxifloxacin hydrochloride ophthalmic (Moxeza®, Vigamox®)	Quinolone antibiotic	-
Ofloxacin ophthalmic (Ocuflox®*)	Quinolone antibiotic	✔

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[1-8]

Generic Name	Treatment of bacterial conjunctivitis caused by susceptible isolates	Treatment of corneal ulcers caused by susceptible isolates
Besifloxacin	✔	
Ciprofloxacin hydrochloride	✔	✔ (solution)
Gatifloxacin	✔	
Levofloxacin	✔	
Moxifloxacin hydrochloride	✔	
Ofloxacin	✔	✔

Ophthalmic fluoroquinolones are also utilized for the treatment of other infectious conditions of the eye. Examples include blepharitis, blepharoconjunctivitis, keratoconjunctivitis, or symptoms of surface ocular infections.[14]

Phrmacokinetics

Limited pharmacokinetic data is available for the ophthalmic antibiotics. Although there is the potential for systemic absorption with the administration of these agents, the true clinical significance of this is not known. Specifically, for ophthalmic levofloxacin solution and ophthalmic moxifloxacin hydrochloride solution, post-administration, maximum mean concentrations were reported to be more than 1,000 times lower than those reported after standard oral doses of the respective oral medications. [1-8]

Clinical Trials

Clinical trials have demonstrated that ophthalmic fluoroquinolones are effective in treating and providing relief of conjunctivitis and corneal ulcers in pediatric and adult patients.[15-39] Several studies comparing ophthalmic fluoroquinolones to either placebo or vehicle have concluded that these medications resulted in significantly higher clinical resolution rates at days one through five.[15-20] Several studies have also been published comparing the efficacy of ophthalmic fluoroquinolones to other ophthalmic antibiotics and also themselves.[21-39]

Head-to-head trials evaluating the efficacy of ophthalmic antibiotics for the treatment of bacterial conjunctivitis have found that no one medication was inferior to another.[21-30] In one trial, significantly more patients in the ophthalmic moxifloxacin group had complete resolution of ocular signs and symptoms at 48 hours when compared to patients treated with ophthalmic polymyxin B sulfate/trimethoprim (P=0.001).[22] One study found levofloxacin 0.5% to have statistically greater microbial eradication in pediatric patients two to 11 years of age with bacterial conjunctivitis (P≤0.032) compared to ofloxacin 0.3% in, but not in any other pediatric age group.[26] In a seven 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 two treatments (P value not reported).[27] In a small meta-analysis, moxifloxacin was found to be associated with fewer drop-outs for treatment failure (P=0.002) compared to ofloxacin.[28] 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. 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.

In patients with a diagnosis of corneal ulcer, ophthalmic ciprofloxacin hydrochloride was shown to be efficacious treatment options.[31,32] Specifically, in one trial of patients with a diagnosis of infectious keratitis ophthalmic ciprofloxacin had a shorter average time to healing as compared to ophthalmic cefazolin

sodium fortified with gentamicin sulfate, although this was not found to be significant (*P* value not reported).[32]

A number of studies consisted of patients with multiple diagnoses such as blepharitis, blepharoconjunctivitis, bacterial conjunctivitis and blepharitis, keratoconjunctivitis, or symptoms of surface ocular infections. These studies found that the ophthalmic formulations of ciprofloxacin, gentamicin sulfate, ofloxacin, tobramycin solution, and polymyxin B sulfate/trimethoprim were efficacious in resolving or curing multiple ocular infections.[34-39] 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 three through five in patients with conjunctival hyperemia, eyelid crusting or discharge, and positive bacterial culture when compared to ophthalmic gentamicin sulfate ($P<0.05$); however, there were no significant differences between the two treatments with regard to clinical, microbial and overall improvement rates ($P=0.089$ for all outcomes).[39] In studies of patients with multiple diagnoses, the most commonly reported adverse events were not significantly different between treatment groups. The most common adverse events included burning, mild discomfort and stinging on instillation.[34-39]

Table 3. Clinical Trials

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
Bacterial Conjunctivitis				
Karpecki et al[15] Besifloxacin 0.6% 1 drop into the affected eye(s) TID for 5 days vs vehicle 1 drop into the affected eye(s) TID for 5 days	DB, MC, PC, PG, PRO, RCT Patients ages 1 year and older, in good health, with a clinical diagnosis of acute bacterial conjunctivitis as evidenced by a minimum of grade 1 for purulent conjunctival discharge and a minimum of grade 1 for either bulbar or palpebral conjunctival injection in at least 1 eye on ocular examination, with pinhole visual acuity of 20/200 or better in each eye, and females of childbearing potential using a reliable method of contraception	N=269 5 days	Primary: Clinical resolution defined as the absence of conjunctival discharge and bulbar conjunctival injection at visit three Secondary: Eradication of baseline bacterial infection, defined as the absence at visit three of bacterial species that were present at or above the threshold on day one, clinical resolution of baseline conjunctivitis at visit two, eradication of the baseline bacterial infection at visit two,	Primary: Clinical resolution of baseline conjunctivitis at visit three was significantly higher in the besifloxacin group when compared to the vehicle group (73.3 vs 43.1% respectively; *P*<0.001). Secondary: Clinical resolution of conjunctivitis at visit two did not show significant differences between besifloxacin and vehicle (33.3 vs 17.2% respectively; *P* value not reported), while eradication of bacterial infection at visit two was significantly greater with besifloxacin (90.0 vs 46.6% respectively; *P*<0.0001). Investigators' ratings of individual signs and symptoms were significantly higher in the treatment group when compared to the vehicle group at visit two (ocular discharge; *P*=0.008, bulbar conjunctival injection; *P*=0.004, visit two overall; *P*=0.003) as well as at visit two (*P*=0.013). Ratings of global changes in signs and symptoms were also found to be significantly greater in the treatment group at visit two and visit three (*P*=0.004 and *P*<0.001 respectively).

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
			improvements in investigators' ratings of global change in clinical signs and symptoms	
Hwang et al[16] Levofloxacin 0.5% 1 to 2 drops into the affected eye(s) while awake on days 1 and 2 then every 4 hours while awake on days 3 through 5 vs placebo 1 to 2 drops into the affected eye(s) while awake on days 1 and 2 then every 4 hours while awake on days 3 through 5	DB, MC, PC, RCT Patients ≥2 years of age with a clinical diagnosis of bacterial conjunctivitis characterized by purulent ocular discharge and redness in at least one eye	N=249 5 days	Primary: Antimicrobial efficacy, clinical efficacy, resolution of ocular signs and symptoms, safety Secondary: Not reported	Primary: Microbial eradication rates were significantly higher in the levofloxacin group at study visits one, two and three when compared to placebo (95 vs 49%; *P*<0.001, 92 vs 53%; *P*<0.001, and 90 vs 53%; *P*<0.001 respectively). Approximately twice as many patients in the treatment group achieved microbial eradication as those in the placebo group (*P*<0.001). Clinical cure rates were significantly greater in the levofloxacin group when compared to placebo at both the final visit and the last observation made for patients who did not attend all visits (*P*=0.020 and *P*=0.026 respectively). Resolution of ocular signs and symptoms were consistently higher in the treatment group than with placebo at all study visits (*P* value not reported). Statistically significant differences were seen favoring the levofloxacin group with regard to resolution of the ocular signs of conjunctival discharge (*P*=0.027), bulbar conjunctival injection (*P*=0.018), and for the ocular symptoms of burning and stinging (*P*=0.008), itching (*P*=0.037), and photophobia (*P*=0.023) With regard to safety, 91 adverse events were reported by 75 patients, 31% of the safety population. No significant differences were seen between the levofloxacin group and the placebo group with regard to the incidence of overall adverse events or treatment related events (*P* value not reported). Of the most common adverse events, only erythema and swelling was reported in significantly more patients in the levofloxacin group *(P*=0.672), while there was no statistically significant difference in the rate of conjunctival discharge, photophobia, and burning or stinging (*P*=0.027, *P*=0.023 and *P*=0.008 respectively).

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
				Secondary: Not reported
Tepedino et al[17] Besifloxacin 0.6% 1 drop into the affected eye(s) TID for 5 days vs vehicle 1 drop into the affected eye(s) TID for 5 days	DB, MC, VC Patients ≥1 year of age with clinical manifestations of acute bacterial conjunctivitis in at least one eye	N=957 9 days	Primary: Clinical resolution and microbial eradication of baseline bacterial infection at visit two (day five) Secondary: Clinical resolution and microbial eradication at visit three (day eight or nine), individual clinical outcomes at follow-up visits and safety	Primary: Clinical resolution rates were significantly higher in the besifloxacin treatment group compared to the vehicle group at the second visit (45.2 vs 33.0%; *P*=0.0084). By the second visit, microbial eradication rates were 91.5% and 59.7% for besifloxacin and vehicle, respectively; *P*<0.0001. Secondary: At visit three there was a significantly higher percentage of patients who had clinical resolution compared to the vehicle group (84.4 vs 69.1%; *P*=0.0011). By visit three, the microbial eradication rate continued to be significantly higher with besifloxacin treatment compared to vehicle alone (88.4 vs 71.7%; *P*<0.0001). The percentage of patients treated with besifloxacin who had a resolution of ocular discharge was significantly greater at visit two (73.9 vs 57.6%; *P*=0.0012) and three (93.0 vs 79.1%; *P*=0.0002) compared to those treated with vehicle. A significantly higher percentage of patients treated with besifloxacin had normal bulbar conjunctival injection than those treated with vehicle both at visit two (52.3 vs 36.1%; *P*=0.0007) and visit three (84.9% vs 70.7%; *P*=0.0011). The investigators assessment of cure increased in both the besifloxacin and vehicle groups between visits two and three. At visit two, 39.2 and 29.3% of patients treated with besifloxacin or vehicle, respectively, were considered cured by the investigator (*P*=0.02), while at visit three, the rates were 83.9 and 66.0% (*P*=0.0002). A significantly greater percentage of eyes treated with vehicle experienced at least one ocular adverse event compared to those treated with besifloxacin (13.9 vs 9.2%; *P*=0.0047).

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
Silverstein et al[18] Besifloxacin 0.6% 1 drop into the affected eye(s) BID for 3 days vs vehicle 1 drop into the affected eye(s) BID for 3 days	DB, MC, PG, PRO, RCT, VC Patients ≥1 year of age with a clinical diagnosis of acute bacterial conjunctivitis with purulent discharge, crusty or sticky eyelids, and ocular surface redness, and a minimum of grade 1 severity for both discharge and bulbar conjunctival injection in at least one eye	N=202 7 days	Primary: Clinical resolution and bacterial eradication of the baseline bacterial infection at visit two Secondary: Clinical resolution and bacterial eradication of the baseline bacterial infection at visit three, individual clinical outcomes at the follow- up visits	Primary: At visit two, clinical resolution of conjunctivitis in the study eye was significantly higher in the besifloxacin group compared to vehicle (69.8 vs 37.5%; respectively; *P*<0.001). The eradication of bacterial infection at visit two occurred in significantly more patients in the besifloxacin group compared to the vehicle group (86.8 vs 57.1%; *P*<0.001). Secondary: Rates of eradication of bacterial infection in the study eye at visit three were significantly greater in the besifloxacin group compared to the vehicle group (86.8 vs 69.6%, respectively; *P*=0.038). Rates of clinical resolution of bacterial conjunctivitis at visit three did not differ significantly between the besifloxacin and vehicle treatment groups (73.6 vs 66.1%; *P*=0.717). At visit two, the percentage of patients treated with besifloxacin who had resolution of ocular discharge was significantly greater compared to those who received vehicle (83.0 vs 55.4%, respectively; *P*=0.002) but not at visit three (86.8 vs 76.8%; *P* value not reported). The proportion of patients treated with besifloxacin who had resolution of bulbar conjunctival injection was significantly greater compared to patients receiving vehicle at visit two (77.4 vs 44.6%; *P*<0.001), but not at visit three (83.0 vs 73.2%; *P* value not reported).
DeLeon et al[19] Besifloxacin 0.6% 1 drop into the affected eye(s) BID for 3 days vs vehicle 1 drop into the	DB, MC, PG, RCT, VC Patients ≥1 year of age with acute bacterial conjunctivitis in ≥1 eye based on the presence of	N=474 7 days	Primary: Clinical resolution of conjunctivitis and eradication rates at day four or five in patients with bacterial conjunctivitis	Primary: By day four or five of treatment, bacterial eradication was significantly higher in patients treated with besifloxacin compared to the vehicle (85.2 vs 54.6%; *P*<0.001). Similarly, a clinical resolution by days four or five was also significantly greater in the besifloxacin group compared to the vehicle group (65.9 vs 44.0%, respectively; *P*<0.001).

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
affected eye(s) BID for 3 days	grade one or greater purulent conjunctival discharge and bulbar conjunctival injection, pinhole visual acuity of ≥20/200 in both eyes in age-appropriate individuals and acceptable visual acuity by the investigator's judgment in children too young to provide reliable acuity measurements		Secondary: Bacterial eradication and clinical resolution at day seven, individual clinical outcomes (ocular conjunctival discharge and bulbar conjunctival injection) at each follow-up visit, microbial and clinical outcomes for overall bacterial species and safety	Secondary: The rates of bacterial eradication at day seven continued to be significantly greater in the besifloxacin group compared to the vehicle group (85.2 vs 64.5%, respectively; *P*<0.001); however, rates of clinical resolution did not differ significantly between the treatment groups (76.3 and 66.7%; *P*=0.209). Significantly more patients treated with besifloxacin experienced a resolution of ocular discharge at day four or five compared to patients who received vehicle (77.8 vs 64.5%, respectively; *P*=0.012) and day seven (87.4 vs 77.3%; *P*=0.046). At day four or five, the proportion of patients treated with besifloxacin who experienced a resolution of bulbar conjunctival injection was significantly greater compared to those treated with vehicle (77.0 vs 51.8%; *P*<0.001), but not at day seven (84.4 vs 76.6%; *P*=0.259). Bacterial eradication and clinical resolution were significantly better in patients treated with besifloxacin compared to vehicle for infections caused by either gram-positive or gram-negative organisms at day four or five of treatment. At day seven, only bacterial eradication was significantly better in besifloxacin-treated patients compared to those receiving vehicle and only for infections caused by gram-positive organisms. There were no significant differences between the besifloxacin and vehicle groups in the number of eyes with ≥1 ocular adverse event in either study eye. All ocular adverse events in the besifloxacin ophthalmic suspension and vehicle groups were of mild or moderate severity. The most frequently reported adverse event in the besifloxacin and vehicle groups was bacterial conjunctivitis (2.4% for both). Chalazion occurred in 0.8% of patients treated with besifloxacin compared to vehicle.

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
Tauber et al[20] Moxifloxacin 0.5% 1 drop into the affected eye(s) BID for 3 days vs placebo 1 drop into the affected eye(s) BID for 3 days	DB, MC, PG, RCT, VC Patients ≥28 days old with a diagnosis of bacterial conjunctivitis in one or both eyes based on bulbar conjunctival injection and discharge (score ≥1 on a 4-point scale for each sign) and matting	N=1,180 6 days	Primary: Clinical cure rate, eradication rates by species Secondary: Not reported	Primary: Patients treated with moxifloxacin twice-daily for three days had a microbiological success rate of 74.5% compared to 56.0% of patients treated with vehicle (*P*<0.0001). Moxifloxacin administered BID was significantly more effective than vehicle in eradicating the three principle conjunctivitis pathogens, *H influenzae* (98.5 vs 59.6%; *P*<0.001), *S pneumoniae* (86.4 vs 50.0%; *P*<0.001), and *S aureus* (94.1 vs 80.0%; *P*<0.001).
Gross et al[21] Ciprofloxacin 3 mg/mL 1 drop into the affected eye(s) every 2 hours on days 1 and 2 and every 4 hours on days 3 through 7 vs tobramycin solution 1 drop into the affected eye(s) every 2 hours on days 1 and 2 and every 4 hours on days 3 through 7	DB, MC, RCT Patients ≤12 years of age with bacterial conjunctivitis	N=257 7 days	Primary: Treatment efficacy assessed by microbiological culture and physicians' judgment of overall resolution Secondary: Safety	Primary: Microbiological eradication was shown to be higher in the ciprofloxacin group when compared to the tobramycin group, however this difference was not significant (P=0.29). Physicians judgment of overall resolution was higher in the tobramycin group than in the ciprofloxacin group, however this difference was not significant (89.9 vs 87.0%; P>0.5). Secondary: No serious adverse events were attributed to either treatment.
Granet et al[22] Polymyxin B sulfate/ trimethoprim 1 drop into	MC, RCT Patients ≤18 years of age with	N=56	Primary: Relief of all signs and symptoms of bacterial	Primary: At the 48 hour visit complete resolution of ocular signs and symptoms were reported in significantly more patients in the moxifloxacin group when compared to the polymyxin B sulfate/trimethoprim group (81 vs

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
the affected eye(s) QID for 7 days vs moxifloxacin 0.5% 1 drop into the affected eye(s) TID for 7 days	a clinical diagnosis of bacterial conjunctivitis	7 days	conjunctivitis Secondary: Safety	44%; P=0.001). Secondary: No adverse events were reported in either group.
Leibowitz et al[23] Ciprofloxacin 0.3% vs tobramycin 0.3% vs placebo	2 MC, PRO, RCT Patients with bacterial conjunctivitis	N=288 Duration not specified	Primary: Antibacterial efficacy, and eradication of bacterial pathogens Secondary: Not reported	Primary: In one study, ciprofloxacin was shown to be significantly more effective than placebo (P<0.001), and eradicated or reduced the various bacterial pathogens in more patients when compared to placebo (93.6 vs 59.5%; P value not reported). In a second study ciprofloxacin and tobramycin were found to be equally effective in antibacterial efficacy (94.5 vs 91.9%; P value not reported). Secondary: Not reported
Williams et al[24] Moxifloxacin hydrochloride 0.5% drops TID vs polymyxin B/trimethoprim drops QID	NI, RCT Patients one to 18 years of age with acute conjunctivitis	N=120 7 days	Primary: Response to treatment on days four to six and on days seven to 10 Secondary: Not reported	Primary: Of the 114 patients who completed the four to six day evaluation, 56/62 (90%) were in the moxifloxacin group and 58/62 (93%) were in the polymyxin B/trimethoprim group. At the four to six day follow-up, 43/56 (77%) of the moxifloxacin hydrochloride group and 42/58 (72%) of the polymyxin B/trimethoprim group were categorized as clinically cured. The noninferiority test with a margin of 20% showed that the clinical cure rate of the polymyxin B/trimethoprim group is not statistically lower than that of moxifloxacin group (difference, -0.05; 90% CI, -0.20 to 0.11; P=0.04;). Cure rates were not different for the two treatment groups (P=0.59). No patients reported worsening of symptoms at four to six days. In the subgroup of initial culture-positive patients, 75 (39/41 in the moxifloxacin hydrocholroide group and 36/39 in the polymyxin B/trimethoprim group) completed the four to six day evaluation. In this

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
				subgroup, 30/39 (77%) of moxifloxacin treated patients and 26/36 (72%) of the polymyxin B/trimethoprim treated patients were clinically cured (P=0.10). At the final follow-up, a total of 89 patients (39/56 in the moxifloxacin hysdrochloride group and 50/58 in the polymyxin B/trimethoprim group) completed the seven to 10 day evaluation. At seven to 10 days, 37/39 (95%) of the entire moxifloxacin group and 49/51 (96%) of the entire polymyxin B/trimethoprim group were clinically cured (noninferiority test P<0.01). In the subgroup of initial culture-positive patients, 26/28 (93%) of the moxifloxacin hydrochloride group and 30/32 (94%) of the polymyxin B/trimethoprim group patients were considered clinically cured at seven to 10 days (P<0.01). The bacteriologic cure rate was 22/28 (79%) in the moxifloxacin hydrochloride group and 19/31 (61%) in the polymyxin B/trimethoprim group (P=0.52). Of the six patients with bacteriologic failure in the moxifloxacin group, four had *H influenzae* and two had *S pneumonia* isolated. Among the 12 polymyxin B/trimethoprim bacteriologic failures, five had *H influenzae*, one had *M catarrhalis*, and six had *S pneumoniae* isolated. Secondary: Not reported
McDonald et al[25] Besifloxacin 0.6% 1 drop into the affected eye(s) TID for 5 days vs moxifloxacin 0.5% 1 drop into the affected eye(s) TID for 5 days	DB, MC, NI, PG, RCT Patients ≥1 year of age in good health, with a clinical diagnosis of bacterial conjunctivitis as evidenced a grade of one or	N=1,161 8 days	Primary: Clinical resolution on day five, microbial eradication on day five of all accepted ocular bacterial species that were present at or above threshold	Primary: Findings on day five showed that there was no statistically significant difference in clinical resolution between the besifloxacin group and the moxifloxacin group (58.0 vs 59.4%, respectively; P=0.652). Besifloxacin was found to be NI to moxifloxacin (95% CI, -9.48 to 7.29). Besifloxacin was shown to be NI to moxifloxacin with regard to microbial eradication on day five (93.3 vs 91.1%, respectively; P=0.124). Secondary:

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
	greater purulent conjunctival discharge and bulbar conjunctival injection in ≥1 eye, pinhole visual acuity of 20/200 or greater in both eyes, willing to discontinue contact lens use during the study, and females of childbearing potential using a reliable method of contraception		at baseline Secondary: Clinical resolution on day eight, microbial eradication on day eight of all accepted ocular bacterial species that were present at or above threshold at baseline, and safety	On day eight there was no statistical difference seen with regard to clinical resolution between the besifloxacin and moxifloxacin groups (84.5 vs 84.0%, respectively; P=0.501). Besifloxacin was found to be NI to moxifloxacin on day eight (95% CI, -5.67 to 6.75). On day eight besifloxacin was shown to be NI to moxifloxacin with regard to microbial eradication (87.3 vs 84.7%, respectively; P=0.061). No significant differences were seen with regard to adverse events between the besifloxacin group and the moxifloxacin group (12.0 vs 14.0% respectively; P=0.224). One eye irritation was statistically different between the besifloxacin group and the moxifloxacin group (0.3 vs 1.4%, respectively; P=0.020).
Lichtenstein et al[26] Levofloxacin 0.5% 1 drop into the affected eye(s) every 2 hours on days 1 and 2 and every 4 hours on days 3 through 5 vs ofloxacin 0.3% 1 drop into the affected eye(s) every 2 hours on days 1 and 2 and every 4 hours on days 3 through 5 vs	DB, MC, PG, RCT Patients 1 to 16 years of age with a diagnosis of bacterial conjunctivitis	N=167 10 days	Primary: Rate of microbial eradication Secondary: Not reported	Primary: At the last observation the levofloxacin 0.5% group showed higher rates of microbial eradication when compared to ofloxacin 0.3% (P value not reported). In children ages two to 11 years this finding was statistically significant in favor of the levofloxacin 0.5% group when compared to both ofloxacin 0.3% and placebo (87 vs 62%; P<0.032 and 88 vs 24%; P<0.001). No statistically significant differences were observed between the three groups in the other age subgroups. Secondary: Not reported

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
placebo 1 drop into the affected eye(s) every 2 hours on days 1 and 2 and every 4 hours on days 3 through 5				
Schwab et al[27] Levofloxacin 0.5% 1 drop into the affected eye(s) every 2 hours on days 1 and 2 and every 4 hours on days 3 through 5 vs ofloxacin 0.3% 1 drop into the affected eye(s) every 2 hours on days 1 and 2 and every 4 hours on days 3 through 5	AC, DB, MC, RCT Patients ≥1 year of age with a diagnosis of bacterial conjunctivitis, characteristic purulent conjunctival discharge (minimum score of 1 on a 4-point scale), and redness (≥1 on a 4-point scale for bulbar and/or palpebral injection) in at least one eye	N=423 7 days	Primary: Microbial eradication and clinical cures Secondary: Evaluations of ocular signs and symptoms, safety	Primary: A significantly greater proportion of patients receiving 0.5% levofloxacin experienced microbial eradication compared to patients receiving 0.3% ofloxacin at both the final visit (89 vs 80%; P=0.034) and last available evaluation (90 vs 81%; P=0.038). Clinical cure rates were similar between the 0.5% levofloxacin and 0.3% ofloxacin treatment groups at all time points assessed. At the last evaluation period, clinical cure rates were 76% in each treatment group (P value not reported). Secondary: No significant differences were noted between the two treatment groups in resolution of baseline ocular signs at either the final visit or endpoint. In each treatment group, there was a trend toward resolution of the ocular signs of conjunctival discharge, bulbar and palpebral conjunctival injection and erythema/swelling, with most subjects (>80%) showing resolution by the completion of the study. There was however, a significantly lower incidence of photophobia associated with ofloxacin compared to levofloxacin (P=0.006). There were no significant differences between treatment groups in the overall incidence of adverse events. The most frequently reported nonocular adverse event was headache (3%). The most common ocular adverse events were conjunctivitis in the nonstudy eye or worsening conjunctivitis in the infected eye (8%), burning (2%), eye pain (2%) and decrease in visual acuity (2%).
Kodjikian et al (abstract)[28] Moxifloxacin	MA (5 RCT) Patients with a	N=not	Primary: Clinical efficacy and drop-out	Primary: Patients treated with moxifloxacin were more likely to achieve a clinical cure (OR, 1.59; 95% CI, 1.21 to 2.04; *P*<0.001) and were less likely to

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
vs ofloxacin vs levofloxacin	clinical diagnosis of acute bacterial conjunctivitis in one or more eyes	reported Duration not reported	rates for all reasons including lack of efficacy Secondary: Not reported	experience a treatment failure compared to treatment with placebo (OR, 3.61; 95% CI, 2.30 to 5.65; *P*<0.001). Moxifloxacin treatment was associated with less risk of discontinuing therapy compared to placebo (OR, 2.22; 95% CI, 1.62 to 3.03; *P*<0.001). In comparison to ofloxacin, patients treated with moxifloxacin had fewer dropouts for reasons other than treatment failure (OR, 1.92; 95% CI, 1.28 to 2.89; *P*=0.02) and fewer dropouts for treatment failure (OR, 2.53; 95% CI, 1.41 to 4.56; *P*=0.002).
Silver et al[29] Moxifloxacin 0.5% 1 drop into the affected eye(s) TID for 4 days vs ofloxacin 0.3% 1 drop into the affected eye(s) QID for 4 days vs ciprofloxacin 0.3% 1 drop into the affected eye(s) TID for 4 days vs vehicle	MA Male and female patients of any race, with a diagnosis of bacterial conjunctivitis	N=1,978 7 to 9 days	Primary: Safety Secondary: Not reported	Primary: The most frequent adverse events experienced by all patients were ocular discomfort, and transient burning and stinging, which were reported in more patients in the moxifloxacin group than the vehicle group (2.8 vs 2.1%; P value not reported). In pediatric patients similar results were found with ocular discomfort, transient burning and stinging reported as the most frequent adverse events experienced; these adverse events were reported in less patients the moxifloxacin group when compared to the vehicle group (1.9 vs 2.2%; P value not reported). The most common systemic adverse event reported in pediatric patients was increased cough that occurred in more patients in the moxifloxacin group than the vehicle group (3.2 vs 2.8%; P value not reported). Similar rates of adverse events were reported in a study comparing moxifloxacin to ofloxacin with regard to keratitis, corneal infiltrate, and ocular hyperemia (P value not reported). In a study comparing moxifloxacin to ciprofloxacin, adverse events were also similar between the two groups with regard to tearing, ocular hyperemia, rash, and rhinitis (P value not reported). Secondary: Not reported
Sheikh et al[30]	MA	N=1,034	Primary: Early clinical	Primary: When bacitracin/polymyxin was compared to vehicle with regard to

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
Bacitracin/polymyxin 500 units/g and 10,000 units/g vs ciprofloxacin 0.3% vs chloramphenicol 0.5%* vs fusidic acid gel 1%* vs norfoloxacin 0.3%* vs vehicle	Patients ages one month and older, with acute bacterial conjunctivitis, and symptoms of less than four weeks duration	Duration not specified	remission, early microbiological remission, late clinical remission, and late microbiological remission Secondary: Not reported	early clinical remission, bacitracin/polymyxin was favored at days three through five (RR, 2.20; 95% CI, 1.19 to 4.06). When bacitracin/polymyxin was compared to vehicle with regard to microbiological remission during days three through five it was found that bacitracin/polymyxin was favored (RR, 3.76; 95% CI, 1.77 to 8.00). Ciprofloxacin was also favored when compared to vehicle with regard to early microbiological remission, at day three (RR, 1.59; 95% CI, 1.21 to 2.08). Bacitracin/polymyxin was favored over vehicle with regard to late clinical remission at days eight to 10 (RR, 1.27; 95% CI, 1.00 to 1.61) as well as for late microbiological remission in days eight through 10 (RR, 2.54; 95% CI, 1.48 to 4.37). Secondary: Not reported
Corneal Ulcer				
Booranapong et al[31] Ciprofloxacin 0.3% vs lomefloxacin 0.3%*	DB, PRO, RCT Patients with suspected bacterial corneal ulcers	N=41 Duration not specified	Primary: Time to cure, treatment failure, and resolution of clinical signs and symptoms Secondary: Safety	Primary: No statistically significant differences were found with regard to time to cure, treatment failure, or the resolution of clinical signs and symptoms (*P*>0.05 for all). Secondary: No statistically significant difference was found between the two groups with regard to adverse events (*P*>0.05).
Kosrirukvongs et al[32]	RCT	N=41	Primary: Rate of	Primary: A higher number of patients in the ciprofloxacin group had

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
Ciprofloxacin 0.3% applied into the affected eye(s) every 15 minutes for the first 6 hours, then every 30 minutes on the first day, then every hour while awake till midnight until complete recovery without staining of fluorescein and no culture growth vs cefazolin 50 mg/mL fortified with gentamicin 14 mg/mL applied into the affected eye(s) every 15 minutes for the first 6 hours, then every 30 minutes on the first day, then every hour while awake till midnight until complete recovery without staining of fluorescein and no culture growth	Patients with suspected corneal ulcers	16 days	therapeutically successful treatment, and mean duration for healing Secondary: Not reported	therapeutically successful treatment when compared to the cefazolin fortified with gentamicin group; however this difference was not found to be statistically significant (70.6 vs 62.5%, respectively; *P* value not reported). The mean duration for healing after treatment was found to be less in the ciprofloxacin group but was not found to be statistically significant (14.6 vs 15.6 days, respectively; *P* value not reported). Secondary: Not reported
Keratitis				
Parks et al[33] Ciprofloxacin 3 mg/mL vs cefazolin 50 mg/mL fortified with gentamicin sulfate 9.1 mg/mL	RETRO Patients with infectious keratitis	N=44 Duration not specified	Primary: Average time to healing, and duration of antibiotic therapy Secondary: Not reported	Primary: Average time to healing in the ciprofloxacin group was less than that seen in the cefazolin fortified with gentamicin sulfate group, however this was not found to be statistically significant (34±33 vs 45±71 days; P value not reported). The duration of antibiotic therapy in the ciprofloxacin group was also less than that seen in the cefazolin fortified with gentamicin sulfate group (27±15 vs 33±50 days; P value not reported).

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
				Secondary: Not reported
Multiple/unspecified external ocular infection				
Bloom et al[34] Ciprofloxacin treatment to affected eye(s) for 7 days vs tobramycin treatment to affected eye(s) for 7 days	DB, MC, RCT Patients with blepharitis and blepharoconjunctivitis	N=464 7 days	Primary: Eradication or reduction of potentially pathogenic bacteria, improvement or cure rate after seven days, and adverse events Secondary: Not reported	Primary: Eradication or reduction of potentially pathogenic bacteria after seven days of treatment was reported in more patients in the ciprofloxacin group than in the tobramycin group (93.7 vs 88.9% respectively; P value not reported). More than 80% of patients in both groups were cured or improved after seven days. However, no statistically significant differences were seen between the two groups (P value not reported). No serious adverse events were reported in either group. Secondary: Not reported
Adenis et al[35] Ciprofloxacin 0.3% vs fusidic acid 1%*	OL, PG, RCT Patients with bacterial conjunctivitis and blepharitis	N=39 7 days	Primary: Eradication of infecting organism, clinical cure rate, and adverse events Secondary: Not reported	Primary: The infecting organism was documented to be eradicated in more patients in the ciprofloxacin group than those in the fusidic acid group (81 vs 72%, respectively; P value not reported). Clinical cure rates were also found to be higher in the ciprofloxacin group when compared to the fusidic acid group (95 vs 89%, respectively; P value not reported). Two patients in the ciprofloxacin group reported adverse events, mild discomfort and stinging on instillation, while one patient in the fusidic acid group reported moderate edema and discomfort (P value not reported). Secondary: Not reported

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
Adenis et al[36] Ciprofloxacin 0.3% vs rifamycin 1%*	DB, PG, RCT Patients with bacterial conjunctivitis and blepharitis	N=41 7 days	Primary: Clinical cure rate on day seven, bacteriological eradication rate, and adverse events Secondary: Not reported	Primary: Clinical cure rates on day seven were shown to be higher in the ciprofloxacin group than the rifamycin group, however this difference was not found to be statistically significant (53 vs 23%, respectively; P=0.061). Bacteriological eradication rates were similar in both groups (68 vs 77%, respectively; P value not reported). No serious adverse events were reported in either treatment group. Secondary: Not reported
Bron et al[37] Ofloxacin 0.3% 1 drop into the affected eye(s) every 2 to 4 hours on days 1 and 2 and QID on days 3 through 7 vs chloramphenicol 0.5%* 1 drop into the affected eye(s) every 2 to 4 hours on days 1 and 2 and QID on days 3 through 7	DB, MC, PG, RCT Patients with suspected bacterial ocular infection	N=167 8 days	Primary: Clinical improvement as defined as a decline in symptoms of external ocular infection , microbiological improvement rate, and clinical improvement rate Secondary: Safety	Primary: High rates of improvement were seen in both groups with no statistically or clinically significant differences seen with regard to microbiological, clinical or overall improvement rates of the initial culture-positive group (P value not reported). Microbiological improvement rates were similar between the ofloxacin group and the chloramphenicol group (85 vs 88%, respectively; P value not reported). Clinical improvement rates were also high for both the ofloxacin group and the chloramphenicol group (100 vs 95%, respectively; P value not reported). Secondary: No significant differences were seen between the two groups for any symptom present at visit three or with regard to adverse events (P value not reported).
Gwon et al[38] Ofloxacin 0.3% 1 drop into the affected eye(s) every 2 to 4 hours on days 1 and 2	DB, RCT Patients with suspected external ocular	N=194 11 days	Primary: Clinical, microbiological, and overall improvement	Primary: Ofloxacin was found to have higher rates of clinical (98 vs 92%), microbiological (78 vs 67%), and overall (78 vs 63%) improvement rates when compared to gentamicin however none of these differences were statistically significant (P=0.089 for all outcomes).

Study and Drug Regimen	Design and Demographics	Sample Size and Duration	End Points	Results
and QID on days 3 through 7 vs gentamicin 0.3% 1 drop into the affected eye(s) every 2 to 4 hours on days 1 and 2 and QID on days 3 through 7	bacterial infection including conjunctivitis, blepharitis, and blepharoconjunctivitis		rates Secondary: Safety	 Secondary: Adverse events were reported in 3.2% of the ofloxacin group and in 7.1% of the gentamicin group with the most common reactions including burning, stinging, and photophobia (P value not reported).
Gwon et al[39] Ofloxacin 0.3% 1 drop into the affected eye(s) every 2 to 4 hours on days 1 and 2 and QID on days 3 through 10 vs tobramycin 0.3% 1 drop into the affected eye(s) every 2 to 4 hours on days 1 and 2 and QID on days 3 through 10	DB, MC, RCT Patients with the presence of conjunctival hyperemia, either eyelid crusting or discharge, and positive bacterial culture	N=345 11 days	Primary: Clinical, microbiological, and overall improvement rates Secondary: Change in cumulative summary score of 10 key biomicroscopic and symptomatologic variables, and safety	Primary: Ofloxacin was found to have higher rates of microbiological (85.2 vs 77.6%), and overall (84.0 vs 77.6%) improvement rates when compared to tobramycin at day 11, while tobramycin was shown to have a higher clinical improvement rate (98.9 vs 100%), however none of these differences were found to be statistically significant (P=0.089 for all outcomes). Secondary: The decrease in cumulative summary score was found to be significantly greater in the ofloxacin group when compared to the tobramycin group at visits on days three to five (P<0.050) Adverse reactions occurred more frequently in the tobramycin group, however this was not found to be significant (0.6 vs 2.9%, respectively; P value not reported).

*Agent not available in the United States
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, VC=vehicle controlled

Special Populations

Table 4. Special Populations[1-8]

Generic Name	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Besifloxacin	No overall differences in safety or efficacy observed in the elderly. Safety and efficacy in pediatric patients <1 year of age have not been established.	Not reported	Not reported	C	Unknown
Ciprofloxacin	No overall differences in safety or efficacy observed in the elderly. Ophthalmic ointment: Safety and efficacy in pediatric patients <2 years of age have not been established. Ophthalmic solution: Safety and efficacy in pediatric patients <1 year of age have not been established.	Not reported	Not reported	C	Unknown
Gatifloxacin	No overall differences in safety or efficacy observed in the elderly. Safety and efficacy in pediatric patients<1 year of age have not been established.	Not reported	Not reported	C	Unknown
Levofloxacin	No overall differences in safety or efficacy observed in the elderly. Safety and efficacy in pediatric patients <1 year of age have not been established.	Not reported	Not reported	C	Unknown
Moxifloxacin	No overall	Not reported	Not reported	C	Unknown

hydrochloride	differences in safety or efficacy observed in the elderly. Moxeza®: Safety and efficacy in pediatric patients <4 months of age have not been established. Vigamox®: Safety and efficacy in pediatric patients <1 year of age have not been established.				
Ofloxacin	No overall differences in safety or efficacy observed in the elderly. Safety and efficacy in pediatric patients <1 year of age have not been established.	Not reported	Not reported	C	Unknown

Adverse Drug Events

Table 5. Adverse Drug Events[1-8]

Adverse Events	Besifloxacin	Ciprofloxacin Hydrochloride Solution	Ciprofloxacin Hydrochloride Ointment	Gatifloxacin	Levofloxacin	Moxifloxacin Hydrochloride	Ofloxacin
Cardiovascular							
Hyperemia	-	-	<1	-	-	-	-
Central Nervous System							
Dizziness	-	-	-	-	-	-	✔
Headache	1 to 2	-	-	1 to 4	1 to 3	-	-
Itching	-	<10	-	-	-	-	✔
Pruritus	-	-	<1	-	-	-	-
Dermatologic							
Dermatitis	-	-	<1	-	-	-	-
Rash	-	-	-	-	-	1 to 4	-
Endocrine							
Edema	-	-	<1	-	-	-	✔
Gastrointestinal							
Diarrhea	-	-	-	-	-	-	-
Dyspepsia	-	-	-	-	-	-	-
Nausea	-	<1	<1	-	-	-	✔
Ocular							
Blurred vision	1 to 2	-	<1	-	-	-	✔
Burning	-	✔	-	-	-	-	-
Chemical conjunctivitis	-	-	-	-	-	-	✔
Chemical keratitis	-	-	-	-	-	-	✔
Chemosis	-	-	-	1 to 4	-	-	-
Conjunctival hemorrhage	-	-	-	1 to 4	-	-	-
Conjunctival hyperemia	-	<10	-	-	-	-	-
Conjunctival irritation	-	-	-	5 to 10	-	-	-
Conjunctival redness	2	-	-	-	-	-	-
Conjunctivitis	-	-	-	-	-	1 to 6	-
Corneal erosion	-	-	-	-	-	-	-
Corneal infiltrates	-	<1	-	-	-	-	-

Adverse Events	Besifloxacin	Ciprofloxacin Hydrochloride Solution	Ciprofloxacin Hydrochloride Ointment	Gatifloxacin	Levofloxacin	Moxifloxacin Hydrochloride	Ofloxacin
Corneal staining	-	<1	<1	-	-	-	-
Corneal ulcer	-	-	-	-	-	-	-
Crystals/scales	-	<10	-	-	-	-	-
Decreased vision	-	<1	-	-	1 to 3	-	-
Decreased visual acuity	-	-	<1	1 to 4	-	1 to 6	-
Diplopia	-	-	-	-	-	-	-
Dry eye	-	-	<1	1 to 4	-	1 to 6	-
Dryness	-	-	-	-	-	-	✔
Epitheliopathy	-	-	<1	-	-	-	-
Eye discharge	-	-	-	1 to 4	-	-	-
Eye discomfort	-	✔	2	-	-	-	-
Eye irritation	1 to 2	-	<1	1 to 4	-	1 to 2	-
Eye pain	1 to 2	-	<1	1 to 4	-	-	✔
Eye pruritus	1 to 2	-	-	-	-	-	-
Eyelid edema	-	-	-	1 to 4	-	-	-
Floaters	-	-	-	-	-	-	-
Foreign body sensation	-	<10	<1	-	1 to 3	-	✔
Keratoconjunctivitis	-	-	<1	-	-	-	-
Keratopathy	-	<1	2	-	-	-	-
Keratitis	-	<1	-	5 to 10	-	1 to 6	-
Lid edema	-	<1	-	-	<1	-	-
Lid erythema	-	-	<1	-	-	-	-
Lid margin crusting	-	<10	-	-	-	-	-
Lid margin hyperemia	-	-	<1	-	-	-	-
Ocular discomfort	-	-	-	-	1 to 3	1 to 6	-
Ocular dryness	-	-	-	-	<1	-	-
Ocular hyperemia	-	-	-	-	-	1 to 6	-
Ocular infection	-	-	-	-	-	-	-
Ocular itching	-	-	-	-	<1	-	-
Ocular pain	-	-	-	-	1 to 3	1 to 6	-
Ocular pruritus	-	-	-	-	-	1 to 6	-
Papillary conjunctivitis	-	-	-	5 to 10	-	-	-

Adverse Events	Besifloxacin	Ciprofloxacin Hydrochloride Solution	Ciprofloxacin Hydrochloride Ointment	Gatifloxacin	Levofloxacin	Moxifloxacin Hydrochloride	Ofloxacin
Redness	-	-	-	1 to 4	-	-	✔
Stinging	-	-	-	-	-	-	✔
Subconjunctival hemorrhage	-	-	-	-	-	1 to 6	-
Tearing	-	<1	<1	5 to 10	-	1 to 6	✔
Transient ocular burning	-	-	-	-	1 to 3	-	✔
Transient ocular discomfort	-	-	-	-	-	-	✔
White crystalline precipitates	-	17	-	-	-	-	-
Respiratory							
Increased cough	-	-	-	-	-	1 to 4	-
Pharyngitis	-	-	-	-	1 to 3	1 to 4	-
Rhinitis	-	-	-	-	-	1 to 4	-
Other							
Allergic reactions	-	<1	<1	-	<1	-	-
Bad taste following instillation	-	<10	-	-	-	-	-
Fever	-	-	-	-	1 to 3	1 to 4	-
Infection	-	-	-	-	-	1 to 4	-
Otitis media	-	-	-	-	-	1 to 4	-
Photophobia	-	<1	<1	-	1 to 3	-	✔
Pyrexia	-	-	-	-	-	1 to 2	-
Taste perversion	-	-	<1	1 to 4	-	-	-
Throat irritation	-	-	-	-	-	-	-

Drug Interactions[1-8]

Since ophthalmic medications have minimal systemic absorption, studies have not been conducted to assess drug interactions associated with these medications.

Contraindications

Table 6. Contraindications[1-8]

Adverse Events	Besifloxacin	Ciprofloxacin Hydrochloride Solution	Ciprofloxacin Hydrochloride Ointment	Gatifloxacin	Levofloxacin	Moxifloxacin Hydrochloride	Ofloxacin
Hypersensitivity to any components of the product	-	✔	✔	-	✔	✔	✔

Warnings/Precautions

Table 7. Warnings and Precautions[1-8]

Warning/Precaution	Besifloxacin	Ciprofloxacin Hydrochloride Solution	Ciprofloxacin Hydrochloride Ointment	Gatifloxacin	Levofloxacin	Moxifloxacin Hydrochloride	Ofloxacin
Contact Lenses; patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during therapy with ophthalmic quinolones.	✔	✔	✔	✔	✔	✔	-
Hypersensitivity reaction; serious and sometime fatal anaphylactic reactions may occur, requiring emergency care.	-	✔	✔	-	✔	✔	✔
Hypersensitivity reaction; discontinue use at the first appearance of a skin rash or any other sign of reactions.	-	✔	✔	-	-	-	✔
Ophthalmic ointments may retard corneal healing and cause visual blurring.	-	-	✔	-	-	-	-
Resistant organisms with prolonged use may occur; overgrowth of non-susceptible organisms, including fungi; discontinue use and institute alternative therapy if super-infection occurs.	✔	✔	✔	✔	✔	✔	✔
Topical use only; not for injection into the eye.	✔	✔	✔	✔	✔	✔	✔
White crystalline precipitate may be observed and resolved most patients by day 44; did not preclude quinolone use.	-	✔	-	-	-	-	-

Dosage and Administration

Table 8. Dosing and Administration[1-8]

Generic Name	Adult Dose	Pediatric Dose	Availability
Besifloxacin	Treatment of bacterial conjunctivitis caused by susceptible isolates: Instill one drop into affected eye(s) three times a day, four to 12 hours apart for seven days	Safety and efficacy in pediatric patients <1 year of age have not been established.	Ophthalmic suspension: 0.6% (5 mL)
Ciprofloxacin hydrochloride	Treatment of bacterial conjunctivitis caused by susceptible isolates: Ophthalmic ointment: apply ½ inch ribbon into conjunctival sac(s) three times a day for the first two days, then apply ½ inch ribbon two times a day for the next five days Ophthalmic solution: instill one or two drops into conjunctival sac(s) every two hours while awake for two days, then one or two drops every four hours while awake for the next five days Treatment of corneal ulcers caused by susceptible isolates: Ophthalmic solution: on day one instill two drops into the affected eye(s) every 15 minutes for the first six hours and then two drops into the affected eye(s) every 30 minutes for the remainder of the first day, then on day two instill two drops into the affected eye(s) every hour, and then instill two drops into the affected eye(s) every four hours for days three through 14	Ophthalmic ointment: safety and efficacy in pediatric patients <2 years of age have not been established. Ophthalmic solution: safety and efficacy in pediatric patients <1 year of age have not been established.	Ophthalmic ointment: 0.3% (3.5 g) Ophthalmic solution: 0.3% (2.5, 5, 10 mL)
Gatifloxacin	Treatment of bacterial conjunctivitis caused by susceptible isolates: On day one instill one drop into affected eye(s) every two hours while awake up to eight times, then on days two through seven instill one drop into affected eye(s) two to four times a day while awake	Safety and efficacy in pediatric patients <1 year of age have not been established.	Ophthalmic solution: 0.5% (2.5 mL)
Levofloxacin	Treatment of bacterial conjunctivitis caused by susceptible isolates: On days one and two, instill one to two drops into the affected eye(s) every two hours while awake up to eight times per day, then on days three through seven instill one to two drops into the affected eye(s)	Safety and efficacy in pediatric patients <1 year of age have not been established.	Ophthalmic solution: 0.5% (5 mL)

Generic Name	Adult Dose	Pediatric Dose	Availability
	every four hours while awake up to four times daily		
Moxifloxacin hydrochloride	Treatment of bacterial conjunctivitis caused by susceptible isolates: Moxeza®: instill one drop into the affected eye(s) two times daily for seven days Vigamox®: instill one drop into the affected eye(s) three times a day for seven days	Moxeza®: Safety and efficacy in pediatric patients <4 months of age have not been established. Vigamox®: Safety and efficacy in pediatric patients <1 year of age have not been established.	Ophthalmic solution: 0.5% (3 mL)
Ofloxacin	Treatment of bacterial conjunctivitis caused by susceptible isolates: On days one and two instill one to two drops into the affected eye(s) every two to four hours, and on days three through seven instill one to two drops into the affected eye(s) four times daily Treatment of corneal ulcers caused by susceptible isolates: On days one and two instill one to two drops into the affected eye(s) every 30 minutes while awake and awaken four to six hours after retiring to instill one to two drops, then on days three through seven to nine instill one to two drops into the affected eye(s) hourly while awake, then on days seven to nine through treatment completion instill one to two drops into the affected eye(s) four times daily	Safety and efficacy in pediatric patients <1 year of age have not been established.	Ophthalmic solution: 0.3% (5, 10 mL)

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Ophthalmology: **Preferred Practice Pattern: Conjunctivitis (2013)**[11]	Seasonal allergic conjunctivitis • Treatment of conjunctivitis is ideally directed at the root cause. Indiscriminate use of topical antibiotics or corticosteroids should be avoided because antibiotics can induce toxicity, and corticosteroids can potentially prolong adenoviral infections and worsen herpes simplex virus infections. • Treat mild allergic conjunctivitis with an over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist. The guideline does not give preference to one OTC antihistamine/vasoconstrictor or antihistamine vs another. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. • If the condition is frequently recurrent or persistent, use mast-cell stabilizers. The guideline does not give preference to one mast-cell stabilizer vs another. • Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. The guideline does not give preference to one antihistamine/mast-cell stabilizer vs another. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used. • Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), is also Food and Drug Administration (FDA)-approved for the treatment of allergic conjunctivitis. • Additional measures include allergen avoidance and using cool compresses, oral antihistamines and artificial tears, which dilute allergens and treat coexisting tear deficiency. Frequent clothes washing and bathing before bedtime may also be helpful. • Consultation with an allergist or dermatologist may be helpful for patients with disease that cannot be adequately controlled with topical medications and oral antihistamines. Vernal/atopic conjunctivitis • General treatment measures include modifying the environment to minimize exposure to allergens or irritants and using cool compresses and ocular lubricants. Topical and oral antihistamines and topical mast-cell stabilizers may be beneficial in maintaining comfort. • For acute exacerbations, topical corticosteroids are usually necessary to control severe symptoms. The minimal amount of corticosteroid should be used based on patient response and tolerance. Topical cyclosporine is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis. For entities such as vernal keratoconjunctivitis, which may require repeat short-term therapy with topical corticosteroid, patients should be informed about potential complications of corticosteroid therapy, and general strategies to minimize corticosteroid use should be discussed. • For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, supratarsal injection of corticosteroid can be considered. • Systemic immunosuppression may rarely be warranted. • In patients two years of age or older, eyelid involvement may be treated with

Clinical Guideline	Recommendations
	pimecrolimus cream or tacrolimus ointment. Patients should be told to keep these medications away from the conjunctival and corneal surface and from the tear film. Both agents are rarely associated with the development of skin cancer and lymphoma. • Frequency of follow-up visits is based on the severity of disease presentation, etiology and treatment. Consultation with a dermatologist is often helpful. If corticosteroids are prescribed, baseline and periodic measurement of intraocular pressure and papillary dilation should be performed to evaluate for glaucoma and cataract(s). <u>Mild bacterial conjunctivitis</u> • Mild bacterial conjunctivitis may be self-limited and resolve spontaneously without treatment in immunocompetent adults. • Ophthalmic antibacterial therapy is associated with earlier clinical and microbiological remission compared to placebo at days two to five of treatment. The advantages persist over six to 10 days, but the benefit over placebo lessens over time. • The choice of ophthalmic antibiotic is usually empirical. • A five to seven day course of ophthalmic broad-spectrum antibiotic is usually effective. • The most convenient or least expensive option can be selected. <u>Severe bacterial conjunctivitis</u> • Severe bacterial conjunctivitis is characterized by copious purulent discharge, pain and marked inflammation of the eye. • The choice of ophthalmic antibiotic is guided by the results of laboratory tests. • Methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated with increasing frequency from patients with bacterial conjunctivitis. Many MRSA organisms are resistant to commercially available ophthalmic antibiotics. • Systemic antibiotic therapy is necessary to treat conjunctivitis due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. • If corneal involvement is present, the patient should also be treated topically for bacterial keratitis. <u>Herpes simplex virus conjunctivitis</u> • Topical and/or oral antiviral treatment is recommended for herpes simplex virus conjunctivitis to prevent corneal infection. • Possible options include topical ganciclovir 0.15% gel applied three to five times per day, trifluridine 1% solution applied five to eight times per day, or oral acyclovir 200 to 400 mg administered five times per day. • Oral valacyclovir and famciclovir also can be used. • Topical antiviral agents may cause toxicity if used for more than two weeks. • Topical corticosteroids potentiate herpes simplex virus infection and should be avoided. • Follow-up care management within one week of treatment is advised and should include an interval history, visual acuity measurement, and slit-lamp biomicroscopy. • Neonates require prompt consultation with the pediatrician or primary care physician, because systemic herpes simplex virus infection is a life-threatening condition.
American	<u>Allergic conjunctivitis (includes atopic keratoconjunctivitis, simple allergic</u>

Clinical Guideline	Recommendations
Optometric Association: Optometric Clinical Practice Guideline: **Care of the Patient With Conjunctivitis (2007)** [12]	conjunctivitis, seasonal or perennial conjunctivitis and vernal conjunctivitis) • The treatment of allergic conjunctivitis is based upon identification of specific antigens and elimination of specific pathogens, when practical, and upon the use of medications that decrease or mediate the immune response. The use of supportive treatment, including unpreserved lubricants and cold compresses, may provide symptomatic relief. • The following agents are useful in treating allergic conjunctivitis: topical corticosteroids (numerous products listed), vasoconstrictors/antihistamines (specific products not listed), antihistamines (azelastine, emedastine and levocabastine*), NSAIDs (ketorolac), mast cell stabilizers (cromolyn, lodoxamide, nedocromil and pemirolast), antihistamines/mast cell stabilizers (ketotifen and olopatadine) and immunosuppressants; and systemic immunosuppressants and antihistamines. • Topical corticosteroids are effective in relieving the acute symptoms of allergy; however, their use should be limited to the acute suppression of symptoms because of the potential for adverse side effects with prolonged use (e.g., cataract formation and elevated intraocular pressure). • Topical vasoconstrictors/antihistamines cause vascular constriction, decrease vascular permeability and reduce ocular itching by blocking histamine H_1 receptors. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. • Topical antihistamines competitively bind with histamine receptor sites and reduce itching and vasodilation. Azelastine, emedastine and levocabastine* are effective in reducing the symptoms of allergic conjunctivitis, and emedastine may be more efficacious than levocabastine*. • Topical diclofenac and ketorolac, which are both NSAIDS, are effective in reducing the signs and symptoms associated with allergic conjunctivitis, although only ketorolac is FDA approved for this indication. • Nedocromil, an effective treatment for seasonal allergic conjunctivitis, is more effective than cromolyn (2%†) in treating vernal conjunctivitis. Nedocromil was less effective than fluorometholone in treating severe vernal keratoconjunctivitis but has fewer side effects. Lodoxamide has demonstrated a greater improvement in the signs and symptoms of allergic eye disease, including vernal keratoconjunctivitis, than cromolyn (2† or 4%). Pemirolast has FDA approval as a treatment to relieve (to prevent) itching associated with allergic conjunctivitis. • Ketotifen and olopatadine are selective histamine H_1-receptor antagonists that also have mast cell stabilizing properties. Olopatadine may be more effective than other mast cell stabilizing agents in targeting the subtype of mast cell found in the conjunctiva. Compared to ketorolac or ketotifen, olopatadine is more effective in relieving the itching and redness associated with acute allergic conjunctivitis. • Systemically administered cyclosporine may be an effective treatment for patients with severe atopic keratoconjunctivitis. Topical cyclosporine is an alternative to topical corticosteroids for treatment of patients with severe atopic keratoconjunctivitis. Topical cyclosporine may also be beneficial in patients with vernal keratoconjunctivitis who have failed conventional therapy. • Systemic antihistamines are useful when the allergic response is associated with lid edema, dermatitis, rhinitis or sinusitis. They should be used with caution because of the sedating and anticholinergic effects of some first-generation antihistamines. Newer antihistamines are much less likely to

Clinical Guideline	Recommendations
	cause sedation, but their use may result in increased ocular surface dryness. Bacterial conjunctivitis • The ideal method of treating bacterial conjunctivitis is to identify the causative organism and initiate specific antimicrobial treatment known to be effective against the offending organism. • Commonly available topical antimicrobial drugs include: aminoglycosides, bacitracin, chloramphenicol, erythromycin, quinolones (ciprofloxacin, ofloxacin, levofloxacin), polymyxin B/neomycin, polymyxin B/trimethoprim sulfate, sodium sulfacetamide, sulfisoxazole diolamine, and tetracycline. • In the absence of a culture or smear, the etiologic agent should be considered in the context of the patient's age, environment, and related ocular findings. • In most cases, a broad-spectrum topical antibiotic is the treatment of choice. • Although most cases of bacterial conjunctivitis are self-limited, treatment with effective antibiotics can lessen the patient's symptoms, decrease the duration of the infection, and reduce the chances of its recurrence. • Hyperacute conjunctivitis requires special consideration because of potential blinding from inadequately treated gonococcal infections. Conjunctival smears and cultures should be obtained before beginning treatment. The administration of systemic antibiotics that are effective against the identified organisms should be started immediately. Saline lavage may be beneficial in removing purulent discharge. • In the case of gonococcal infection, the Centers for Disease Control and Prevention recommend the administration of a single dose of intramuscular ceftriaxone. Although the CDC does not recommend topical treatment, practitioners may wish to consider the addition of a topical fluoroquinolone as adjunctive therapy. • Patients should also be evaluated for co-infection with other sexually transmitted diseases. Care of the patient with sexually transmitted disease should be coordinated with the patient's primary care physician. Viral conjunctivitis • Most viral conjunctivitis is related to adenoviral infection; however, no antiviral agent has been demonstrated to be effective in treating these infections. • Topical NSAID therapies have shown no benefit in reducing viral replication, decreasing the incidence of sub-epithelial infiltrates or alleviating symptoms. • Topical antibiotics are not routinely used to treat viral conjunctivitis, unless there is evidence of secondary bacterial infection. • The treatment of herpes simplex conjunctivitis may include the use of antiviral agents such as trifluridine, although there is no evidence that this therapy results in a lower incidence of recurrent disease or keratitis. • Supportive therapy, including lubricants and cold compresses, which may be as effective as antiviral drugs, eliminates the potential for toxic side effects. • Topical steroids are specifically contraindicated in treating herpes simplex conjunctivitis
American Academy of Ophthalmology: **Preferred Practice Pattern: Bacterial**	Initial treatment • Ophthalmic antibiotic eye drops are the preferred method of treatment in most cases of bacterial keratitis. • Ophthalmic ointments may be useful at bedtime in less severe cases and may be useful for adjunctive therapy. • Ophthalmic broad-spectrum antibiotics are used initially in the empiric

Clinical Guideline	Recommendations
Keratitis (2013)[13]	treatment of bacterial keratitis. Central or severe keratitis is usually treated using a loading dose (every five to 15 minutes) followed by frequent applications (every 30 minutes to one hour around the clock). Less severe keratitis requires less frequent dosing. • The recommended ophthalmic empiric treatments include: o No organism identified or multiple types of organisms: ophthalmic cefazolin sodium (with gentamicin sulfate or tobramycin) or ophthalmic fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones). o Gram-positive cocci: ophthalmic cefazolin sodium, vancomycin (for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy), ophthalmic bacitracin (for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy), or ophthalmic fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones). o Gram-negative rods: ophthalmic formulations of tobramycin or gentamicin sulfate, ceftazidime, or fluoroquinolones. o Gram-negative cocci: ophthalmic ceftazidime, ceftriaxone sodium, or fluoroquinolones (systemic therapy is necessary for suspected gonococcal infection). o Nontuberculous mycobacteria: ophthalmic amikacin sulfate, azithromycin, clarithromycin, or fluoroquinolones. o Nocardia: ophthalmic amikacin sulfate, sulfacetamide sodium, or trimethoprim/sulfamethoxazole. • Single-drug therapy using an ophthalmic fluoroquinolone has been shown to be as effective as combination therapy with ophthalmic antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics. Ciprofloxacin 0.3%, ofloxacin 0.3% and levofloxacin 1.5% are FDA-approved for this indication. The fourth generation fluoroquinolones have not been approved for the treatment of bacteria keratitis, however, both agents have performed at least as well as standard therapy, fortified cefazolin/tobramycin combination therapy and potentially better than ciprofloxacin. • Some pathogens (e.g., *Streptococci*, anaerobes) reportedly have variable susceptibility to ophthalmic fluoroquinolones and the prevalence of resistance to fluoroquinolones appears to be increasing. • Combination fortified-antibiotic therapy is an alternative to consider for severe infection and for eyes unresponsive to initial treatment. • Treatment with more than one agent may be necessary for nontuberculous mycobacteria; infection with this pathogen has been reported in association with Laser in Situ Keratomileusis. • MRSA has been isolated with increasing frequency from patients with bacterial keratitis and has been reported following kerato-refractive surgery. Ophthalmic fluoroquinolones are generally poorly effective against MRSA ocular isolates. MRSA isolates are generally sensitive to ophthalmic vancomycin. • Systemic antibiotics are rarely needed, but they may be considered in severe cases where the infectious process has extended to adjacent tissues (e.g., the sclera) or when there is impending or frank perforation of the cornea. • Systemic therapy is necessary in cases of gonococcal keratitis. <u>Modification of therapy</u>

Clinical Guideline	Recommendations
	• Efficacy of the regimen is judged primarily by clinical response. The results of cultures and sensitivity testing may have an impact on therapeutic decision making, especially if the patient is not responding to initial therapy. • Dual antibiotic treatment designed to achieve broad-spectrum coverage may become unnecessary once the causative organism has been isolated. • The initial therapeutic regimen should be modified (change in type, concentration or frequency of antibiotic) when the eye shows a lack of improvement or stabilization within 48 hours. • Most antibiotic eye drops should not be tapered below three to four times a day, because low doses are sub-therapeutic and may increase the risk of developing antibiotic resistance. <u>Corticosteroid therapy</u> • Ophthalmic corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis due to the probable suppression of inflammation, which may reduce subsequent corneal scarring and associated visual loss. • Potential disadvantages of ophthalmic corticosteroid use include infection reoccurrence, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting, and increased intraocular pressure. • There is no conclusive evidence that ophthalmic corticosteroids alter clinical outcome. • Despite risks involved, it is believed that sensible use of ophthalmic corticosteroids can reduce morbidity. • Patients being treated with ophthalmic corticosteroids at the time of presentation of suspected bacterial keratitis should have their ophthalmic corticosteroid regimen reduced or eliminated until the infection has been controlled. • Inflammation may temporarily increase as ophthalmic corticosteroids are reduced. • The minimum amount of ophthalmic corticosteroid required should be used to achieve control of inflammation. • Ophthalmic corticosteroids should not be part of initial treatment of presumed bacterial ulcers, and ideally, they should not be used until the organism has been determined by cultures. • The use of ophthalmic corticosteroids in the initial treatment of corneal ulcers has been determined to be a risk factor for requiring a penetrating keratoplasty. • Ophthalmic antibiotics, which are generally administered more frequently than ophthalmic corticosteroids during treatment of active infection, are continued at high levels and tapered gradually. • Patient compliance is essential, intraocular pressure must be monitored frequently, and the patient should be examined within one to two days after initiation of ophthalmic corticosteroid therapy.

Conclusions

Ophthalmic fluoroquinolone are used for the treatment of bacterial conjunctivitis and corneal ulcers. 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.[11] Although effective, quinolones are generally regarded as second-line agents for routine bacterial conjunctivitis because of resistance and cost concerns.[9,11,12] They are the considered the treatment of choice for corneal ulcers and for infections caused by *Pseudomonas* species.[9,13] Currently, ofloxacin, levofloxacin, gatifloxacin and ciprofloxacin hydrochloride (solution) are available generically. All medications are formulated as drops (either solution or suspension) with only ciprofloxacin hydrochloride being formulated as an ointment (Ciloxan®).[3] Although generally considered equally effective, differences in resistance exist, with fewer gram-positive cocci being resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones.[13] Frequency and duration of therapy varies depending on specific agents. Treatment for bacterial conjunctivitis with besifloxacin and moxifloxacin hydrochloride is usually dosed twice or three times daily, while the others are generally prescribed every two to four hours.[1-8] Most ophthalmic quinolones are indicated for use in patients one year of age or older; however, moxifloxacin hydrochloride (Moxeza®) is indicated for use in children four months of age and older and ciprofloxacin hydrochloride ointment is only indicated for use in children two years of age or older.[1-8]

Clinical trials have demonstrated that ophthalmic fluoroquinolones are effective in treating and providing relief of conjunctivitis and corneal ulcers in pediatric and adult patients.[15-40] Several studies comparing ophthalmic fluoroquinolones to either placebo or vehicle have concluded that these medications resulted in significantly higher clinical resolution rates at days one through five. Several studies have also been published comparing the efficacy of ophthalmic fluoroquinolones to other ophthalmic antibiotics and also themselves.[31-39] Head-to-head trials evaluating the efficacy of ophthalmic antibiotics for the treatment of bacterial conjunctivitis have found that no one medication was inferior to another. In patients with a diagnosis of corneal ulcer, ophthalmic ciprofloxacin hydrochloride was shown to be an efficacious treatment options.[31,32]

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