Chapter 9
Anti-infective Therapy for Ocular Infection

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Early antibiotic administration and ability to penetrate the infected site can be critical in preserving vision when treating various types of ocular infections [1]. An understanding of the pharmacokinetics and pharmacodynamics of antibiotics while acknowledging the bactericidal or bacteriostatic properties of these agents aids in prescribing appropriate therapy. A variety of antibiotic agents are currently available to treat ocular infections. Topical antibiotic agents are most commonly used to treat superficial or external ocular infections, whereas infections that are located farther away from the cornea or within the eye require additional methods of administration (i.e., intravitreal injection or parenteral therapy) to achieve therapeutic concentration at the site of infection [2]. Therefore, early identification of the depth of eye involvement and potential causative microorganisms is essential in choosing the most appropriate mode of medication administration and therapeutic option. This chapter provides the enumeration of relevant antibiotics by class, antimicrobial activity, antibiotic mechanism of action, mode of application, and antibiotic toxicity.

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Overview of Antibiotics: Mechanisms of Action, Spectrum of Activity

Topical Antibiotics

Topical antibiotic agents can provide direct delivery of antibiotic in high concentration at the site of infection when treating bacterial conjunctivitis, keratitis, or uncomplicated blepharitis [1, 3]. Ophthalmic antibiotic solutions are preferred in adults as they do not interfere with vision, although more frequent administration is required due to short contact time with the eye. Antibiotic ointments have prolonged contact time and will be more resistant to medication loss through dilution by tears [4]. Often, ointments are recommended in children or adults who do not have concerns for visual interference.

The most extensively developed topical antibiotic class with a broad spectrum of activity is the fluoroquinolones (Table 9.1) [5–12]. Fluoroquinolones (besifloxacin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and ofloxacin) cause rapid bacterial cell death due to inhibition of bacterial DNA synthesis. These agents limit the activity of two key topoisomerase classes of enzymes that play an important role in bacterial DNA replication. DNA gyrase introduces negative supercoils into DNA within the bacterial cell, and topoisomerase IV divides the chromosomal DNA during bacterial cell division [13]. Antibacterial activities of fluoroquinolones vary between the generations. Although the initial generations such as ofloxacin and ciprofloxacin have limited gram-positive activity, especially against streptococci, ciprofloxacin still shows the best activity against *Pseudomonas aeruginosa* [13]. New generations such as levofloxacin, gatifloxacin, moxifloxacin, and besifloxacin have a broader spectrum of activity including methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), and *Streptococcus* species [13]. In a recent surveillance study that reviewed ocular microorganisms and antibiotic activity, ciprofloxacin was the least potent agent against staphylococcal isolates with 80 % resistance to MRSA, whereas besifloxacin was the most potent agent in the class followed by moxifloxacin [14]. All fluoroquinolones have great atypical coverage such as *Chlamydia trachomatis*; however moxifloxacin is the only fluoroquinolone that has additional anaerobic coverage [13].

Macrolides (azithromycin, erythromycin) are generally thought to inhibit RNA-dependent protein synthesis at the chain elongation step; however the ability to bind to the 50S ribosomal subunit differs between azithromycin and erythromycin which results in varying antibacterial activities [15–17]. When compared to erythromycin, azithromycin may have better penetrating ability to the outer envelope of gram-negative organisms such as *Moraxella catarrhalis* and *Haemophilus influenzae*. Also, *C. trachomatis* coverage is much better with azithromycin compared to erythromycin [18]. With regard to gram-negative and atypical coverage, macrolides have great activity against *Neisseria gonorrhoeae* and *M. catarrhalis*. Macrolides also have activity against actinomycetes and mycobacteria which have been identified as causative pathogens in canaliculitis and keratitis [3].

Table 9.1 Topical antibiotic agents of ocular infections

Drug (brand name)	FDA-approved indication(s)	Dosage
Aminoglycosides		
Gentamicin 0.3 % solution	Conjunctivitis Keratitis Keratoconjunctivitis Corneal ulcers Blepharitis Blepharoconjunctivitis Acute meibomianitis Dacryocystitis	1–2 drops every 4 h
Gentamicin 0.3 % ointment (Gentak®)		½ inch ribbon 2–3×/day
Tobramycin 0.3 % solution (Tobrex®)	Superficial ocular infection (conjunctivitis, keratitis)	1–2 drops every 4 h; 2 drops hourly (severe cases)
Tobramycin 0.3 % ointment (Tobrex®)	Treatment of external infections of the eye and its adnexa	½ inch ribbon every 3–4 h up to 2–3×/day (dosing based on severity of infection)
Fluoroquinolones		
Besifloxacin 0.6 % suspension (Besivance®)	Bacterial conjunctivitis	1 drop 3×/day 4–12 h apart for 7 days
Ciprofloxacin 0.3 % solution (Ciloxan®)	Bacterial conjunctivitis	1–2 drops every 2 h while awake for 2 days then 1–2 drops every 4 h while awake for 5 days
	Corneal ulcers	Day 1: 2 drops every 15 min for 6 h, then every 30 min Day 2: 2 drops every hour Day 3–14: 2 drops every 4 h
Ciprofloxacin 0.3 % ointment (Ciloxan®)	Bacterial conjunctivitis	½ inch 3×/day for 2 days then ½ inch 2×/day for 5 days
Gatifloxacin 0.3 % solution (Zymaxid®)	Bacterial conjunctivitis	1 drop every 2 h (up to 8 times) while awake for 2 days then 1 drop up to 4×/day while awake for 5 days
Levofloxacin 0.5 % solution (Quixin®)	Bacterial conjunctivitis	1–2 drops every 2 h (up to 8 times) while awake for 2 days Day 3–7: 1–2 drops every 4 h while awake up to 4×/day
Levofloxacin 1.5 % solution (Iquix®)	Corneal ulcers	Day 1–3: 1–2 drops every 30 min to 2 h while awake and every 4–6 h after retiring Days 4 through treatment completion: 1–2 drops every 1–4 h while awake
Moxifloxacin 0.5 % solution (Vigamox®)	Bacterial conjunctivitis	1 drop 3×/day for 7 days

(continued)

Table 9.1 (continued)

Drug (brand name)	FDA-approved indication(s)	Dosage
Ofloxacin 0.3 % solution (Ocuflox®)	Bacterial conjunctivitis	1–2 drops every 2–4 h for 2 days then 1–2 drops 4×/day for 5 days
	Corneal ulcers	Days 1–2: 1–2 drops every 30 min while awake. Awaken at ~4–6 h after retiring and instill 1–2 drops Days 3–7: 1–2 drops hourly, while awake Days 7 through treatment completion: 1–2 drops 4×/day
Macrolides		
Azithromycin 1 % solution (Azasite™)	Bacterial conjunctivitis	1 drop in the affected eye(s) 2×/day for the first 2 days then 1 drop daily for the next 5 days
Erythromycin 0.5 % ointment (Romycin®)	Superficial ocular infection involving the conjunctiva or cornea	½ inch to affected eye (s) every 4–6 h
Others		
Bacitracin	Superficial ocular infection involving the conjunctiva or cornea	½ inch every 3–4 h for 7–10 days
Sulfacetamide 10 % ointment	Conjunctivitis Superficial ocular infections	½ inch 4×/day and bedtime for 7–10 days
Sulfacetamide solution (Bleph®-10)	Bacterial conjunctivitis Superficial ocular infections Adjunctive therapy with systemic sulfonamide therapy for trachoma	1–2 drops every 1–3 h while awake, less frequently at night for 7–10 days
Combination therapy		
Bacitracin/polymyxin B ointment	Bacterial conjunctivitis Keratitis Keratoconjunctivitis Blepharitis Blepharoconjunctivitis	Thin film every 3–4 h for 7–10 days
Gramicidin/neomycin/ polymyxin B (Neosporin®)		Up to 2 drops every hour then 1–2 drops every 4 h for 7–10 days
Trimethoprim/polymyxin B (Polytrim®)	Bacterial conjunctivitis Blepharoconjunctivitis Superficial ocular infection	1 drop every 3 h up to 6 doses daily for 7–10 days

Macrolides have been highly potent against *S. pneumoniae* and group A streptococcus isolates; however, the prevalence of erythromycin resistance to *S. pneumoniae* is continuously increasing in the United States and worldwide [19–21]. Although group A streptococcus resistance to erythromycin has been reported, the prevalence of resistance is not as high as is seen with *S. pneumoniae* [22, 23]. Erythromycin has activity against viridans group streptococcus; however, Europe and Asia have higher resistance rates than those that occurred in North America

[24]. MRSA is generally resistant to erythromycin; therefore, the use of erythromycin should be based on the local antibiogram or culture result [15].

Aminoglycosides such as gentamicin and tobramycin have limited activity against gram-positive organisms and anaerobic bacteria [25–27]. These agents work by binding to the 30S ribosomal subunit to inhibit protein synthesis and require aerobic metabolism to cause antibacterial effect [28]. In general, aminoglycosides have great activity against gram-negative bacilli such as *Enterobacteriaceae*, *P. aeruginosa*, and *Acinetobacte*r spp.; however, no activity has been shown for *Stenotrophomonas maltophilia* or *Burkholderia cepacia*.

Combination topical antibiotics are typically paired with narrow spectrum antibiotics to expand the overall spectrum of activity. Polymyxin B is a polypeptide with high molecular weight and works by penetrating the cell membrane of bacteria and interacting with phospholipids [29, 30]. The main antibacterial activity of polymyxin B is *P. aeruginosa*, *Acinetobacter baumannii*, and carbapenem-resistant *Enterobacteriaceae* (CRE). Most gram-positive organisms are resistant to polymyxin B; thus it is commonly paired with another antibiotic with good gram-positive coverage such as bacitracin or trimethoprim. Bacitracin inhibits cell wall synthesis by preventing transfer of mucopeptides into the growing cell wall [31]. As a combination agent, bacitracin zinc/polymyxin B sulfate has activity against *S. aureus*, *S. pneumoniae*, *Escherichia coli*, *H. influenzae*, *Klebsiella/Enterobacter* species, *Neisseri*a species, and *P. aeruginosa* [32]. Trimethoprim is a synthetic antibacterial agent that blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. It has good activity against gram-positive and gram-negative organisms such as *S. aureus*, *S. epidermidis*, *S. pyogenes*, *S. pneumoniae*, *H. influenzae*, *E. coli*, *Proteus vulgaris*, *E. aerogenes*, and *Serratia marcescens* [33, 34].

Sulfonamides have bacteriostatic properties and inhibit bacterial growth by interfering with folic acid synthesis [35]. The sulfonamides show antibacterial activity against *S. aureus*, *S. pneumoniae*, viridans group streptococcus, *E. coli*, *H. influenzae*, *Klebsiella* species, and *Enterobacter* species. These agents should not be used empirically for *Neisseria* species, *S. marcescens*, *P. aeruginosa*, or resistant *Staphylococcus* species [36].

Topical Antifungal/Antiviral

Natamycin eyedrops (5 % suspension) is the only antifungal agent that is commercially available. Natamycin is a tetraene polyene agent that works by binding to the sterol of the fungal cell membrane, which causes membrane permeability changes [37]. It is used for the treatment of fungal keratitis caused by *Candida* species, *Aspergillus*, *Cephalosporium*, *Fusarium*, and *Penicillium*; however, poor corneal tissue penetration limits its use in intraocular infections [3, 37]. Amphotericin B, nystatin, fluconazole, miconazole, and flucytosine eyedrops have been compounded

for use [3, 38], but extemporaneous preparations of these products are not widely used. Furthermore, topical amphotericin B made with a deoxycholate formulation is known to be toxic to the cornea [39].

Commercially available topical antiviral agents are more common than antifungal agents. Trifluridine ophthalmic suspension is used for the treatment of herpes simplex keratitis and keratoconjunctivitis [3]. It inhibits viral DNA synthesis and has activity against herpes simplex virus (HSV) types 1 and 2, cytomegalovirus (CMV), and adenoviruses [40]. Vidarabine ointment is also available for the treatment of HSV keratitis. It has activity against idoxuridine-resistant and acyclovir-resistant HSV; however, it is more toxic and less effective compared to trifluridine for the treatment of HSV keratoconjunctivitis [3, 40]. Idoxuridine is approved for the treatment of HSV keratitis. Its mechanism of action is not completely understood, and it is also inferior to trifluridine and acyclovir for the treatment of HSV epithelial keratitis [40]. Topical 0.15 % ganciclovir ophthalmic gel is indicated for the treatment of acute herpetic keratitis [41]. Finally, topical acyclovir is not available in the United States [3].

Intravitreal/Subconjunctival Injection

Table 9.2 shows a list of commonly used antibiotic agents for intravitreal/subconjunctival injection. These agents are used since topical antibiotics are ineffective in treating endophthalmitis due to their inability to penetrate the intraocular site [42]. Antifungal agents such as voriconazole and conventional amphotericin B are often used for intravitreal infection, which result in rapid achievement of high concentration in the posterior chamber [43, 44].

Systemic Therapy

The data for intraocular penetration of antibiotic therapy delivered via parenteral routes is limited. There are a few antibiotic classes that are used as adjunctive therapy when treating endophthalmitis or when the use of systemic antibiotics is the

Table 9.2 Commonly used anti-infective agents for intravitreal injection

Anti-infective agents	Dose	Concentration
Amphotericin B	5–10 mcg/0.1 mL	50–100 mg/mL
Ampicillin	4 mg	50 mg/mL
Amikacin	0.2–0.1 mg	4 mg/mL
Ceftazidime	2–2.25 mg	22.5 mg/mL
Gentamicin	0.1–0.2 mg	1 mg/mL
Tobramycin	0.1–0.2 mg	1 mg/mL
Vancomycin	1 mg	10 mg/mL
Voriconazole	100 mcg/0.1 mL	1 mg/mL

Data are from Lopez-Carbezas et al. [42] and Pappas et al. [44]

Table 9.3 Pathogens and systemic treatment for ocular infections

Pathogens	Antimicrobial treatment (s)
Gram-positive Methicillin-susceptible *S. epidermidis* (MSSE) *S. aureus* (MSSA)	Nafcillin, cefazolin, vancomycin[a], linezolid[a]
Methicillin-resistant *S. epidermidis* (MRSE) *S. aureus* (MRSA)	Vancomycin, linezolid
Streptococci	Ampicillin/sulbactam, ceftriaxone, vancomycin[a]
Enterococci *E. faecalis. E. faecium*	Ampicillin (if ampicillin susceptible) Linezolid (if resistant to ampicillin and vancomycin)
Bacillus cereus	Carbapenem vancomycin
Propionibacterium acnes	Vancomycin, linezolid
Gram-negative *Enterobacteriaceae* *E. coli* *Klebsiella* spp. *Proteus* spp. *H. influenzae* *Moraxella* spp. *Pseudomonas aeruginosa*[b]	Ceftriaxone, ceftazidime[b], cefepime[b], ampicillin/sulbactam, piperacillin/tazobactam[b], meropenem[b], moxifloxacin, levofloxacin[b], ciprofloxacin[b]

[a]For patients with penicillin and/or cephalosporin allergies
[b]Antibiotics with pseudomonas activity

best treatment option (i.e., orbital cellulitis, preseptal cellulitis) [42, 45]. All B-lactams inhibit bacterial cell wall synthesis by inhibiting high-molecular-weight penicillin-binding proteins (PBPs) [46]. Vancomycin is a tricyclic glycopeptide that works by binding to the D-alanyl-D-alanine part of a cell wall precursor and thus inhibiting the late stages of bacterial cell wall synthesis [47]. Linezolid is one of the oxazolidinones that works by inhibiting protein synthesis. It binds to the 50S ribosome within the 30S unit to prevent 70S complex formation [48]. B-lactam antibiotics (penicillins, cephalosporins, and carbapenems), vancomycin, and linezolid may be added to cover gram-positive and gram-negative organisms depending on the culture result (Table 9.3).

Invasive ocular infections caused by fungi are rare but associated with poor response rate; thus the treatment consists of systemic antifungal agents in combination with surgery, intravitreal injections, or both. Amphotericin B has been most studied and experienced in treating intraocular fungal infection to date [43]. It is a fungicidal agent that works by binding to ergosterol in the cell membrane of susceptible fungi and changes membrane permeability, which results in the leakage of intracellular potassium and other molecules and cell death [49]. Currently there are four different amphotericin B formulations: amphotericin B deoxycholate, amphotericin B colloidal dispersion, amphotericin B lipid complex, and liposomal amphotericin B. It is a broad-spectrum antifungal agent that has activity against most *Candida* species except for *C. lusitaniae*; dimorphic fungi such as *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*; and filamentous

fungi such as *Aspergillus* spp. and the *Mucorales* group [50]. Spectrum of activity is not influenced by different amphotericin B products.

Flucytosine is often used with amphotericin B as it is synergistic against *Candida* spp. and *Cryptococcus neoformans*. It is a fluorinated pyrimidine that works by disrupting RNA and DNA synthesis [43]. Flucytosine lacks activity against the dimorphic fungi and filamentous fungi, and it should not be used as monotherapy due to rapid development of resistance for the treatment of candidiasis [49].

Azoles are ergosterol synthesis inhibitors, and each azole has slight variation in its spectrum of activities. Fluconazole is mainly active against *Candida* species, *C. neoformans*, and dimorphic fungi such as *C. immitis*, *H. capsulatum*, and *B. dermatitidis*. Although most *Candida albicans* are susceptible to fluconazole, fluconazole-resistant *C. albicans* has been reported. Resistance in other *Candida* species such as *Candida glabrata* has been noted [43]. Fluconazole is not active against *Candida krusei*, *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., and *Mucorales* [50]. Itraconazole is active against some *Candida* species, dimorphic fungi, and *Aspergillus* species; however, it does not penetrate the ocular structure well [49]. Similarly, posaconazole has poor ocular penetration. It has a broad-spectrum coverage including *Candida* species, *C. neoformans*, *Aspergillus* species, *Fusarium* species, and *Zygomycetes* [49, 51]. Voriconazole is a broad-spectrum azole that is the drug of choice for treatment of invasive aspergillosis. It also has activity against *Candida* species, *C. neoformans*, *Scedosporium* species, and *Curvularia* species [49, 51]. Unlike posaconazole and itraconazole, voriconazole penetrates the eye and can adjust the dose based on the trough goal level of 2–5 mg/L [52, 53]. The newest addition to the class of azole is isavuconazonium sulfate. It is a prodrug of isavuconazole with broad spectrum of activity including most *Candida* species, dimorphic fungi, *C. neoformans*, *Aspergillus* species, and *Mucorales* [54]. To date, no data are available regarding ocular penetration of this new agent.

Echinocandins work by inhibiting the synthesis of 1, 3-β-D-glucan, which is the predominant component of the fungal cell wall. Currently there are three echinocandins on the market: caspofungin, micafungin, and anidulafungin. In general, echinocandins are active against *Candida* species and *Aspergillus* species, but lack activity for *Fusarium*, *Scedosporium*, and *Zygomycetes* [49, 51]. Furthermore, echinocandins do not penetrate the ocular structure; therefore, it is not widely used to treat invasive ocular infections.

Viral conjunctivitis can be caused by HSV and adenovirus [55]. Although no effective treatment is available for viral conjunctivitis caused by adenovirus, oral antivirals are used to shorten the course of HSV conjunctivitis [55]. Acyclovir and valacyclovir work by blocking viral DNA synthesis and are much more potent against HSV type 1 and 2 compared to cytomegalovirus [40]. Ganciclovir and valganciclovir are potent against CMV and have better activity against herpes B virus compared to acyclovir [40].

Table 9.4 Factors to improve corneal absorption

Nonionic surfactants
Polymers
Viscous preparations
Solvents
Improving drug stability

Data are from McCloskey [2]

Mode of Administration and Pharmacokinetics

Delivering a therapeutic concentration of antibiotic at the site of infection is a challenge. Important factors that could influence the intraocular penetration of antibiotics are the charge of the drug, corneal epithelium status, drug formulation, drug concentration, and the dosage regimen [1]. Natural barriers such as eyelids, iris, tears, and cornea prevent diffusion of antibiotics into intraocular tissue. In order to promote corneal absorption, certain formulation factors should be considered (Table 9.4) [2]. Furthermore, the corneal area can only contain about 30 μl; therefore, topical solutions are given more frequently to ensure adequate absorption of medication [2]. Ophthalmic medications that have both lipid- and water-soluble properties will help enhance overall drug absorption [4]. Due to these challenges of the topical application method, infections involving vitreous humor, sclera, or cornea may require additional strategies to administer drug therapy.

Unlike topical antibiotic application, subconjunctival injection can reach high antibiotic concentration in sclera and cornea. This mode of administration is used to treat intraocular infection as it gains access to the episcleral and conjunctival vessels [4]. However, subconjunctival injection does not provide adequate antibiotic penetration into the vitreous humor [42].

Intravitreal injection of air has been practiced by ophthalmologists to repair retinal detachments since 1911 [56]. Intravitreal injection is used to treat endophthalmitis, cytomegalovirus (CMV) retinitis, and more. This method provides direct exposure of antibiotic to the infected site for a prolonged period with minimal systemic absorption [57]. Thus, bypassing the blood-retinal barrier ensures immediate high concentration of antibiotic in the vitreous cavity [42].

Systemic antibiotic therapy is used as an adjunctive strategy to intravitreal injection, subconjunctival injection, and/or topical administration. This mode of administration is added when treating ocular infections that involve the posterior segment of the eye or the orbit (i.e., endophthalmitis, orbital cellulitis, or chorioretinitis), where topical antibiotics will provide negligible drug penetration [4]. Limited data concerning systemic antibiotics and ocular penetration are available; however, linezolid and fluoroquinolones such as levofloxacin and moxifloxacin have been shown to achieve good ocular penetration [42].

Antibiotic Toxicity

Antibiotics can cause serious side effects if not used appropriately. Topical antibiotics are concentrated locally; therefore, systemic side effects should not occur. However, topical antibiotic formulations can cause some serious tissue side effects. Tissue side effects could be due to the antibiotic or the preservatives and vehicles used in the formulation [1]. Topical chloramphenicol is no longer used, but this drug had been known to cause idiosyncratic bone marrow suppression, aplastic anemia, and death [1, 4]. Topical neomycin is in multiple combination products such as Polytrim® and Neosporin®. Neomycin has been associated with punctate staining of the cornea [1]; therefore, patients should be informed about this undesirable side effect. Fluoroquinolones are one of the commonly used topical antibiotics, yet these agents also have side effects. One study found that moxifloxacin had the least cytotoxic effects against corneal and/or conjunctival epithelial cells compared to other fluoroquinolones, while all caused thinning of the corneal epithelial layer after 7 days of treatment [58]; however, other studies have not shown the same effects [59, 60]. The conflicting data on moxifloxacin was explained by the absence of preservatives such as 0.005 % or 0.006 % benzalkonium chloride, whereas other fluoroquinolones have preservatives which have been associated with tissue toxicity [61].

The preservatives or vehicles in the ophthalmic formulation can cause additive side effects such as hypersensitivity reaction or reduction in antimicrobial activity, which are mainly known from experience with thimerosal (a common preservative in contact lens solution) [1, 4]. As previously mentioned, benzalkonium chloride may inhibit epithelial adhesion, cause a loss of superficial epithelial cells, and delay healing of the epithelium [1].

Antibiotic toxicity could also occur due to the mode of administration. Retinal toxicity has been reported from intravitreal injection as well as subconjunctival injection of aminoglycosides. These modes of antibiotic administration will reach high concentration in the intraocular site; however, it increases the exposure of high drug concentration near the retina which could cause chemical damage. Multiple case series have shown that retinal toxicity and macular ischemia can occur with intravitreal injection of aminoglycosides such as amikacin or gentamicin [62, 63]. When using intravitreal injection, these medications should be administered close to the anterior part of the vitreous cavity to help avoid retinal side effects [42]. Another mode of administration is intracameral antibiotic injection which can be done after cataract surgery to prevent postoperative bacterial endophthalmitis [64]. This is often completed with cefuroxime, and multiple cases have been reported with retinal toxicity and hemorrhagic retinal infarction [65, 66].

Parenteral antibiotics are known to have numerous adverse side effects. Penicillin derivatives are most commonly associated with hypersensitivity reactions that range from minor drug rash to life-threatening reactions such as Stevens-Johnson syndrome or anaphylaxis [4, 46]. Patients may also develop serum sickness with fever, urticaria, joint pains, and angioneurotic edema; however, this syndrome is very rare.

Penicillin and penicillin derivatives can also cause renal toxicity such as allergic angiitis or interstitial nephritis. Antistaphylococcal penicillins (i.e., methicillin or nafcillin) have been highly associated with interstitial nephritis which presents with fever, macular rash, eosinophilia, proteinuria, eosinophiluria, and hematuria [46]. Penicillin and penicillin derivatives can lower the seizure threshold; however, this effect is more common with large doses and in patient with renal dysfunction. When prescribing penicillin derivatives to treat ocular infections, it is important to obtain the patient's allergy history to ensure that these antibiotics are appropriate for the specific patient.

Cephalosporins have adverse reactions that are similar to those encountered with penicillin and penicillin derivatives, but these medications are generally well tolerated. Hypersensitivity reactions can occur, although not as commonly as with the penicillins [67]. Adverse reactions between the different generations of cephalosporins include gastrointestinal, hematologic, and central nervous system effects that are mostly similar. However, the third-generation cephalosporin, ceftriaxone, has been specifically associated with obstructive biliary toxicity [68, 69]. This syndrome is reversible after antibiotic cessation [67], but the ophthalmologist should consider an alternative therapy in patients with known hepatic diseases and neonates younger than 28 days. Elevation of serum creatinine has been reported; however, renal toxicity is not as common as is seen with the penicillins [70]. Although cephalosporins may not play a significant role in renal toxicity, cefepime should be used with caution as encephalopathy and seizures have been reported in patients with renal insufficiency [71–73].

Carbapenems do not have major adverse effects and are generally well tolerated. The most serious side effect that requires monitoring is seizure activity, as all carbapenems possess a structural similarity to γ-aminobutyric acid (GABA) and can have an antagonistic effect on the action of this neurotransmitter [74]. Cross-reactivity with the penicillins has been documented as between 0 and 11 %; however, carbapenem use is considered safe if the penicillin skin test is negative [75].

Fluoroquinolones can cause severe adverse effects that need close monitoring. Although not generally severe or serious, gastrointestinal-related symptoms are the most common side effects. Similar to carbapenems, adverse events involving the central nervous system such as headache, dizziness, insomnia, and seizures can manifest with fluoroquinolone [13]. Cardiovascular effects, especially QT interval prolongation, are well known with the older quinolones; the newer generations also possess these side effects but with a lesser intensity [76–78]. Although tendinitis and joint toxicity have been reported with fluoroquinolones, these side effects are not as common. One adverse event of concern in ophthalmology patients is the potential for retinal detachment with fluoroquinolones. Due to their ability to achieve high concentration in the ocular tissue and cause collagen and connective tissue damage, the patients in one study who were prescribed fluoroquinolones carried a 4.5-fold increased risk for retinal detachment [79]. Another study has shown a similar result when fluoroquinolones were compared to amoxicillin [80]; however, a third study did not show the same effect [81]. Ophthalmologists should use cau-

tion when prescribing oral fluoroquinolones, especially in patients with high risk for retinal detachment.

As resistance has been increasing, more broad-spectrum antibiotics such as vancomycin and linezolid have been used to treat intraocular infection with methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin has been used for the past 50 years, and its adverse effects have been studied extensively. The most common side effect of vancomycin is related to medication infusion rate, also known as red man syndrome. This can be minimized with reduction of infusion rate or premedication with antihistamines. Numerous studies have been done to find the risk factors for vancomycin-associated nephrotoxicity. Such risk factors are large total daily dose (≥4 g/day), obesity (weight ≥ 101.4 kg) [82], higher vancomycin trough levels (≥15 μg/mL), concomitant use of nephrotoxic medications, and prolonged duration of therapy [83, 84]. Other adverse events such as drug rash, drug-related fever, thrombocytopenia, and neutropenia can occur, but these effects are not as common [47].

Thrombocytopenia with linezolid has been well documented in the literature. The decrease in platelet count occurs with longer duration of therapy, at least 2 weeks; however, it can occur earlier and thus requires close monitoring [85]. Another serious side effect associated with linezolid is a potential drug interaction with serotonergic agents and serotonin syndrome with fever, agitation, mental status changes, and tremor [85]. Therefore, caution should be practiced when prescribing linezolid to a patient who is already taking other serotonergic agents. Although not as common, peripheral neuropathy and optic neuropathy can occur when taking linezolid [86]. Optic neuropathy is another consequence of its enhanced ability to penetrate the eye which can cause vision loss [48]. Therefore, patients who are taking linezolid for a prolonged duration should follow up with an ophthalmologist for early detection of any vision changes to prevent visual loss.

One of the serious side effects associated with amphotericin B is nephrotoxicity. It damages renal tubular cells, which disrupts tubular basement membrane and causes functioning nephron loss [49]. It also leads to electrolyte wasting, especially of potassium, magnesium, and bicarbonate [49]. This is associated with all four formulations; however, amphotericin B deoxycholate is associated with acute infusion-related reactions such as chills, fever, and tachycardia. Nausea, vomiting, and liver enzyme elevations have been associated with amphotericin B. Similarly, flucytosine should be used with caution in patients with renal dysfunction. It can cause fatal bone marrow toxicity such as leukopenia and thrombocytopenia [49]. Therapeutic drug monitoring is recommended for flucytosine twice weekly. It is also teratogenic, therefore, contraindicated in pregnancy. Azoles are generally well tolerated with minimal side effects such as gastrointestinal and hepatic toxicity. Voriconazole has been known to cause visual disturbances, hallucination, and confusion [49]. For patients who are intolerant to voriconazole due to visual disturbances, the newest azole, isavuconazonium sulfate, could be an alternative option if broad-spectrum coverage is necessary. Echinocandins infrequently cause adverse reactions. Occasionally histamine-mediated symptoms such as rash, pruritus, dyspnea, and hypotension may occur, but echinocandins are not hepatotoxic or nephrotoxic [49].

Intravenous acyclovir can cause reversible renal dysfunction and neurotoxicity. Clinical manifestations such as lethargy, confusion, hallucinations, seizures, or coma could occur, and patients can experience neurotoxicity within 1–3 days of treatment [40]. This is more common with valacyclovir. Oral acyclovir is generally well tolerated but could cause diarrhea, rash, and headache. Ganciclovir and valganciclovir cause myelosuppression and CNS toxicity. The most common reasons for early discontinuation of these agents are severe neutropenia and thrombocytopenia [40].

Summary

Ocular infections can be treated with topical antibiotic agents, subconjunctival or intravitreal antibiotic injections, or systemic antibiotics depending on the type of infection and the depth of intraocular eye involvement. Each mode of administration has advantages and disadvantages with regard to delivery of an appropriate drug concentration at the site of infection and the potential for antibiotic toxicity. Choosing the right therapy with appropriate bacterial, fungal, and/or viral coverage, mode of administration, and pharmacologic activity is critical when treating ocular infections.

References

1. Snyder RW, Glasser DB. Antibiotic therapy for ocular infection. West J Med. 1994;161:579–84.
2. McCloskey R. Topical antimicrobial agents and antibiotics for the eye. Med Clin North Am. 1988;72:717–22.
3. Baum J. Infections of the eye. Clin Infect Dis. 1995;21:479–86.
4. Stein HA, Stein RM, Freeman MI. Pharmacology. In: The ophthalmic assistant. A text for allied and associated ophthalmic personnel. 9th ed. Philadelphia: Saunders; 2012. p. 49–66.
5. Besivance®. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a3e6d688-7e5e-4ca3-b27e-79756c322a32&audience=consumer. Accessed 30 Aug 2015.
6. Ciloxan® ointment. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1c292706-a900-4d6f-979e-9c42d6ff2fb2&audience=consumer. Accessed 30 Aug 2015.
7. Ciloxan® solution. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=614af481-f9ef-44ac-9cb8-f421660d9cdd&audience=consumer. Accessed 30 Aug 2015.
8. Gatifloxacin. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1160b16c-929a-4e85-9c0b-1d8c96a7678b&audience=consumer. Accessed 30 Aug 2015.
9. Quixin®. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=09b3a912-97f9-45ae-a162-9f45c860dc22&audience=consumer. Accessed 30 Aug 2015.
10. Iquix®. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=067ea8ec-99a3-4a0b-9116-4ffd6160b24b&audience=consumer. Accessed 30 Aug 2015.

11. Vigamox®. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0e6ab6ba-5eeb-4faf-ba80-4bf21a74228a&audience=consumer. Accessed 30 Aug 2015.
12. Ocuflox®. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7aab4449-3dda-4e2c-8e40-b3244a548bf5&audience=consumer. Accessed 30 Aug 2015.
13. Hooper D, Strahilevitz J. Quinolones. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 419–39.
14. Hass W, Pillar CM, Torres M, Morris TW, Sahm DF. Monitoring antibiotic resistance in ocular microorganisms: results from the Antibiotic Resistance Monitoring in Ocular micRorganisms (ARMOR) 2009 surveillance study. Am J Ophthalmol. 2011;152:567–74.e3. doi:10.1016/j.ajo.2011.03.010. Epub 2011 Jun 8.
15. Sivapalasingam S, Steigbigel NH. Macrolides, clindamycin, and ketolides. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 358–76.e6.
16. Azasite™. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5dc0f75a-1e14-469f-af4f-c668a32f2328&audience=consumer. Accessed 30 Aug 2015.
17. Erythromycin ointment. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f4b57b8a-089e-4bbc-bcc7-3a9b9b600930&audience=consumer. Accessed 30 Aug 2015.
18. Neu HC. Clinical microbiology of azithromycin. Am J Med. 1991;91:12S–8.
19. Thornsberry C, Sahm DF, Kelly LJ, Critchley IA, Jones ME, Evangelista AT, et al. Regional trends in antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States: results from the TRUST Surveillance Program, 1999–2000. Clin Infect Dis. 2002;34 Suppl 1:S4–16.
20. Hsueh PR, Liu CY, Luh KT. Current status of antimicrobial resistance in Taiwan. Emerg Infect Dis. 2002;8:132–7.
21. Farrell DJ, File TM, Jenkins SG. Prevalence and antibacterial susceptibility of mef(A)-positive macrolide-resistant *Streptococcus pneumoniae* over 4 years (2000–2004) of the PROTEKT US Study. J Clin Microbiol. 2007;45:290–3.
22. Green MD, Beall B, Marcon MJ, Allen CH, Bradley JS, Dashefsky B, et al. Multicentre surveillance of the prevalence and molecular epidemiology of macrolide resistance among pharyngeal isolates of group A streptococci in the USA. J Antimicrob Chemother. 2006;57:1240–3.
23. Villaseñor-Sierra A, Katahira E, Jaramillo-Valdivia AN, de los Angeles Barajas-Garćia M, Bryant A, Morfin-Otero R, et al. Phenotypes and genotypes of erythromycin-resistant *Streptococcus pyogenes* strains isolated from invasive and non-invasive infections from Mexico and the USA during 1999–2010. Int J Infect Dis. 2012;16:e178–81.
24. Gordon KA, Beach ML, Biedenbach DJ, Jones RN, Rhomberg PR, Mutnick AH. Antimicrobial susceptibility patterns of beta-hemolytic and viridans group streptococci: report from the SENTRY Antimicrobial Surveillance Program (1997–2000). Diagn Microbiol Infect Dis. 2002;43:157–62.
25. Gentak®. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=561cf436-74b8-452c-9fd2-e42f859c87dd&audience=consumer. Accessed 30 Aug 2015.
26. Tobrex®. DailyMed, Bethesda.2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cdd423c5-a231-47d4-bf51-00b5c29e6a60&audience=consumer. Accessed 30 Aug 2015.
27. Egger SF, Ruckhofer J, Alzner E, Hell W, Hitzl W, Huber-Spitzy V, et al. In vitro susceptibilities to topical antibiotics of bacteria isolated from the surface of clinically symptomatic eyes. Ophthalmic Res. 2001;33:117–20.
28. Leggett JE. Aminoglycosides. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 310–21.e7.

29. Robert PY, Adenis JP. Comparative review of topical ophthalmic antibacterial preparations. Drugs. 2001;61:175–85.
30. Kaye KS, Pogue JM, Kaye D. Polymyxins (polymyxin B and colistin). In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 401–405.e1.
31. Bacitracin. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6ed2f2bd-9d2f-46af-a44c-95a02ca034de&audience=consumer. Accessed 30 Aug 2015.
32. Polycin®. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3abbfb58-26d1-460d-a60f-db63c0193a0d. Accessed 29 Aug 2015.
33. Polytrim®. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5ce95658-d2eb-4d35-b387-ded0d7e4a122. Accessed 29 Aug 2015.
34. Neosporin®. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=33e9b6d3-2b2b-4036-dd89-47177e23fcfe. Accessed 30 Aug 2015.
35. Zinner S, Myer KH. Sulfonamides and trimethoprim. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 410–8.e2.
36. Bleph®-10. DailyMed, Bethesda. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=27c8bd30-89ec-464c-b7ac-ca2dbe27e861. Accessed 29 Aug 2015.
37. Natamycin®. DailyMed, Bethesda. 2013. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d262661c-860d-482e-aa8d-3cf1f252b32a. Accessed 13 Mar 2016.
38. Behrens-Baumann W. Topical antimycotics in ophthalmology. Ophthalmolgica. 1997;211 Suppl 1:33–8.
39. Klotz SA, Penn CC, Negvesky GJ, Butrus SI. Fungal and parasitic infections of the eye. Clin Microbiol Rev. 2000;13:662–85.
40. Aoki FY. Antivirals against herpes viruses. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 546–62.e7.
41. Zirgan (ganciclovir ophthalmic gel 0.15%) [prescribing information]. Tampa: Bausch & Lomb Inc; 2014.
44. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016. doi:10.1093/cid/civ933.
42. Lopez-Carbezas C, Muner DS, Massa MR, Mensa Puevo JM. Antibiotics in endophthalmitis: microbiological and pharmacokinetic considerations. Curr Clin Pharmacol. 2010;5:47–54.
43. Riddell 4th J, Comer GM, Kauffman CA. Treatment of endogenous fungal endophthalmitis: focus on new antifungal agents. Clin Infect Dis. 2011;52:648–53.
45. Thielen TL, Castle SS, Terry JE. Anterior ocular infections: an overview of pathophysiology and treatment. Ann Pharmacother. 2000;34:235–46.
46. Doi Y, Chambers HF. Penicillins and beta lactamase inhibitors. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 263–77.e3.
47. Murray BE, Arias CA, Nannini EC. Glycopeptides (vancomycin and teicoplanin), streptogramins (quinupristin-dalfopristin), lipopeptides (daptomycin), and lipoglycopeptides (telavancin). In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 377–400.e4.
48. Cox HL, Donowitz GR. Linezolid and other oxazolidinones. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 406–9.e2.
49. Rex JH, Stevens DA. Drugs active against fungi, pneumocystis, and microsporidia. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 479–94.e4.
50. Nett JE, Andes DR. Antifungal agents: spectrum of activity, pharmacology, and clinical indications. Infect Dis Clin North Am. 2016. doi:10.1016/j.idc.2015.10.012.
51. Chhablani J. Fungal endophthalmitis. Expert Rev Anti Infect Ther. 2011;9:1991–201.

52. Smith J, Safdar N, Knasinski V, Simmons W, Bhavnani SM, Ambrose PG, et al. Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother. 2006;50:1570–2.
53. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis. 2008;46:201–11.
54. Cresemba (isavuconazonium) [prescribing information]. Northbrook: Astellas Pharma US Inc; 2015.
55. Azari AA, Barney NP. Conjunctivitis: a systemic review of diagnosis and treatment. JAMA. 2013;310:1721–9.
56. Jager RD, Aiello LP, Patel SC, Cunningham Jr ET. Risks of intravitreous injection: a comprehensive review. Retina. 2004;24:676–98.
57. Intravitreal Injections. In: American academy of ophthalmology. 2015. http://www.aao.org/clinical-statement/intravitreal-injections--november-2008. Accessed 20 Aug 2015.
58. Sosa AB, Epstein SP, Asbell PA. Evaluation of toxicity of commercial ophthalmic fluoroquinolone antibiotics as assessed on immortalized corneal and conjunctival epithelial cells. Cornea. 2008;27:930–4. doi:10.1097/ICO.0b013e31816f27ab.
59. Tsai T-H, Chen WL, Hu FR. Comparison of fluoroquinolones: cytotoxicity on human corneal epithelial cells. Eye (Lond). 2010;24:909–17. doi:10.1038/eye.2009.179. Epub 2009 Jul 24.
60. Kim SY, Lim JA, Choi JS, Choi EC, Joo CK. Comparison of antibiotic effect and corneal epithelial toxicity of levofloxacin and moxifloxacin in vitro. Cornea. 2007;26:720–5.
61. Alfonso E, Crider J. Ophthalmic infections and their anti-infective challenges. Surv Ophthalmol. 2005;50 Suppl 1:S1–6.
62. Campochiaro PA, Lim JI. Aminoglycoside toxicity in the treatment of endophthalmitis. The Aminoglycoside Toxicity Study Group. Arch Ophthalmol. 1994;112:48–53.
63. Seawright AA, Bourke RD, Cooling RJ. Macula toxicity after intravitreal amikacin. Aust N Z J Ophthalmol. 1996;24:143–6.
64. Braga-Mele R, Chang DF, Henderson BA, Mamalis N, Talley-Rostov A, Vasavada A. Intracameral antibiotics: safety, efficacy, and preparation. J Cataract Refract Surg. 2014;40:2134–42.
65. Faure C, Perreira D, Audo I. Retinal toxicity after intracameral use of a standard dose of cefuroxime during cataract surgery. Doc Ophthalmol. 2015;130:57–63. doi:10.1007/s10633-014-9465-7. Epub 2014 Oct 16.
66. Ciftci S, Ciftci L, Daq U. Hemorrhagic retinal infarction due to inadvertent overdose of cefuroxime in cases of complicated cataract surgery: retrospective case series. Am J Ophthalmol. 2014;157:421–5.e2. doi:10.1016/j.ajo.2013.10.018. Epub 2013 Nov 6.
67. Craig W, Andes DR. Cephalosporins. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 278–292.e4.
68. Heim-Duthoy KL, Caperton EM, Pollock R, Matzke GR, Enthoven D, Peterson PK. Apparent biliary pseudolithiasis during ceftriaxone therapy. Antimicrob Agents Chemother. 1990;34:1146–9.
69. Park HZ, Lee SP, Schy AL. Ceftriaxone-associated gallbladder sludge. Identification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. Gastroenterology. 1991;100:1665–70.
70. Letellier G, Desjarlais F. Analytical interference of drugs in clinical chemistry: II. The interference of three cephalosporins with the determination of serum creatinine concentration by the Jaffe reaction. Clin Biochem. 1985;18:352–6.
71. Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. Ann Pharmacol. 2008;42:1843–50.
72. Martinez-Rodriguez JE, Barriga FJ, Santamaria J, Iranzo A, Pareja JA, Revilla M, et al. Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. Am J Med. 2001;111:115–9.

73. Lamoth F, Buclin T, Pascual A, Vora S, Bolay S, Decosterd LA, et al. High cefepime plasma concentrations and neurological toxicity in febrile neutropenic patients with mild impairment of renal function. Antimicrob Agents Chemother. 2010;54:4360–7.
74. Miller AD, Ball AM, Bookstaver PB, Dornblaser EK, Bennett CL. Epileptogenic potential of carbapenem agents: mechanism of action, seizure rates, and clinical considerations. Pharmacotherapy. 2011;31:408–23.
75. Doi Y, Chambers HF. Other beta-lactam antibiotics. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Saunders; 2015. p. 293–7.e2.
76. Noel GJ, Natarajan J, Chien S, Hunt TL, Goodman DB, Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. Clin Pharmacol Ther. 2003;73:292–303.
77. Morganroth J, Dimarco JP, Anzueto A, Niederman MS, Choudhri S, CAPRIE Study Group. A randomized trial comparing the cardiac rhythm safety of moxifloxacin vs levofloxacin in elderly patients hospitalized with community-acquired pneumonia. Chest. 2005;128:3398–406.
78. Briasoulis A, Agarwal V, Pierce WJ. QT prolongation and torsade de pointes induced by fluoroquinolones: infrequent side effects from commonly used medications. Cardiology. 2011;120:103–10.
79. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. JAMA. 2012;307:1414–9.
80. Kuo SC, Chen YT, Lee YT, Fan NW, Chen SJ, Li SY, et al. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. Clin Infect Dis. 2014;58:197–203.
81. Pasternak B, Svanström H, Melbye M, Hviid A. Association between oral fluoroquinolone use and retinal detachment. JAMA. 2013;310:2184–90.
82. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother. 2008;52:1330–6.
83. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med. 2006;166:2138–44.
84. Jeffres MN, Isakow W, Doherty JA, McKinnon PS, Ritchie DJ, Micek ST, et al. Predictors of mortality for methicillin-resistant *Staphylococcus aureus* health-care-associated pneumonia: specific evaluation of vancomycin pharmacokinetic indices. Chest. 2006;130:947–55.
85. Zyvox® (linezolid) [package insert]. New York: Pharmacia and Upjohn Company; 2012.
86. Narita M, Tsuji BT, Yu VL. Linezolid-associated peripheral and optic neuropathy, lactic acidosis, and serotonin syndrome. Pharmacotherapy. 2007;27:1189–97.