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New Antimicrobials in Ophthalmology

Brett A. Levinson, MD, Allan R. Rutzen, MD*

Department of Ophthalmology and Visual Sciences, University of Maryland Medical Center, 419 West Redwood Street, Suite 580, Baltimore, MD 21201, USA

Throughout the history of recorded medicine, physicians have attempted to use sluces, salves, and balms to cure disease and speed the return to good health. In the late nineteenth century, Joseph Lister, Jules Francois Joubert, William Roberts, and Louis Pasteur all made observations that certain species of molds would prevent bacterial growth [1].

Although the use of silver nitrate to treat "ophthalmia" had been documented in the 1830s, Dr. Carl Credé in the 1880s was the first to advocate silver nitrate for prophylaxis of neonatal gonococcal conjunctivitis [2]. Continuing the detailed and systematic work of Credé, ophthalmologists have been searching for newer, stronger, and safer antimicrobials.

Selman Waksman, who along with Albert Schatz discovered streptomycin, is credited with coining the term *antibiotic*— meaning "against life" in Greek [3]. Today, the word is commonly used to signify antibacterials. In this article, we use the term *antimicrobials* to indicate any agent that has activity against pathogens.

In a perfect world, antimicrobials would be 100% selective for their targets, have no host toxicity, and kill the infection completely. The ability of an antimicrobial agent to attack pathogens selectively and leave the host unscathed relies on the blocking of microbial biochemical pathways that are not present in the host system.

In the real world, antimicrobials all have some relative degree of host toxicity and are either microbicidal or microbiostatic. Antimicrobials that cause death of the pathogen are microbicidal (eg, bactericidal, virucidal, fungicidal). Bactericidal drugs include the β-lactam family (penicillins and cephalosporins), aminoglycosides, and fluoroquinolones.

Agents that retard the growth of microbes are referred to as microbiostatic (eg, bacteriostatic, virustatic, fungistatic). Drugs that inhibit pathogenic replication require concomitant action by the host immune system to deliver the *coup de grâce*. Once a static drug is removed from the system, the microbe may resume its growth and spread. Examples of bacteriostatic drugs include tetracyclines and sulfonamides.

It is important to note that *microbiostatic* and *microbicidal* are relative terms. Some drugs that are bacteriostatic become bactericidal after extended exposure, whereas some bactericidal drugs may be less effective against particular strains of bacteria [4].

This article reviews the new developments in antibacterial, antiviral, and antifungal agents used in ophthalmology, particularly focusing on new developments in the literature. New topical medications and new oral medications that have implications in ophthalmology are covered.

Pharmacokinetics of topical medications

Less than 5% of medication instilled via eye drops enters the systemic circulation. Topical administration of antimicrobials has the advantage of applying the medication directly to the site of the infection. The relative degree of water and lipid solubility determines the penetration of eye drops. Absorption through the corneal epithelium requires fat solubility, and water solubility is required for diffusion through the corneal stroma into the anterior chamber. Increas-

* Corresponding author.
E-mail address: arutzen@umaryland.edu (A.R. Rutzen).

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ing the concentration of the medication can also increase speed of absorption [5].

Barriers to diffusion (eg, corneal epithelium, blood-retina barrier, blood-aqueous barrier) can be surmounted in several ways. Barriers can be bypassed, such as through an intravitreal injection. Alternatively, barriers can be disrupted, as in a corneal epithelial defect or toxicity from topical preparations, such as benzalkonium chloride (BAK). Severe inflammation can weaken the blood-aqueous and blood-retina barriers, allowing greater penetration of oral mediations into the eye; however, intraocular inflammation can also decrease the effective half-life of intravitreal medicines by increasing diffusion out of the eye. Also, the retinal pigment epithelium actively pumps out certain medications, such as cephalosporins. Other antibiotics, such as aminoglycosides and vancomycin, leave the vitreous primarily via passive transport through the anterior chamber [5].

Sensitivity

The minimum inhibitory concentration (MIC) is defined as the lowest concentration of an antimicrobial needed to halt microbial growth. The MIC for antibiotics is often expressed as the MIC_{90}—the concentration of antibiotic needed to inhibit 90% of a bacterial isolate. If the concentration of the antimicrobial at the site of infection is sufficient to inhibit or kill the microbe and is tolerated by the host organism, the pathogen is considered susceptible to the antimicrobial agent. Conversely, if a sufficient concentration cannot be reached to inhibit microbial growth, the pathogen is considered resistant. Generally, bacteria are considered to be sensitive to an antibiotic if the achievable serum level is four times the MIC [6].

When bacterial sensitivities are reported, the breakpoint for susceptible versus resistant is based on achievable concentrations in serum. This must be considered when using an antimicrobial topically or intravitreally, where concentrations of the drug may be higher than in serum. Therefore, bacteria reported as resistant because of lower achievable concentrations in serum may be susceptible when the medication is used topically because of the higher achievable concentration with frequent topical dosing [6].

Resistance

Bacteria have four main methods of developing resistance to antibiotics. Bacteria can alter the composition of their cell walls, thus creating a barrier to entrance of the medication. Second, the bacteria can upregulate active transport mechanisms to remove pharmacologic agents from the cell. Third, the bacterial target enzyme can be altered in its three-dimensional conformation to prevent the action of the antimicrobial, although still permitting function of the enzyme for bacterial processes. A final method of antibiotic resistance is induction of or de novo development of a bacterial enzyme that can deactivate or neutralize the drug [4].

Antibiotics

Fluoroquinolones

In 1963, nalidixic acid was discovered during chloroquine synthesis and was noted to have antibacterial properties, but it was excreted too quickly to have any significant systemic antibacterial effects. This problem was solved in 1967, however, by fluorinating the quinolones, which gave these compounds far greater antibacterial activity, therapeutic blood levels, and low toxicity. Fluoroquinolones are bactericidal and inhibit bacterial DNA synthesis by blocking the action of two of the topoisomerase enzymes, which are present only in bacteria. Topoisomerase II, also known as DNA gyrase, allows the uncoiling and supercoiling of double-stranded DNA, and topoisomerase IV cleaves the doubled DNA of replicating DNA, allowing daughter cell formation [4].

Bacteria can develop resistance to fluoroquinolones by altering their target enzymes, altering the permeability of the drug into the organism, increasing efflux pumps, and upregulating a gene conferring quinolone resistance (present in some *Staphylococcus aureus*). Spontaneous mutations to areas of the bacterial genome called "quinolone-resistance determining regions" occur at a rate of 10^{-9}; however, more frequently, resistance is conferred by plasmids. Creation of a novel enzyme able to deactivate fluoroquinolones is not yet a significant factor in bacterial resistance. Although some laboratory testing has demonstrated fluoroquinolone resistance in vitro, the high concentration in topical dosing may overcome resistance in the clinical setting [4].

Second- and third-generation fluoroquinolones

The second-generation fluoroquinolones include ciprofloxacin and ofloxacin, which have broad-spectrum coverage against gram-positive and gram-

negative bacteria. The initial ophthalmic use of the fluoroquinolones was to treat corneal and conjunctival infections; however, they have also gained wide acceptance in the prophylaxis of bacterial endophthalmitis after intraocular surgery.

Ciprofloxacin, a second-generation fluoroquinolone, was approved in 1990 and is a solution of ciprofloxacin 0.3% with 0.006% BAK as a preservative and a pH of 4.5. Ofloxacin, a second-generation fluoroquinolone, contains ofloxacin 0.3% and 0.005% BAK and has a pH of 6.4 [7]. Ofloxacin has a greater solubility at neutral pH than ciprofloxacin, allowing it to be constituted at a more physiologic pH and permitting less drug precipitation. The higher concentration of ofloxacin creates an increased effective tear concentration. Because ofloxacin is more lipophilic than ciprofloxacin, it has greater penetration through the corneal epithelium [8,9]. Ciprofloxacin has a lower solubility at neutral pH, which can lead to corneal precipitates. According to the manufacturer's data, ciprofloxacin precipitates were identified in 16.6% of 210 patients treated for corneal ulcers with frequent dosing [7].

Levofloxacin, the L-isomer of ofloxacin, is considered a third-generation fluoroquinolone. It was FDA approved in 2000 and has a higher solubility at neutral pH, allowing for a higher concentration of medication, 0.5%. It has a pH of 6.5 and is preserved with 0.005% BAK [10]. Adverse reactions to topical second- and third-generation fluoroquinolones are mild and include discomfort, chemosis, hyperemia, eyelid edema, and punctate epithelial keratitis [10].

Several studies investigated the use of ofloxacin and ciprofloxacin versus fortified cefazolin and tobramycin (double-fortified antibiotic therapy), the prior standard of care in treating bacterial keratitis. In a double-masked, randomized, multicenter study with 140 patients, O'Brien and colleagues [11] found that ofloxacin was as efficacious as double-fortified antibiotics with less toxic effects and increased ease of preparation. Other smaller, randomized, double-masked studies found similar results [12,13]. Hyndiuk and coworkers [14] compared ciprofloxacin with double-fortified antibiotics in a multicenter, double-masked, prospective, randomized study of 176 patients and found no statistically significant difference in resolution of clinical symptoms, duration of infection, or rates of treatment failure. The patients in the ciprofloxacin group reported less ocular discomfort than patients on the double-fortified regimen.

In clinical practice, the authors of this article still use double-fortified antibiotics for patients with dense central ulcers, monocular patients, and patients who have been referred for evaluation of refractory bacterial corneal ulcers. Although the use of a single quinolone is acceptable, given the broad spectrum of coverage, and this use is supported in the literature, some clinicians may choose to rely on double-fortified antibiotics if the broadest antibiotic coverage is desired.

According to the prescribing information, ciprofloxacin and ofloxacin are both indicated for treatment of corneal ulcers and bacterial conjunctivitis. The manufacturer's instructions for treatment of corneal ulcers with ciprofloxacin are two drops every 15 minutes for the first 6 hours and then two drops into the affected eye every 30 minutes for the rest of the first day. On the second day, use two drops every hour and then use 2 drops every 4 hours for the consecutive days of treatment. For corneal ulcers, the prescribing information for ofloxacin recommends one to two drops every 30 minutes while awake and one to two drops once during the night for 2 days. For days 3 through 7 of treatment, use drops hourly, and then four times a day for the remainder of the treatment. For treatment of bacterial conjunctivitis, ciprofloxacin and ofloxacin dosage instructions are similar—one to two drops every 2 to 4 hours for 2 days and then every 4 hours for 5 days [10].

Multiple studies have investigated the aqueous humor penetration of ofloxacin and ciprofloxacin in various clinical settings and with different dosing regimens (Table 1). Ofloxacin was consistently shown to have higher penetration into the aqueous humor than ciprofloxacin, although the difference was not always statistically significant. Despite the greater penetration of ofloxacin, ciprofloxacin has higher antimicrobial activity (lower MIC_{90}) than ofloxacin (Tables 2 and 3) [9,15,16]. Later studies investigating levofloxacin found it to have a lower MIC_{90} than ofloxacin and ciprofloxacin [17,18].

Ciprofloxacin has also been shown to achieve a concentration in the tear film greater than its MIC_{90} for key ocular microbes [19]. Although some studies showed that ciprofloxacin and ofloxacin both achieved significant concentrations in the aqueous [9,20], other studies showed that ciprofloxacin failed to reach the MIC_{90} for the most common pathogens [21]. Ofloxacin and levofloxacin more consistently reached significant aqueous levels [15,22–25].

Although most studies used anterior chamber levels of fluoroquinolones a marker for efficacy, one study investigated the in vivo reduction of bacterial flora on human conjunctiva after use of ciprofloxacin and ofloxacin. In this study, ciprofloxacin was found to reduce the bacterial flora severely within 15 min-

Table 1
Comparative penetration into aqueous humor of humans of second- and third-generation fluoroquinolones

Dosing	Cipro (μg/mL)	Oflox (μg/mL)	Levo (μg/mL)	Stat sig
1 drop q h × 6 (63 pt) [20]	2.80 ± 1.07	2.95 ± 1.19		No
1 drop q 5 min × 5, q 30 min × 3 (18 pt) [9]	1.13 ± 1.90	2.06 ± 1.06		No[a]
1 drop q h × 6 [79]	0.35 ± 0.07	1.43 ± 0.26		Yes
1 drop q 15 min × 4 (59 pt) [25]	0.08		0.728	Yes
1 drop q 15 min × 8 (224 pt) [15]	0.38 ± .33	0.563 ± 0.372		Yes
1 drop q 30 min × 8 (36 eyes) [80]	0.21 ± 0.20	0.75 ± 0.48		Yes[b]
2 drops 90 min before surgery, 2 drops 30 min after surgery (32 pt) [81]	0.072	0.338		Yes
1 drop qid × 2 days, then 5 doses 1 hr before surgery [23]	241.5 ± 206.8		1618 ± 780	Yes

Abbreviations: Cipro, ciprofloxacin; h, hour; Levo, levofloxacin; min, minute; Oflox, ofloxacin; pt, patients; q, every; qid, four times daily; Stat sig, statistically significant.

[a] This study had a large range of concentrations, and if an outlier of 6.34 μg/mL is excluded, the mean ciprofloxacin concentration in the aqueous is 0.55 ± 0.46, which was lower than the concentration of antibiotic needed to inhibit 90% of a bacterial isolate for *Staphylococcus epidermidis*.

[b] In eyes with functioning filtering blebs.

Data from Refs. [9,23,25,79–81].

utes, with an antimicrobial effect lasting at least 2 hours, whereas ofloxacin did not result in a significant reduction in bacterial flora [16].

In a large, retrospective, cross-sectional, multicenter study, Jensen and colleagues [26] investigated endophthalmitis rates after cataract extraction over a 4-year period in more than 9000 patients who received ciprofloxacin or ofloxacin. Equal numbers of patients received the two antibiotics. The rate of endophthalmitis was 5.5 times greater in patients who received ciprofloxacin after phacoemulsification than in patients who received ofloxacin (0.48% versus 0.08%) After completion of this review, the authors changed their postoperative protocol to using only ofloxacin, and only one case of endophthalmitis was reported in 3000 cases for a rate of 0.03%.

Possible explanations for the results of this study include the higher penetration of ofloxacin into the anterior chamber as discussed previously. Other explanations may include increasing resistance to ciprofloxacin. The most commonly isolated bacteria in the study were coagulase-negative *Staphylococcus* and *S aureus* [26]. The rate of ciprofloxacin resistance of *Staphylococcus* has been steadily increasing. In the years 1990 through 1995, only 8% of methicillin-sensitive *S aureus* (MSSA) was resistant to ciprofloxacin, whereas the rate increased to 20.7% in the years 1996 through 2001. The rate of resistance to MSSA was higher in ciprofloxacin than in levofloxacin, but the resistances to both are increasing [27]. In 2001, Kowalski and coworkers [28] found that *S aureus* with fluoroquinolone resistance was susceptible to levofloxacin, ofloxacin, and ciprofloxacin in 22%, 10%, and 3% of their cases, respec-

Table 2
In vitro activity of ofloxacin

Bacterium	MIC_{90} (μg/mL)
Streptococcus pneumoniae	2.00
Staphylococcus epidermidis	0.50
Staphylococcus aureus	0.50
Escherichia coli	0.12
Proteus mirabilis	0.12
Klebsiella pneumoniae	0.50
Pseudomonas aeruginosa	4.00

Abbreviation: MIC_{90}, concentration of antibiotic needed to inhibit 90% of a bacterial isolate.

Table 3
In vitro activity of ciprofloxacin

Bacterium	MIC_{90} (μg/mL)
Streptococcus pneumoniae	2.00
Staphylococcus epidermidis	0.50
Staphylococcus aureus	0.61
Escherichia coli	2.00
Proteus mirabilis	0.18
Klebsiella pneumoniae	0.24
Pseudomonas aeruginosa	0.73

Abbreviation: MIC_{90}, concentration of antibiotic needed to inhibit 90% of a bacterial isolate.

Data from Yalvac IS, Basci NE, Bozkurt A, et al. Penetration of topically applied ciprofloxacin and ofloxacin into the aqueous humor and vitreous. J Cataract Refract Surg 2003;29(3):487–91.

Table 4
Minimum inhibitory concentrations of 90% (μg/mL) for bacterial keratitis isolates to fluoroquinolone antibiotics

	n	MIC_{90}	Susceptibility
Staphylococcus aureus			
fluoroquinolone susceptible			
Moxifloxacin	25	0.047	100%
Gatifloxacin	25	0.22	100%
Levofloxacin	25	0.38	100%
Ciprofloxacin	25	0.5	100%
Ofloxacin	25	0.75	100%
Staphylococcus aureus			
fluoroquinolone resistant			
Moxifloxacin	25	4.0	68%
Gatifloxacin	25	12.0	8%
Levofloxacin	25	32.0	0%
Ciprofloxacin	25	128.0	0%
Ofloxacin	25	64.0	0%
Coagulase-negative			
Staphylococcus			
fluoroquinolone susceptible			
Moxifloxacin	10	0.125	100%
Gatifloxacin	10	0.19	100%
Levofloxacin	10	0.19	100%
Ciprofloxacin	10	0..38	100%
Ofloxacin	10	0.75	100%
Coagulase-negative			
Staphylococcus			
fluoroquinolone resistant			
Moxifloxacin	10	3.0	50%
Gatifloxacin	10	3.0	40%
Levofloxacin	10	64.0	10%
Ciprofloxacin	10	64.0	0%
Ofloxacin	10	64.0	0%
Streptococcus pneumoniae			
Moxifloxacin	20	0.19	100%
Gatifloxacin	20	0.25	100%
Levofloxacin	20	1.0	95%
Ciprofloxacin	20	2.0	85%
Ofloxacin	20	4.0	70%
Streptococcus viridans			
group			
Moxifloxacin	20	0.19	100%
Gatifloxacin	20	0.38	100%
Levofloxacin	20	1.0	100%
Ciprofloxacin	20	4.0	60%
Ofloxacin	20	4.0	55%
Pseudomonas aeruginosa			
fluoroquinolone susceptible[a]			
Moxifloxacin	25	0.75	100%
Gatifloxacin	25	0.38	100%
Levofloxacin	25	0.5	100%
Ciprofloxacin	25	0.125	100%
Ofloxacin	25	1.5	100%
Serratia marcescens			
Moxifloxacin	10	0.38	100%
Gatifloxacin	10	0.38	100%
Levofloxacin	10	0.25	100%
Ciprofloxacin	10	0.094	100%
Ofloxacin	10	0.75	100%
Haemophilus species			
Moxifloxacin	10	0.19	100%
Gatifloxacin	10	0.064	100%
Levofloxacin	10	0.032	100%
Ciprofloxacin	10	0.032	100%
Ofloxacin	10	0.125	100%
Moraxella species			
Moxifloxacin	10	0.047	100%
Gatifloxacin	10	0.032	100%
Levofloxacin	10	0.064	100%
Ciprofloxacin	10	0.064	100%
Ofloxacin	10	0.19	100%

Abbreviation: $MIC_{90,}$ concentration of antibiotic needed to inhibit 90% of a bacterial isolate.

[a] *Pseudomonas aeruginosa* fluoroquinolone-resistant antibiotics are resistant to all fluoroquinolones.

From Kowalski RP, Dhaliwal DK, Karenchak LM, et al. Gatifloxacin and moxifloxacin: an in vitro susceptibility comparison to levofloxacin, ciprofloxacin, and ofloxacin using bacterial keratitis isolates. Am J Ophthalmol 2003; 136(3):502–3; with permission.

tively. Increasing resistance can also be seen for *Pseudomonas aeruginosa*. One study demonstrated that all current fluoroquinolones (including the fourth generation) were not effective against ciprofloxacin-resistant *Pseudomonas,* indicating that these strains of *Pseudomonas* are resistant to all fluoroquinolones, regardless of the generation [7].

Fourth-generation fluoroquinolones

The fourth-generation fluoroquinolones, moxifloxacin and gatifloxacin, were approved by the US Food and Drug Administration (FDA) in 2003. The former is moxifloxacin 0.5% with a pH of 6.8 and contains boric acid but no BAK [10]. The latter is gatifloxacin 0.3% with a pH of 6 and 0.005% BAK. The older fluoroquinolones bound more strongly to topoisomerase II (DNA gyrase), an enzyme more important in gram-negative bacteria, than to topoisomerase IV. With the addition of a methoxy group on carbon 8, the newer fluoroquinolones bind more effectively to topoisomerase II and IV, giving these medications better clinical efficacy against gram-positive organisms. Because these drugs affect two targets in the bacterial replication process, it may be theoretically

harder for resistance to these drugs to develop, because sensitive bacteria would have to develop two mechanisms for resistance [4]. Theoretically, assuming a standard rate of bacterial mutation, only 1 in 10 trillion susceptible bacteria would develop the two genetic mutations required for resistance to the fourth-generation fluoroquinolones. Approximately 1 million bacteria live on the eyelids or in an infected cornea, making the odds of developing resistance theoretically quite low [29].

Reports from several studies support the conclusion that moxifloxacin and gatifloxacin have a lower MIC_{90} against gram-positive bacteria than the second- and third-generation fluoroquinolones. Susceptibility data show that isolates of fluoroquinolone-susceptible *S aureus*, fluoroquinolone-susceptible coagulase-negative *Staphylococcus*, and *Streptococcus pneumoniae* are all uniformly susceptible to the second-, third-, and fourth-generation fluoroquinolones, however [30,31].

The fourth-generation fluoroquinolones are particularly efficacious against coagulase-negative *Staphylococcus* and *Streptococcus viridans,* two of the most common causes of postsurgical endophthalmitis, as shown in a report by Kowalski and colleagues [30]. Fluoroquinolone-sensitive coagulase-negative *Staphylococcus* is sensitive to all generations of fluoroquinolones. Fluoroquinolone-resistant coagulase-negative *Staphylococcus* has moderate susceptibility to moxifloxacin (50% of isolates) and gatifloxacin (40%) of isolates, whereas only 10% of isolates were susceptible to levofloxacin and 0% was susceptible to ciprofloxacin and ofloxacin (Tables 4–7).

As noted previously, the incidence of fluoroquinolone-resistant *S aureus* to second- and third-generation fluoroquinolones is increasing. Moxifloxacin has been shown to have good efficacy against fluoroquinolone-resistant isolates of *S aureus*, whereas gatifloxacin has shown limited efficacy. Mather and coworkers [29] found that 87.5% (7 of 8) of isolates of fluoroquinolone-resistant *S aureus* were sensitive to moxifloxacin and 12.5% (1 of 8 isolates) were sensitive to gatifloxacin. In a larger study, Kowalski and colleagues [30] found that 68% (17 of 25) of isolates of fluoroquinolone-resistant *S aureus* were sensitive to moxifloxacin and 2 of 25 were sensitive to gatifloxacin (see Table 4).

Overall, fourth-generation fluoroquinolones are equally efficacious against gram-negative bacteria as the earlier fluoroquinolones. For example, *Serratia*, *Moraxella*, and *Haemophilus* show similar susceptibilities to all fluoroquinolones. Kowalski and colleagues [30] found that 25 of 25 fluoroquinolone-sensitive *Pseudomonas* isolates were uniformly susceptible to all generations of fluoroquinolones, whereas 0 of 25 fluoroquinolone-resistant *Pseudomonas* isolates were susceptible to any fluoroquinolone. (When fluoroquinolone resistance develops in *Pseudomonas*, it becomes resistant to all generations of fluoroquinolone). Additional data from Kowalski's

Table 5
Susceptibility[a] of bacterial isolates from keratitis to common antibiotics (percent susceptible)(1993 to January 1, 2005)

Bacteria	No.	BAC	CHL	VAN	GEN	CIP	OFX	TRI	PB	CEF	TOB	SULF	OXA*	GAT*	MOX*
Staphylococcus aureus	300	97	98	100	91	73	73	90	1	93	72	96	66(139)	70(46)	78(46)
Coagulase-negative *Staphylococcus*	113	95	92	100	75	50	50	55	26	91	68	87	32(68)	77(22)	82(22)
Streptococcus pneumoniae	60	100	98	100	10	97	97	52	2	100	0	95	—	100(10)	100(10)
Streptococcus viridans	80	100	97	100	45	76	93	43	5	99	21	100	—	100(8)	100(8)
Other Gram-positives	68	84	85	100	73	70	72	36	51	78	56	56	—	71(7)	71(7)
Pseudomonas aeruginosa	152	0	0	0	95	94	93	0	100	0	97	1	—	84(32)	84(32)
Serratia marcescens	133	0	99	0	99	100	100	90	5	0	97	84	—	100(13)	100(13)
Moraxella species	45	100	100	98	100	100	100	5	100	98	100	98	—	100(4)	100(4)
Haemophilus species	33	3	100	3	100	100	100	85	97	53	100	67	—	100(9)	100(9)
Other Gram-negatives	132	14	80	11	89	96	96	49	77	42	88	95	—	90(2)	90(2)
Gram-negative (contact lens)	145	3	—	4	54	97	92	—	86	9	53	82	—	87(15)	93(15)

Abbreviations: BAC, bacitracin; CEF, cefazolin; CHL, chloramphenicol; CIP, ciprofloxacin; GAT, gatifloxacin; GEN, gentamicin; MOX, moxifloxacin; OFX, ofloxacin; OXA, oxacillin; PB, polymyxin B; SULF, sulfasoxazole; TOB, tobramycin; TRI, trimethoprim; VAN, vancomycin; —, not done.

[a] Disk diffusion susceptibilities based on National Committee for Clinical Lab Standards serum standards.

* Number of isolates in parentheses.

From Susceptibility of bacterial isolates: the Charles T. Campbell Eye Microbiology Lab. Available at: http://eyemicrobiology.upmc.com.

Table 6
Susceptibility[a] of bacterial isolates from conjunctivitis and blepharitis to common antibiotics (percent susceptible) (1993 to January 1, 2005)

Bacteria	No.	BAC	CHL	ERY	NEO	GEN	CIP	OFX	TRI	PB	TOB	SULF	TET	OXA*	GAT*	MOX*
Staphylococcus aureus	362	98	99	64	87	93	82	82	93	2	83	96	88	69(26)	82(44)	82(44)
Coagulase-negative *Staphylococcus*	162	94	98	39	88	84	71	70	72	39	75	81	54	—	100(3)	100(3)
Streptococcus pneumoniae	188	99	99	92	1	13	100	100	61	1	1	96	88	—	100(11)	100(11)
Haemophilus species	188	1	99	5	85	96	100	100	91	100	95	73	26	—	100(18)	100(18)
Moraxella species	17	76	100	94	100	100	100	100	12	100	94	100	92	—	100(3)	100(3)
Acinetobacter species	15	20	46	21	100	100	100	100	12	100	100	100	43	—	100(2)	100(2)
Other Gram-positives	58	98	96	61	35	61	80	85	62	29	38	64	71	—	100(8)	100(8)
Other Gram-negatives	117	21	80	12	90	97	98	98	51	67	91	73	40	—	94(16)	94(16)

Abbreviations: BAC, bacitracin; CHL, chloramphenicol; CIP, ciprofloxacin; ERY, erythromycin; GAT, gatifloxacin; GEN, gentamicin; MOX, moxifloxacin; NEO, neomycin; OFX, ofloxacin; OXA, oxacillin; PB, polymyxin B; SULF, sulfasoxazole; TOB, tobramycin; TET, tetracycline; TRI, trimethoprim; —, not done.

[a] Disk diffusion susceptibilities based on National Committee for Clinical Lab Standards serum standards.

* Number of isolates in parentheses.

From Susceptibility of bacterial isolates: the Charles T. Campbell Eye Microbiology Lab. Available at: http://eyemicrobiology.upmc.com.

group [31] show that 27 (84%) of 32 *Pseudomonas* isolates from keratitis were sensitive to gatifloxacin and moxifloxacin, whereas 143 (94%) of 152 were sensitive to ciprofloxacin and 141 (93%) of 152 were sensitive to ofloxacin. These data may be explained by the fact that the *Pseudomonas* isolates in the fourth-generation subset were cultured more recently, and the lower susceptibility may represent the increasing overall resistance in the *Pseudomonas* population.

Moxifloxacin and gatifloxacin penetrate well into the anterior chamber and have levels in excess of the MIC_{90} for most pathogenic organisms. One study investigated cataract patients who received moxifloxacin 0.5%, gatifloxacin 0.3%, or ciprofloxacin 0.3% four times a day for 3 days before surgery and then every 15 minutes 3 times 1 hour before surgery. Anterior chamber drug levels were significantly higher in patients taking moxifloxacin 0.5% than in patients taking gatifloxacin 0.3%, a difference that the authors postulate may be attributable to differences in concentrations of the preparations (Table 8) [32].

One study in rabbits demonstrated that the anterior chamber concentration of moxifloxacin was significantly higher than that of gatifloxacin when dosed at a rate of one drop every 15 minutes for 4 hours [33]. When aqueous levels were adjusted for the difference in the two formulations (moxifloxacin 0.5% versus gatifloxacin 0.3%), however, there was no significant difference in the anterior chamber levels when adjusted for the higher con-

Table 7
Susceptibility[a] of bacterial isolates from endophthalmitis to common antibiotics (percent susceptible) (1993 to January 1, 2005)

Bacteria	No.	VAN	GEN	CIP	OFX	CEF	AMK	CAZ	OXA	AMP	CLIN	GAT*	MOX*
Coagulase-negative *Staphylococcus*	224	100	83	59	56	98	96	75	52	19	81	76(46)	72(46)
Staphylococcus aureus	48	100	90	50	44	87	81	73	69	6	60	20(10)	30(10)
Streptococcus species	80	100	45	81	94	94	5	88	—	95	82	100(18)	100(18)
Gram-negative bacteria	24	8	92	92	95	33	92	92	—	44	10	75(4)	75(4)
Other Gram-positive bacteria	20	95	80	79	75	65	80	47	—	70	79	100(1)	100(1)

Abbreviations: AMK, amikacin; AMP, ampicillin; CAZ, ceftazidime; CEF, cefazolin; CLIN, clindamicinm; CIP, ciprofloxacin; GAT, gatifloxacin; GEN, gentamicin; MOX, moxifloxacin; OFX, ofloxacin; OXA, oxacillin; VAN, vancomycin; —, not done.

[a] Disk diffusion susceptibilities based on National Committee for Clinical Lab Standards serum standards.

* Number of isolates in parentheses.

From Susceptibility of bacterial isolates: the Charles T. Campbell Eye Microbiology Lab. Available at: http://eyemicrobiology.upmc.com.

Table 8
Comparative penetration into aqueous humor of fourth-generation fluoroquinolones

Dosing	Gati (μg/mL)	Moxi (μg/mL)	Subject	Stat sig
1 drop q 15 min × 4 h (n = 9) [33]	7.57 ± 2.22	11.06 ± 3.55	Rabbit	Yes[a]
1 drop qid × 10 days (n = 6) [33]	1.21 ± 0.72	1.75 ± 1.19	Rabbit	No
1 drop qid × 3 days [82]	0.31 ± 0.75	1.42 ± 0.61	Rabbit	Yes
1 drop qid × 3 then every 15 min × 3 before surgery [32]	0.63 ± 0.30	1.31 ± 0.46	Human	Yes

Abbreviations: Gati, gatifloxacin; h, hour; min, minute; Moxi, moxifloxacin; q, every; qid, four times daily; Stat sig, statistically significant.

[a] When aqueous levels were adjusted for the difference in the two formulations (moxifloxacin 0.5% versus gatifloxican 0.3%), the difference was not statistically significant.

Data from Refs. [32,33,82].

centration of moxifloxacin. Using a second dosing regimen intended to replicate cataract surgery prophylaxis (four times a day for 10 days), no difference in anterior chamber concentration between moxifloxacin and gatifloxacin was found.

Given the broad-spectrum activity of these antibiotics and their frequent perioperative use, a study was designed to investigate the use of moxifloxacin for prophylaxis against endophthalmitis [34]. This study found that moxifloxacin prevented endophthalmitis in rabbits when given before and after an *S aureus* challenge. The authors determined the amount of *S aureus* needed to develop endophthalmitis when placed in the anterior chamber of rabbits. In rabbits receiving five drops of moxifloxacin over 1 hour before the challenge and then drops every 6 hours for 1 day, none of the rabbits had clinical signs of endophthalmitis and no *Staphylococcus* was recovered from the anterior chamber. The rabbits in the control group all had clinical signs of endophthalmitis.

One study designed to gauge epithelial toxicity after topical fluoroquinolone use found that ciprofloxacin, ofloxacin, levofloxacin, and gatifloxacin all caused thinning of the corneal epithelium in rabbits after dosing at a rate of four times a day for 6 days when viewed under confocal microscopy. The study found that artificial tears and moxifloxacin caused no epithelial thinning, which the authors attribute to the lack of BAK in moxifloxacin [35]. A study of high-frequency dosing of moxifloxacin and gatifloxacin on rabbit corneas found no difference in the amount of epithelial damage when viewed under scanning electron microscopy, however [36]. In a study of clinical tolerability, Donnenfeld and colleagues [37] found that gatifloxacin had a better ocular tolerability in terms of pain and irritation on instillation and less ocular redness. Moxifloxacin was also found to cause slight miosis, whereas gatifloxacin did not have this effect. Other reported side effects of fourth-generation topical fluoroquinolones include discomfort, hyperemia, conjunctivitis, and itching (Tables 9 and 10).

In summary, the fourth-generation fluoroquinolones play an important role in the treatment of bacterial conjunctivitis and keratitis and in the peri-

Table 9
Side effects of topical antimicrobials

Generic name	Adverse reactions	Precautions
Ciprofloxacin Ofloxacin Levofloxacin	Discomfort, chemosis, hyperemia, eyelid edema, punctate epithelial keratitis, corneal precipitation, tearing, photophobia, dryness, itching, foreign body sensation (ciprofloxacin only)	Hypersensitivity to fluoroquinolones
Gatifloxacin	Irritation, tearing, keratitis, papillary conjunctivitis (5%–10% incidence), chemosis, conjunctival hemorrhage, dry eye, discharge, eye lid edema, eye pain, headache, hyperemia, reduced visual acuity, taste disturbance (1%–4% incidence)	Hypersensitivity to fluoroquinolones
Moxifloxacin	Hyperemia, itching, conjunctivitis, decreased visual acuity, dry eye, tearing, subconjunctival hemorrhage, eye pain (1%–6% incidence)	Hypersensitivity to fluoroquinolones

Data from Rhee D, Rappuano CJ, Weisbecker CA, et al. Physicians' desk reference for ophthalmic medicines, vol. 32. Montvale, NJ: Thomson PDR; 2004. p. v.

Table 10
Side effects of oral medications

Generic name	Adverse reactions	Precautions
Gatifloxacin Moxifloxacin	GI reaction (nausea, vomiting, diarrhea), CNS reactions (headache, dizziness, insomnia), prolongation of QT interval, tendon rupture (studies in immature animals have shown erosions in the cartilage of weight-bearing joints)	Systemic use in children, pregnant or lactating women, proarrhythmic conditions, prolonged Q-T interval
Linezolid	Reversible and dose-dependent thrombocytopenia, diarrhea, headache, skin rash, increase in hepatic enzymes and creatinine	Avoid foods or medications with monoamine-oxidase inhibition
Quinupristin-dalfopristin	Mild to severe arthralgias/myalgias, venous irritation, elevation of conjugated bilirubin	Hypersensitivity to strepogramins
Valganciclovir	Diarrhea, neutropenia, anemia, thrombocytopenia	Neutropenia, anemia, thrombocytopenia
Voriconazole	Photopsias, blurry vision, changes in color vision, photophobia, rash, photosensitivity, facial erythema, cheilitis, elevations in liver enzymes	Cardiac arrhythmias, prolonged Q-T interval
Posaconazole	Mild to moderate elevations in hepatic enzymes	Hypersensitivity to azoles
Caspofungin	Fever, phlebitis, headache, rash	Hypersensitivity to echinocandins
Acyclovir	Nausea, vomiting, itching, rash, hives	Caution in severely immunocompromised patients (rare reports of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome and renal impairment)
Valaciclovir	Nausea, headache, vomiting	Severely immunocompromised patients and in allogenic bone marrow and renal transplant patients
Famciclovir	Nausea, headache, vomiting, itching, rash	Caution in renal impairment

Abbreviations: CNS, central nervous system; GI, gastrointestinal.
Data from Refs. [49,64,70,83,84].

operative prophylaxis against endophthalmitis. In general, because they have excellent efficacy against gram-negative bacteria and improved efficacy against gram-positive bacteria, they demonstrate a broad spectrum of activity against various bacterial pathogens that are common in conjunctivitis, keratitis, and endophthalmitis.

Fluoroquinolones in treatment of endophthalmitis

Several authors have investigated the penetration of fluoroquinolones into the posterior segment and discussed the usefulness of topical treatment for endophthalmitis. In 1993, Kowalski and coworkers [38] investigated the penetration of ciprofloxacin into the vitreous and concluded that although the concentration was adequate for gram-negative isolates, the concentration was not high enough to ensure treatment of gram-positive organisms. A later study demonstrated that neither ofloxacin nor ciprofloxacin reached adequate levels in the vitreous humor for empiric treatment of endophthalmitis [9]. Hariprasad and colleagues [39] demonstrated that two oral doses of gatifloxacin, 400 mg, can reach therapeutic levels in the vitreous. Garcia-Saenz and coworkers [40] found that after one oral dose of moxifloxacin, 400 mg, and one oral dose of levofloxacin, 400 mg, the vitreous levels of the medication were in excess of the MIC_{90} against most of the common pathogens in endophthalmitis. Ciprofloxacin did not achieve adequate levels in the vitreous after two oral doses of 500 mg.

Benz and colleagues [41] performed a retrospective review of patients with culture-positive endophthalmitis over 6 years in one hospital. The authors identified 313 organisms from 278 patients, and 78.5% were gram-positive, 11.8% were gram-negative, and 8.6% were fungal. The most common organisms were *Staphylococcus epidermidis* (27.8%), *S viridans* group (12.8%), other coagulase-negative *Staphylococcus* (9.3%), and *Propionibacterium acnes* (7.0%). The sensitivities for the gram-positive organisms were 100% for vancomycin, 78.4% for gentamycin, 68.3% for ciprofloxacin, 63.6% for ceftazidime, and 66.8% for cefazolin. The sensitivities for the gram-negative isolates were 94.2% for ciprofloxacin, 80.9% for amikacin, 80.0% for ceftazidime, and 75.0% for gentamicin.

Empiric endophthalmitis treatment needs to be broadly based, because no one antibiotic effectively

covers all the most common isolates. The use of intravitreal injections with a combination of agents is the standard of care (eg, intravitreal vancomycin and intravitreal ceftazidime or amikacin). After culture results are obtained, therapy can be tailored accordingly. The Endophthalmitis Vitrectomy Study (EVS) examined the use of intravitreal and intravenous amikacin and ceftazidime. The EVS found no added benefit from the use of systemic amikacin and ceftazidime [42]. One critique of the EVS is that systemic amikacin and ceftazidime do not have good intravitreal penetration [43,44].

Given the better penetration of systemic moxifloxacin and gatifloxacin into the vitreous, these agents may have a role as adjunctive therapy in endophthalmitis treatment but cannot be considered standard of care. A definitive recommendation concerning the use of systemic fluoroquinolones to treat endophthalmitis awaits analysis in a large, multicenter, double-masked clinical trial. Some clinicians have advocated the adjunctive use of systemic fluoroquinolones in patients at a higher risk for endophthalmitis, such as those with a break in sterile technique or intraoperative posterior capsule rupture, or in patients who may be noncompliant with topical medications [4].

Oxazolidinone antibiotics

In 2000, linezolid was the first antibiotic to be approved in a new class called oxazolidinones, and it is structurally unrelated to other available antimicrobials. Bacterial protein synthesis is inhibited by linezolid binding to the 50S ribosomal subunit. Because linezolid blocks the initiation complex in protein synthesis rather than the elongation processes, the production of bacterial virulence factors may be reduced and this may reduce the damage occurring to structures. Some have suggested that linezolid seems to have some anti-inflammatory effects [4].

Linezolid is available for oral or intravenous use and is active primarily against gram-positive bacteria but has minimal activity against gram-negative bacteria. Linezolid is indicated for treatment of vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE) as well as methicillin-resistant *S aureus* (MRSA). Risks include thrombocytopenia, which is reversible and dose-dependent, diarrhea, headache, and skin rash [4]. Linezolid has no known cross-resistance with any other class of antibiotics, and animal studies have shown that it penetrates well into the anterior and posterior segments after systemic dosing [45].

Fiscella and colleagues [45] demonstrated that after two oral doses of 600 mg 12 hours apart, linezolid concentration exceeded the MIC_{90} for all gram-positive bacteria they tested, including VRE, MRSA, and *Streptococcus* species. Mah [4] found that linezolid was effective against all gram-positive keratitis and endophthalmitis isolates tested. Linezolid was also shown to have concentrations in the anterior chamber higher than the MIC_{90} for *S epidermidis* after one 600-mg intravenous infusion [46]. Topical linezolid has also been shown to be as effective as topical vancomycin in treating *S pneumoniae* corneal ulcers in rabbits [47]. One case report describes the use of topical linezolid to treat crystalline keratopathy attributable to VRE. In this case, the commercial preparation of linezolid, 20 mg/mL, was used topically every 2 hours [48].

One advantage that linezolid has over β-lactam antibiotics (eg, penicillin, cephalosporins) is a higher stability in solution [4]. Given its excellent activity against gram-positive bacteria, especially VRE and MRSA, linezolid may have a role in treatment of gram-positive ocular infections with systemic or topical administration. A definitive assessment of the role of systemic or topical linezolid in the treatment of ocular infection awaits validation by clinical trials.

Streptogramin antibiotics

Quinupristin-dalfopristin, which received FDA approval in 1999, is the first antibiotic available in a new class called streptogramins. It is a mixture of two compounds extracted from *Streptomyces pristinaspiralis*. Quinupristin and dalfopristin bind sequentially to separate sites on the 50S ribosome, thus inhibiting protein synthesis [49]. Individually, quinupristin and dalfopristin have only modest in vitro antibacterial activity. When dosed together in a fixed 30:70 weight-to-weight ratio, however, a synergistic effect creates an antimicrobial activity 8 to 16 times greater than the components alone. Quinupristin-dalfopristin is administered intravenously and has a half-life of 1 to 2 hours. Despite the short half-life, the extended postadministration effect and bacterial growth inhibition at sub-MIC concentrations allow for a dosing schedule of every 8 to 12 hours.

Quinupristin-dalfopristin is indicated for treatment of methicillin-resistant *Enterococcus* and VRE as well as vancomycin-resistant *S aureus*. In contrast, quinupristin-dalfopristin is particularly ineffective against VRE, which comprises more than 80% of clinical

enterococcus isolates. The resistance of *E faecalis* to quinupristin-dalfopristin is derived from an efflux pump, conferring an intrinsic resistance [50].

One study examined the in vitro efficacy of quinupristin-dalfopristin, linezolid, and vancomycin against coagulase-negative *Staphylococcus*, given its increasing resistance to fluoroquinolones. One hundred percent of 35 coagulase-negative *Staphylococcus* isolates were susceptible to quinupristin-dalfopristin, linezolid, and vancomycin, whereas 76.5% and 74.2% were susceptible to moxifloxacin and gatifloxacin, respectively [51]. For the reasons noted previously, in a study of endophthalmitis caused by *E faecalis,* all the isolates were resistant to quinupristin-dalfopristin and were susceptible to vancomycin and linezolid [52].

Antivirals

Acyclovir, valacyclovir, and famciclovir

Acyclovir is the "gold standard" for the treatment and prophylaxis of herpes simplex virus (HSV) and herpes zoster virus (HZV) infections. Acyclovir is the mainstay of treatment for herpes zoster ophthalmicus and can be used systemically in the treatment of HSV epithelial keratitis. (Acyclovir ointment is not approved by the FDA for use in the United States.) Acyclovir, 400 mg, administered twice a day was also shown to decrease the recurrence of ocular and nonocular HSV over a 12-month treatment period and a 6-month drug-free follow-up period [53]. Oral acyclovir has few side effects and is available generically but has a short half-life and requires frequent (five times a day) dosing.

Valacyclovir is a prodrug of acyclovir and can be administered two or three times a day for treatment and once a day for prophylaxis regimens. After oral administration, it is rapidly and almost completely converted into acyclovir and has a bioavailability three to five times greater than acyclovir. The bioavailability of acyclovir is 20% and 12% after an oral dose of 200 mg and 800 mg, respectively [54]. Oral valacyclovir, 1000 mg, has a bioavailability of 54%, resulting in plasma levels similar to those achieved with intravenous dosing of acyclovir [55]. Corneal concentrations of acyclovir are directly correlated with plasma levels, and the concentration of acyclovir in the anterior chamber is double after oral valaciclovir dosing compared with oral acyclovir [56].

Given the improved bioavailability of valacyclovir, investigators have compared it with acyclovir for treatment of HZV as well as treatment and prophylaxis of HSV. Twice-daily dosing of valacyclovir, 1000 mg, has been shown to be as effective as dosing five times a day of acyclovir, 200 mg, for treatment of genital HSV [57], and once-daily administration of valacyclovir, 500 mg, has been shown to decrease the risk of transmission of genital HSV [58]. Studies have shown that valacyclovir is effective as a primary treatment for HZV and may accelerate the resolution of herpes zoster–related neuralgia [59,60]. Colin and colleagues [56] conducted a multicenter, randomized, double-masked study and reported that valacyclovir, 500 mg, administered three times a day is as effective as acyclovir, 800 mg, administered five times a day in preventing the ocular complications of herpes zoster ophthalmicus.

Famciclovir is a prodrug of penciclovir that has also been shown to be as efficacious as valacyclovir in treatment of HZV. Patients receiving famciclovir, 500 mg, three times a day had a similar time to resolution of clinical symptoms of HZV and postherpetic neuralgia as patients given valacyclovir, 500 mg. The side effect profile of the two medications is similar [61]. Famciclovir has also been shown to be efficacious in suppressing outbreaks of recurrent genital HSV [62].

Valacyclovir and famciclovir are good alternatives to acyclovir in the treatment of HZV and the treatment and prophylaxis of HSV, given the increased bioavailability, equal efficacy, and decreased frequency of dosing; however, the cost of valacyclovir and famciclovir remains higher than that of the generic acyclovir.

Valganciclovir

Valganciclovir was approved by the FDA in 2001 and has supplanted ganciclovir in the oral treatment of cytomegalovirus (CMV) retinitis. Valganciclovir is a prodrug and is rapidly converted to ganciclovir when administered orally. Oral bioavailability is high (approximately 60%), and a 900-mg dose provides serum levels equivalent to a 5-mg/kg dose of intravenous ganciclovir.

Before valganciclovir, standard therapy for CMV consisted of induction therapy with intravenous ganciclovir, foscarnet, or cidofovir, followed by oral or intravenous maintenance therapy. Intravenous ganciclovir for induction therapy was dosed at a rate of 5 mg/kg every 12 hours for 14 to 21 days, followed by dosing at 5 mg/kg every day for long-term maintenance. High-dose oral ganciclovir, 4500 to 6000 mg each day, is nearly as effective as intra-

venous dosing, possibly with fewer side effects. Without long-term maintenance therapy, most immunocompromised patients have a disease relapse within 30 days of induction therapy [63].

Oral valganciclovir dosed 900 mg twice a day is suitable for induction therapy because therapeutic serum levels can be achieved. In a randomized and controlled trial, Martin and coworkers [64] found that oral valganciclovir, 900 mg, administered twice daily for 3 weeks was as effective as intravenous ganciclovir, 5 mg/kg, administered once daily for induction therapy. Maintenance therapy consists of valganciclovir, 900 mg, administered every day [65].

Oral ganciclovir requires dosing three times a day (with as many as 12 pills per day) and has low bioavailability (approximately 6%–9%), making it unsuitable for induction therapy. The advantage of valganciclovir is the oral dosing as compared with the intravenous route of administration of other anti-CMV therapies. Patients requiring chronic intravenous anti-CMV therapy need placement of an indwelling catheter or daily intravenous infusions. Because these patients are most often severely immunocompromised, the risk of sepsis with indwelling intravenous access is increased [64].

Also, for patients on oral maintenance therapy, valganciclovir has a higher level of systemic distribution compared with ganciclovir, thus decreasing the risk of resistance. The cost of valganciclovir also provides savings over intravenous administration of ganciclovir. Two of the most serious side effects of valganciclovir are neutropenia and anemia. If the immune system is not restored with highly active antiretroviral therapy (HAART), CMV may become resistant to valganciclovir, as with other anti-CMV therapies [65].

Patients with HIV often have CMV retinitis with minimal inflammation. The reconstitution of the host immune system with HAART may allow discontinuation of anti-CMV medications. Some of these patients experience immune recovery uveitis and vision loss from macular edema. In a small (5 patients) open-label study, patients with immune recovery uveitis were treated with valganciclovir, 900 mg, once per day for 3 months. Average vision improved from a baseline of $20/80^{+3}$ to $20/50^{+4}$ after 3 months of therapy and decreased to $20/63^{+4}$ 3 months after cessation of treatment. This study suggests that valganciclovir might be beneficial in immune recovery uveitis, but this possibility requires verification from a larger double-masked study [66]. Case reports have been published that discuss the use of valganciclovir in the treatment of acute retinal necrosis [67] and progressive outer retinal necrosis [68].

Antifungals

Fungal keratitis can be difficult to diagnose and treat because of the challenge of identifying characteristic clinical signs and the difficulty in culturing fungal species. Fungal endophthalmitis is another condition that is vision threatening. Exogenous fungal endophthalmitis can occur from trauma, surgery, or contiguous spread of a fungal infection to ocular structures. Endogenous fungal endophthalmitis occurs primarily in immunocompromised patients and is usually attributable to systemic fungemia. Yeasts, such as *Candida albicans*, are most common. The most common filamentous fungus in endogenous endophthalmitis is *Aspergillus* [69].

Voriconazole

Voriconazole was approved by the FDA in 2002 for the treatment of invasive aspergillosis and infections from *Scedosporium apiospermum* (the asexual form of *Pseudallescheria boydii*) and *Fusarium* species in patients intolerant or refractory to other treatments. Voriconazole is a triazole antifungal agent, a synthetic derivative of fluconazole, and is available in oral and intravenous preparations. Voriconazole has a 96% oral bioavailability and reaches peak plasma concentrations in 2 to 3 hours after oral dosing [70].

The most common side effect, seen in up to 30% of patients, is a reversible visual disturbance [70]. The visual side effects include photopsias, blurry vision, changes in color vision, and photophobia. Symptoms usually occur 30 minutes after administration and during the first week of therapy. Spontaneous resolution usually occurs within 30 minutes after the initial onset. There are no known long-term ocular side effects of voriconazole. Studies in dogs have not found any structural changes in the retina or visual pathways from voriconazole administration [69]. Skin reactions, including rash, photosensitivity, facial erythema, cheilitis, and elevations in liver enzymes, are the other most common side effects [70]. The standard dosage of oral voriconazole is 200 mg administered every 12 hours. A loading dosage of 400 mg administered every 12 hours for the first day may be used [69].

Marangon and colleagues [71] investigated the causes of fungal keratitis and endophthalmitis in south Florida and the in vitro efficacy of voriconazole against these microbes. Of 421 positive corneal cultures, 82% were attributable to mold and 18% were from yeast. *Fusarium* species were the most common (49%), followed species of *Candida* (17%),

Table 11
Range (and average) of minimal inhibitory concentration of 90% (mg/mL) values for fungal isolates

Isolate	Amphotericin B	Fluconazole	Intraconazole	Ketoconazole	Voriconazole
Aspergillus sp (4 total)	1–2 (1.5)	>256	0.256–1 (0.6)	2–4 (3)	0.128–0.5 (0.35)
Paecilomyces sp (1 total)	2	>256	>16	>16	4
Fusarium sp (9 total)	1–2 (1.5)	>256	>16	2 to >16	0.5–4 (1.8)
Candida sp (20 total)	0.256–0.5 (0.47)	0.12–4 (0.63)	0.016–0.256 (0.08)	0.008–0.128 (0.018)	0.008–0.064 (0.02)

Data from Marangon FB, Miller D, Gianconi JA, et al. In vitro investigation of voriconazole susceptibility for keratitis and endophthalmitis fungal pathogens. Am J Ophthalmol 2004;137(5):823.

Curvularia (8%), *Aspergillus* (7%), *Paecilomyces* (5%), and *Colletotrichum* (3%). The most common isolates from 103 culture-positive cases of fungal endophthalmitis were *Candida* species (56%), *Aspergillus* (23%), *Fusarium* (5%), *Paecilomyces* (3%), and *Phialophora* (2%). Every fungal isolate tested was found to be sensitive to voriconazole in vitro. Voriconazole was shown to have a lower MIC_{90} than fluconazole, itraconazole, and ketoconazole for all isolates and a lower MIC_{90} than amphotericin B for *Aspergillus* and *Candida* (Table 11).

Hariprasad and coworkers [69] found that after two doses of oral voriconazole, 400 mg, administered 12 hours apart, aqueous and vitreous concentrations were 1.13 ± 0.57 and 0.81 ± 0.31, respectively, which were greater than the MIC_{90} for all mycotic species tested except *Fusarium* species (Table 12). Aqueous and vitreous concentrations of voriconazole were 53.0% and 38.1% of plasma levels, respectively. In a rodent model, intravitreal voriconazole at concentrations up to 25 μg/mL were shown to cause no electroretinographic or histologic changes [72].

Table 12
In Vitro susceptibilities of voriconazole showing minimal inhibitory concentration of 90%

Organism	Concentration (μg/mL)
Yeast and yeast-like species	
Candida albicans	0.06
Candida parapsilosis	0.12–0.25
Candida tropicalis	0.25 to >16[a]
Cryptococcus neoformans	0.06–0.25
Moniliaceous molds	
Aspergillis fumigatus	0.50
Fusarium species	2.0–8.0
Paecilomyces lilacinus	0.50
Dimorphic fungi	
Histoplasma capsulatum	0.25
Dematiaceous fungi	
Curvularia species	0.06–0.25
Scedosporium apiospermum	0.50

[a] Typically susceptible to voriconazole, except for a single isolate with a concentration of antibiotic needed to inhibit 90% of a bacterial isolate >16.0 μg/mL.
Data from Breit SM, Hariprasad SM, Mieler WF, et al. Management of endogenous fungal endophthalmitis with voriconazole and caspofungin. Am J Ophthalmol 2005; 139(1):135–40.

There are several published reports of successful treatment of refractory fungal keratitis and endophthalmitis with voriconazole. Breit and colleagues [73] reported a case series of five patients who developed *Candida* endophthalmitis and were successfully treated with intravenous and oral voriconazole, caspofungin, or both. Granados and coworkers [74] published the report of a 70-year-old woman with diabetes and persistent corneal ulceration from *C albicans* who progressed to perforation despite topical amphotericin B and oral itraconazole. After emergent placement of an amniotic membrane, the infection was successfully treated with intravenous voriconazole. Kim and colleagues [75] described a case of a 65-year-old woman with *Aspergillus fumigatus* scleritis and an epibulbar abscess from a scleral buckle infection that had been refractory to oral and topical amphotericin B, itraconazole, and ketoconazole. The infection resolved after stopping prior therapy and instituting oral voriconazole, 200 mg, administered twice daily. Reis and coworkers [76] reported a patient with *Fusarium solani* keratitis who developed fungal endophthalmitis. The patient was refractory to other antifungals and responded to intracameral, topical, and systemic voriconazole.

Other triazoles

Posaconazole is an analogue of itraconazole and is currently in clinical trials. In vitro studies show that it has broad-spectrum activity against *Aspergillus*, *Candida*, *Cryptococcus neoformans*, *Trichosporon*, *Zygomycetes*, and dermatophytes [70]. Sponsel and

colleagues [77] reported the case of an immunocompetent contact lens wearer who developed *F solani* keratitis. The infection spread to the anterior chamber despite aggressive therapy with topical and intravenous amphotericin B as well as topical natamycin and ketoconazole. Cultures showed that the *Fusarium* was resistant to amphotericin, and the patient was started on topical and oral posaconazole. The patient had clinical signs of improvement of the keratitis after 1 week and no evidence of the infection after 3 months. Ravuconazole is chemically similar to fluconazole and is still in clinical trials [70].

Echinocandins

Caspofungin is an antifungal of the echinocandin class, and the first of its type to be approved by the FDA, receiving clearance in 2001. This class of medications targets the fungal cell wall, which is composed of β(1-3)-D glucan, mannan, and chitin, which have no human analogue, allowing for selective antifungal toxicity. It is indicated for refractory invasive aspergillosis. Caspofungin has in vitro fungicidal action against *Aspergillus* and *Candida* species, including *C albicans, Candida tropicalis*, and *Candida glabrata*. In vitro studies indicate that caspofungin may be active against biofilms associated with external device-related *Candida* infections. Caspofungin is administered intravenously, and the most frequent side effects are fever, phlebitis, headache, and rash [70].

Caspofungin was examined in a rabbit model of *Candida* keratitis, and the keratitis was noted to be halted in the treatment group versus progression of infection in the control group [78]. As discussed previously, Breit and colleagues [73] reported a case series of patients with fungal endophthalmitis that was refractory to other antifungals who were treated with voriconazole and caspofungin, with excellent results. Anidulafungin and micafungin are antifungals of this class still in clinical trials [70].

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