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Antibacterial agents for ocular therapeutics

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Ocular bacterial infections of animals take a variety of forms. The eyelid, external ocular surface, anterior segment, posterior segment, and orbit are all frequent targets. Effective management of ocular bacterial infections requires specific identification of the offending organism(s) combined with knowledge of the mechanisms of action and the therapeutic characteristics of available antibiotics [1–4].

Guidelines for effective antibacterial therapy

Several factors must be considered when selecting appropriate antibacterial therapy. The animal's history and clinical signs must be assessed to establish a tentative diagnosis, and the clinician must postulate the most likely causative organism. Therapy with one or several agents can be based on this information. For serious or resistant infections, culture and cytology of ocular discharge, aqueous humor, or vitreous may be required for tailored antibiotic therapy.

The clinician should establish a specific and accurate clinical and laboratory diagnosis. An antibacterial drug should be selected that is within the expected or proven scope of sensitivity of the offending microorganism(s). If possible, the least toxic antibacterial drug administered by the most effective and safest route (s) should be selected. Adequate levels of the drug must be established and maintained at the site of the infection. Appropriate frequency, concentration, or dosage of the selected agent must be maintained. Infections must be treated for an appropriate length of time, and indicated proof of organism(s) eradication (eg, follow-up cultures) should be sought. Finally, drug therapy may be augmented with surgical or other medical procedures (eg, conjunctival flap) to assure the functional survival of the ocular compartment involved.

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Although the spectrum of types of bacteria that are primarily pathogenic for an animal's eyes is relatively large, the number of bacterial species that can infect the eye as opportunists is vast. In addition to the commonly considered gram-positive and gram-negative bacteria, *Rickettsia* and *Chlamydophila* are important ocular pathogens of animals. They mimic viruses in that they are intracellular parasites that multiply within other living cells. Rickettsiae are normally harmless parasites of lice, ticks, and mites but are potentially pathogenic to people and animals when they are transmitted by infected ticks. *Chlamydophila* is transmitted through direct contact with infected animals and has a relatively limited species distribution of pathogenicity, including cats and small ruminants. Mycobacteria are relatively uncommon ocular pathogens in companion animals.

Bacteria may become resistant to the antimicrobial drugs used to treat infections. Resistance results from chromosome mutation as well as from extrachromosomal plasmid transfer between resistant and susceptible organisms. Spontaneous chromosomal mutations occur naturally in bacterial populations. Treatment with antibacterial agents may allow drug-resistant mutants to multiply quickly. Plasmids carry mutated genes associated with development of resistance. They can be easily transferred between bacteria. Drug resistance may take several forms, but the most common form involves bacterial production of enzymes that inactivate antimicrobial drugs.

Organism patterns of resistance and susceptibility to antimicrobial therapy are potentially critical to successful antibacterial agent selection and use. In vitro susceptibility testing has its limitations, however. Minimum inhibitory concentration (MIC) is directly compared with the concentration of antibacterial drug obtainable in the blood to determine the resistance or susceptibility. Under some circumstances, organisms may be susceptible to higher concentrations of drugs when administered therapeutically than are commonly used to establish MICs.

Failure of antibacterial therapy should be evaluated systematically. Antimicrobial resistance, inaccurate or nonspecific diagnosis, inadequate drug dosage, and owner noncompliance are common causes. A normal immune response of the patient is considered optimal to facilitate eradication of organisms not affected by antibiotic therapy; immunosuppressed individuals may be incapable of mounting an adequate response. Failure to use adjunctive supportive procedures, such as conjunctival flaps and corneal grafts, early enough or at all may explain failure of survival of infected eyes in spite of accurate diagnosis and effective antimicrobial therapy.

Antibacterial agents

Differences between bacterial and host cells form the basis for potential toxicity of available antibacterial drugs. Bacteria have unique cell walls not

found in host animal cells that are necessary for the structural integrity of the organisms.

The mechanisms of action of available antibacterial agents for ocular therapy fall into four categories:

1. Those that act against the cell wall
2. Those that act against the bacterial cytoplasmic membrane
3. Drugs that affect intermediary metabolism of bacteria
4. Drugs that block or alter bacterial DNA synthesis

Drugs that affect cell wall synthesis

Penicillins, cephalosporins, bacitracin, and vancomycin affect cell wall synthesis.

Penicillins

Pharmacology

Penicillins contain the common nucleus consisting of a thiazolidine ring with a β-lactam ring connected to a side chain. The latter is necessary for biologic activity. Side chains to these two rings determine the antibacterial spectrum, susceptibility to gastric acid and to β-lactamase enzymes, and pharmacokinetic properties. The presence of a β-lactam ring is responsible for the antibacterial activity of all penicillins.

Clinical Uses

The penicillins are effective against gram-positive bacteria. The two most important drugs in this category are penicillin G and penicillin V. Penicillin G is unstable in the presence of gastric acid, so oral therapy limits its absorption. Penicillin V, which is not inactivated by gastric acid, may be used instead. Both penicillin G and B are susceptible to β-lactamases or penicillinases. Because most strains of *Staphylococcus aureus* and many strains of *Staphylococcus epidermidis* produce these enzymes, these drugs are not effective against these gram-positive bacteria. In addition, the varidans group of streptococci is capable of developing resistance to penicillin by the development of altered penicillin-binding proteins that reduce an affinity for penicillin.

Topical use of penicillins for treatment of external eye disease is limited by their narrow spectrum and the high incidence of allergic reaction to these drugs.

Penicillins resistant to penicillinase

Methicillin, oxacillin, cloxacillin, dicloxacillin, and nafcillin are not susceptible to penicillinases. Their specific use is directed at strains of *S aureus* and *S epidermidis* that produce penicillinase.

Penicillins with extended spectrum of activity

Ampicillin and amoxicillin are produced as modifications of the basic penicillin structure with a broader spectrum of activity than penicillin; however, both are inactivated by penicillinase. The addition of a β-lactamase inhibitor to penicillin protects the penicillin component from inactivation. Lactamase inhibitors include clavulanate, clavulanic acid, sulbactam, and tazobactam. These are used in fixed-ratio combinations with penicillins susceptible to enzymatic inactivation when administered alone.

Penicillins with antipseudomonal activity

Carbenicillin, mezlocillin, piperacillin, and ticarcillin have significant activity against *Pseudomonas aeruginosa* and certain *Proteus*, *Enterobacter*, and *Acinetobacter* sp, genera that are not susceptible to most other penicillins. Ticarcillin or piperacillin is commonly used with an aminoglycoside topically and subconjunctivally for the treatment of bacterial corneal ulcers caused by *Pseudomonas* and some other gram-negative rods.

Cephalosporins

Pharmacology

Cephalosporins, like penicillins, contain a β-lactam ring that bestows antimicrobial activity. Thus, cephalosporins and penicillins have the same basic mechanism of action. Acquired resistance to cephalosporins occurs by drug inactivation by β-lactamases. The specific β-lactamases produced by *S aureus* are true penicillinases and do not affect cephalosporin activity. Gram-negative bacteria produce β-lactamases that inactivate many of the cephalosporins. The addition of variable side chains through the cephalosporin nucleus has created a large family of cephalosporin antibiotics. These are typically referred to as first-, second-, or third-generation compounds based on their clinical uses and activity spectrum. Compared with first-generation cephalosporins, third-generation cephalosporins generally have a broader gram-negative spectrum, poorer efficacy against gram-positive organisms, and greater effectiveness against resistant organisms as well as being more expensive. The characteristics of the newer cephalosporins are less distinctly different.

Clinical uses of cephalosporins

First-generation cephalosporins. Cefazolin, cephalexin, and cefadroxil are first-generation cephalosporins. All are effective against gram-positive bacteria, but their activity against gram-negative bacteria is relatively modest. They are sensitive to many of the β-lactamases produced by gram-negative bacteria.

Cefazolin may be used to treat bacterial corneal ulcers as part of a broad-spectrum approach in combination with an aminoglycoside or

fluoroquinolone, such as ciprofloxacin. It is used because its spectrum of activity includes gram-positive cocci, including penicillin-resistant staphylococci. Clinical response is variable in infections caused by the varidans group of streptococci. It is not available as an ophthalmic preparation; cefazolin is administered topically as a specially prepared solution or subconjunctivally.

Second-generation cephalosporins. Cefamandole, cefaclor, cefprozil, cefoxitin, and cefuroxime are second-generation cephalosporins. They are more active against gram-negative enteric bacteria than first-generation drugs but much less effective than third-generation agents. These drugs have found limited use in veterinary ophthalmic practice.

Third-generation cephalosporins. Ceftriaxone, cefixime, cefoperazone, ceftazidime, ceftibuten, cefdinir, and cefepime are third-generation cephalosporins. Compared with first-generation analogues, they are less active against gram-positive bacteria but much more active against gram-negative organisms. Ceftazidime, in particular, has excellent activity against gram-negative bacteria, including *P aeruginosa*. In the treatment of endophthalmitis, ceftazidime has been suggested as an alternative for intravitreal amikacin to cover gram-negative organisms, including *P aeruginosa*. It has a high therapeutic index with a lower risk of retinal toxicity than amikacin.

These drugs are much more resistant to β-lactamase activity than the first-generation drugs. They are useful for treating gram-negative infections with organisms that produce β-lactamase or are resistant to aminoglycosides.

Bacitracin

Pharmacology

Bacitracin inhibits cell wall synthesis of bacteria by a different mechanism than do the β-lactam antibiotics. Most gram-positive bacteria, including streptococci and staphylococci, are susceptible to bacitracin.

Clinical use

Because of its systemic renal toxicity, bacitracin is rarely used parenterally. It is primarily used topically to treat skin and mucous membrane infections caused by gram-positive organisms. Only a few of these bacteria have become resistant to it. Bacitracin is available in topical preparations alone and in fixed combination products. Because it is unstable in solution, it is available only as an ointment. By judicious selection of companion drugs like neomycin and polymyxin B, inclusion of bacitracin can produce broad complementary antibacterial spectra covering most common ocular pathogens. Bacitracin acts primarily against gram-positive bacteria, whereas polymyxin B is most effective against gram-negative bacteria. Neomycin, likewise, targets many gram-negative bacteria.

Vancomycin

Pharmacology

Vancomycin is active against gram-positive cocci, including *Streptococcus*, *Staphylococcus*, *Clostridium*, and *Corynebacterium*.

Clinical uses

Use of vancomycin is reserved for serious infections for which less toxic antibiotics are not indicated, not effective, or not tolerated. Vancomycin is an appropriate alternative to penicillins or cephalosporins for serious infections caused by staphylococci and streptococci. Because of its broad spectrum of activity against gram-positive bacteria, including methicillin- and cephalosporin-resistant staphylococci, it is recommended for intravitreal, topical, and subconjunctival treatment of bacterial endophthalmitis.

Drugs affecting the cytoplasmic membrane

Polymyxin B and gramicidin affect the bacterial cytoplasmic membrane.

Polymyxin B

Pharmacology

Many compounds affect bacterial cytoplasmic membranes; however, most are relatively toxic. Polymyxin B's selective toxicity makes it useful for therapy. It is a surfactant that disrupts the osmotic integrity of bacterial cell membranes.

Clinical uses

Polymyxin B is effective against gram-negative bacteria in combination with other antibacterial drugs (eg, neomycin). It is commonly and appropriately used for bacterial infections of the conjunctiva and eyelids.

Gramicidin

Gramicidin is effective against gram-positive bacteria. Gramaside replaces bacitracin in some fixed combination antimicrobial solutions used topically for eye infections.

Drugs affecting protein synthesis

Aminoglycosides, tetracyclines, and macrolide antibiotics as well as the individual drugs clindamycin and chloramphenicol affect bacterial protein synthesis. Aminoglycosides are potentially effective against many gram-negative bacteria, including *P aeruginosa*, *Proteus*, *Klebsiella*, *Escherichia coli*, *Enterobacter*, and *Serratia*. They are also effective against many strains of staphylococci. Neomycin, in contrast to other aminoglycosides, has

a broad spectrum of activity against gram-positive as well as gram-negative bacteria. An important exception to this spectrum of activity is that neomycin is ineffective against *Pseudomonas*.

Aminoglycosides

Pharmacology

Neomycin, gentamicin, tobramycin, and amikacin are aminoglycosides. They bind to bacterial ribosomes and thus inhibit bacterial protein synthesis. Widespread resistance to the aminoglycosides occurs among gram-negative bacteria. This resistance occurs because of alteration of bacterial ribosomes, decreased antibiotic uptake, or enzymatic inactivation of the drugs. The latter is the most common type of resistance and results in modification of the applied drug, which becomes inactive and antagonistic toward further uptake of active drug by the affected cell. Many different inactivating enzymes are produced by gram-negative bacteria. Cross-resistance involving aminoglycosides is often complete (eg, bacteria resistant to gentamicin are usually also resistant to tobramycin). Known resistance patterns are only helpful in initial selection of an aminoglycoside drug. Specific sensitivity to each aminoglycoside must be determined for each pathogen. Note that penicillins may inactivate aminoglycosides if mixed together in the same solution for injection or used together for topical application. They must be administered separately.

Clinical uses

Neomycin. Neomycin is most commonly administered topically, usually in combination with other antibiotics or corticosteroids. Topical application frequently results in sensitization to the drug: approximately 4% of human patients and an unknown proportion of animals develop contact dermatitis or conjunctivitis. Chronic use of topical preparations containing neomycin should be avoided for this reason.

Gentamicin. Gentamicin is a mainstay of therapy for serious gram-negative bacterial infections. Topical ophthalmic gentamicin has been used to treat many bacterial infections of the external eye, including conjunctivitis, blepharitis, and dacryocystitis. Gentamicin is also used as an antibiotic for the initial treatment of bacterial corneal ulcers. The drug strength (0.3%) in this commercially available ophthalmic solution, however, is considered inadequate for the initial treatment of serious bacterial keratitis. Solutions containing fortified concentrations (9–14 mg/mL) can be prepared from sterile products intended for parenteral use. Therapy with fortified gentamicin or tobramycin solution combined with a penicillinase-resistant cephalosporin is a useful initial treatment for serious bacterial keratitis pending identification of the infecting organism and its antibiotic susceptibility pattern. In people, an initial loading dose of fortified aminoglycoside at

a rate of one drop per minute for 5 minutes increases antibiotic concentrations in the cornea, followed by once-hourly applications.

Tobramycin. The indications for use of tobramycin in treatment of gram-negative infections are essentially the same as for gentamicin. Staphylococci are generally susceptible to tobramycin, whereas streptococci often are not. Bacteria resistant to tobramycin are usually also resistant to gentamicin, but the converse is not always true. For most strains of *Klebsiella*, *Enterobacter*, *E coli*, and *Serratia*, however, cross-resistance between gentamicin and tobramycin is common. Amikacin is usually effective in these instances. In vitro, tobramycin is more potent against *P aeruginosa* than gentamicin. Because of this, tobramycin is often preferred, especially when combined with an antipseudomonal penicillin, such as ticarcillin, for bacterial keratitis.

Amikacin. Amikacin, the first semisynthetic aminoglycoside, has been chemically modified to be protected from aminoglycoside-inactivating enzymes. Clinically, however, the treatment of susceptible organisms is apparently not superior to treatment with gentamicin or tobramycin. Amikacin has become a primary antibiotic for intravitreal injection along with vancomycin for the treatment of bacterial endophthalmitis because of its broad spectrum against resistant gram-negative organisms and its reduced toxicity.

Tetracyclines

Pharmacology

Tetracyclines are broad-spectrum antibacterial drugs with activity against gram-positive, gram-negative, aerobic, and anaerobic bacteria as well as *Spirochetes*, *Mycoplasma*, *Rickettsia*, *Chlamydophila*, and a few protozoa. Tetracycline analogues are classified as short-acting, intermediate-acting, and long-acting. Analogues in each category have generally similar patterns of bacterial susceptibility and resistance. Tetracyclines block protein synthesis within bacteria.

Clinical uses

Despite having a broad spectrum of activity, use of tetracyclines is limited because of the high frequency of bacterial resistance. Alternatively, they are the drugs of choice for a wide variety of infections caused by less common organisms, such as *Brucella*, *Rickettsia*, *Chlamydophila*, and *Bartonella*. Some ocular surface infections caused by susceptible organisms respond satisfactorily to topical tetracyclines. Many organisms, however, develop or already have resistance.

Macrolides

Erythromycin, clarithromycin, and azithromycin are the macrolide antibiotics.

Pharmacology

These drugs inhibit bacterial protein synthesis by binding to the bacterial 50S ribosomal subunit. Because they do not bind to mammalian ribosomes, their toxicity is low. Macrolides are potentially effective against gram-positive cocci, *Streptococcus*, *Staphylococcus*, gram-positive rods, *Mycoplasma*, *Rickettsia*, and *Chlamydophila*.

Erythromycin. Erythromycin is a widely used macrolide antibiotic for human external ocular infections because of its lack of toxicity and its good activity against offending organisms. Its use in veterinary practice has been limited.

Clarithromycin and azithromycin. Clarithromycin is a derivative of erythromycin well absorbed after oral administration. It is considered more active than erythromycin against *Chlamydophila*. It is not available as an ophthalmic formulation. Azithromycin is rapidly absorbed and widely distributed after oral administration. It has been recommended as therapy for feline chlamydial infection. Several extralabel dosage regimens have been anecdotally recommended (eg, 5 mg/kg once daily for 2 doses and then every third day for 5 doses, 5 mg/kg once daily for 5 doses followed by the same dose every 3 days for 5 doses).

Chloramphenicol

Pharmacology

Chloramphenicol binds bacterial ribosomes and blocks protein synthesis.

Clinical uses

Chloramphenicol is active against most gram-positive and gram-negative bacteria (*Rickettsia*, *Chlamydophila*, *Spirochetes*, and *Mycoplasma*). *P aeruginosa* is resistant. Chloramphenicol has the ability to cause fatal aplastic anemia in people, which strictly limits its usefulness for treatment of people and animals (because of potential human exposure). In human beings, indications for chloramphenicol use include severe infections caused by susceptible organisms not responsive to other drugs. Aplastic anemia has occurred in human patients after its topical ocular use. Because the potential for human exposure is inevitable if prescribed for animals, chloramphenicol's veterinary applications are severely limited.

Clindamycin

Pharmacology

Clindamycin binds to the 50S ribosomal subunit inhibiting protein synthesis in bacteria. It is active against most gram-positive and anaerobic gram-negative bacteria. It cannot be obtained as an ophthalmic preparation but is available as oral, intramuscular, and intravenous products.

Clinical uses

Clindamycin is often the drug of choice for treating anaerobic infections and ocular toxoplasmosis. It can cause serious or even fatal pseudomembranous colitis, at least in human beings.

Drugs affecting intermediary metabolism

The sulfonamides pyrimethamine and trimethoprim affect intermediary metabolic pathways of bacteria.

Sulfonamides

Pharmacology

The sulfonamides are broad-spectrum drugs effective against gram-positive and gram-negative bacteria as well as against *Chlamydophila*, *Actinomyces*, *Plasmodia*, and *Toxoplasma*. In general, they exert only a bacteriostatic effect; therefore, cellular and humoral immune mechanisms are potentially more important for eradicating bacterial infections when they are used than for some other antibiotic agents. Sulfonamides act by inhibiting bacterial synthesis of folic acid, which is required for synthesis of nucleic acid and protein. Sulfonamide inhibition has only a minimal effect on host cells. This inhibition can be reversed by several antagonistic compounds of which para-aminobenzoic acid (PABA) is the most prominent. Local anesthetics, such as procaine, tetracaine, and benoxinate (all esters of PABA), also antagonize these drugs in vivo and in vitro. Antibacterial action of sulfonamides is also inhibited by tissue breakdown products, blood, and pus. Thus, sulfonamide treatment is contraindicated for infections with marked suppuration. Acquired resistance to the sulfonamides is widespread; therefore, other agents have replaced them as first lines of therapy for all but a few major infections. Mechanisms of bacterial resistance include overproduction of PABA by bacteria, decreased enzyme affinity for the sulfonamide, decreased bacterial permeability, and an increased inactivation of the drug. Cross-resistance between sulfonamide drugs is frequent.

Clinical uses

Sulfonamides have been used to treat chlamydial diseases, but other antibiotics are now the first choice. Active toxoplasmosis is treated with either clindamycin alone or with oral sulfadiazine in combination with oral pyrimethamine. Topical ophthalmic preparations of sulfonamides include sulfacetamide and sulfasoxasole as well as the former in combination with prednisolone compounds. Although previously used extensively, they are rarely used today because of widespread resistance and availability of more effective drugs.

Pyrimethamine and Trimethoprim

Pharmacology

Pyrimethamine and trimethoprim are two 4-diaminapyrimidines that inhibit folic acid synthesis. They are synergistic when used in combination with the sulfonamides. The sulfonamides inhibit an early step in the synthesis of folic acid, and pyrimethamine and trimethoprim block a later step in the pathway.

Clinical uses

Trimethoprim has significant in vitro activity against gram-positive and gram-negative organisms, including *Staphylococcus*, *Streptococcus*, and gram-negative enterics. It is not, however, active against *Pseudomonas*. The combination of 0.1% trimethoprim and polymyxin B (10,000 U/mL) is available as a topical ophthalmic solution. This combination covers the gram-negative bacteria, including *Pseudomonas*.

Pyrimethamine is used in combination with sulfadiazine for treatment of toxoplasmosis.

Drugs affecting bacterial DNA synthesis

Fluoroquinolones (ciprofloxacin, ofloxacin, norfloxacin, enrofloxacin, orbifloxacin, and others) inhibit bacterial DNA synthesis and are structurally related to nalidixic acid.

Pharmacology

Fluoroquinolones interfere with DNA synthesis during bacterial replication by inhibiting DNA gyrase activity. Most of these drugs demonstrate MICs against gram-positive and gram-negative bacteria. Fluoroquinolone activity against mycobacteria and anaerobes is quite variable, however. Staphylococcal strains, including methicillin-resistant ones, are developing relatively high rates of clinical resistance to ciprofloxacin. *P aeruginosa*, *Klebsiella*, *Citrobacter*, *Enterobacter*, and *S epidermidis* are common pathogens that are developing resistance.

Clinical uses

Ciprofloxacin, ofloxacin, norfloxacin, and levofloxacin are available as topical ophthalmic solutions. Ciprofloxacin is also available as an ointment. Fluoroquinolones have greater efficacy and a broader spectrum of activity than some other antibacterial drugs, including bacitracin, erythromycin, tobramycin, and gentamicin, against ocular pathogens. Fluoroquinolones are active against *S aureus*, *S epidermidis*, *P aeruginosa*, and most other gram-negative bacteria. Topical ciprofloxacin is effective for bacterial conjunctivitis. It also may be used successfully to treat bacterial keratitis

Table 1
Commercially available ophthalmic antibacterial agents

Generic name	Trade name	Concentration ophthalmic solution (%)	Ophthalmic ointment
Individual agents			
Bacitracin	AK-Tracin	NA	500 U/g
	Available generically		
Chloramphenicol	Chloromycetin	0.5%	1%
	Chloroptic	0.5%	1%
Ciprofloxacin hydrochloride	Ciloxan	0.3%	0.3%
Erythromycin	Available generically	NA	0.5%
Gentamicin sulfate	Genoptic	0.3%	0.3%
	Gentacidin	0.3%	NA
	Gentak	0.3%	0.3%
	Available generically	0.3%	0.3%
Levofloxacin	Quixin	0.5%	NA
Norfloxacin	Chibroxin	0.3%	NA
Ofloxacin	Ocuflox	0.3%	NA
Sulfacetamide sodium	AK-Sulf	10%	10%
	Bleph-10	10%	10%
	Sulf-10, preservative-free droperettes	10%	NA
	Available generically	10%	10%
Tobramycin sulfate	AK-Tob	0.3%	NA
	Tobrex	0.3%	0.3%
	Tomycine	0.3%	NA
	Available generically	0.3%	NA
Mixtures			
Polymyxin B/ bacitracin zinc	AK-Poly-Bac	NA	10,000 U
	Polysporin		500 U/g
	Polytracin		
	Available generically		
Polymyxin B/ neomycin/bacitracin	AK-Spore	NA	10,000 U
	Neosporin		3.5 mg
	Polymycin		
	Available generically		400 U/g
Polymyxin B/neomycin/gramicidin	Neosporin	10,000 U	NA
	Polymycin	1.75 mg	
	Available generically	0.025 mg/mL	
Polymyxin B/trimethoprim	Polytrim	10,000 U	NA
	Available generically	1 mg/mL	

Abbreviation: NA, not available.

Data from Weisbecker CA, Fraunfelder FT, Rhee D, et al. Physician's desk reference for ophthalmic medicines 2003. 31st edition. Montvale (NJ): Medical Economics Company; 2002. p. 4.

Table 2
Concentrations and dosage of principal antibiotic agents

Drug name[a]	Topical	Subconjunctival	Intravitreal
Amikacin sulfate	10 mg/mL	25 mg	400 μg
Ampicillin sodium	50 mg/mL	50–150 mg	5 mg
Bacitracin zinc	10,000 U/mL	5000 U	—
Carbenicillin disodium	4–6 mg/mL	100 mg	250–200 μg
Cefazolin sodium	50 mg/mL	100 mg	2250 μg
Ceftazidime	50 mg/mL	100 mg	2000 μg
Ceftriaxone	50 mg/mL	—	—
Clindamycin	50 mg/mL	15–50 mg	1000 μg
Colistimethate sodium	10 mg/mL	15–25 mg	100 μ
Erythromycin	50 mg/mL	100 mg	500 μg
Gentamicin sulfate	8–15 mg/mL	10–20 mg	100–200 μg
Kanamycin sulfate	30–50 mg/mL	30 mg	500 μg
Methicillin sodium	50 mg/mL	50–100 mg	1000–2000 μg
Neomycin sulfate	5–8 mg/mL	125–250 mg	—
Penicillin G	100,000 U/mL	0.5–1.0 million U	300 U
Piperacillin	12.5 mg/mL	100 mg	—
Polymyxin B sulfate	10,000 U/mL	100,000 U	—
Ticarcillin disodium	6 mg/mL	100 mg	—
Tobramycin sulfate	8–15 mg/mL	10–20 mg	100–200 μg
Vancomycin hydrochloride[b]	20–25 mg/mL	25 mg	1000 μg

[a] Most penicillins and cephalosporins are physically incompatible when combined in the same bottle with aminoglycosides, such as amikacin, gentamicin, or tobramycin.

[b] Use discouraged by Centers for Disease Control and Prevention because of increased resistant organisms.

Modified from Weisbecker CA, Fraunfelder FT, Rhee D, et al. Physician's desk reference for ophthalmic medicines 2003. 31st edition. Montvale (NJ): Medical Economics Company; 2002. p. 6.

with a variety of pathogens. Studies of corneal penetration of topical application in human and canine eyes indicate that ofloxacin achieves the highest aqueous concentration [5]. Topical combined with intravenous ofloxacin achieves aqueous and vitreous levels that inhibit many common pathogens; thus, the drug may hold promise for treating intraocular infections. Norfloxacin is indicated for the treatment of bacterial conjunctivitis but not bacterial keratitis, because the commercially available concentration of norfloxacin has less ability to penetrate the cornea than ofloxacin. Levofloxacin recently became available as a 0.5% ophthalmic solution. It has high solubility compared with ciprofloxacin. It may have greater activity against *Streptococcus* species than ciprofloxacin or ofloxacin.

In veterinary practice, use of oral enrofloxacin has been associated with acute retinal degeneration in some treated cats, especially at doses higher than label recommendations; thus, caution is indicated in its selection for feline use. Topical use of fluoroquinolones has not been associated with retinal toxicity in cats.

Moxifloxacin and gatifloxacin will soon be available as topical ophthalmic preparations. Their advantage is even better intraocular

Table 3
Antibiotics in infusion fluid

Agent	Maximum nontoxic dose (μg/mL)	Agent	Maximum nontoxic dose (μg/mL)
Amikacin	10	Methicillin	20
Ceftazidime	40	Oxacillin	10
Clindamycin	9	Tobramycin	10
Gentamicin	8	Vancomycin[a]	30

[a] Use discouraged by Centers for Disease Control and Prevention because of increased resistant organisms.

Modified from Weisbecker CA, Fraunfelder FT, Rhee D, et al. Physician's desk reference for ophthalmic medicines 2003. 31st edition. Montvale (NJ): Medical Economics Company; 2002. p. 5.

penetration after topical use than can be obtained with currently available fluoroquinolones [6,7].

Routes of administration

Topically administered antibiotics are appropriate for external ocular infections, including the conjunctiva and cornea (Table 1). The addition of subconjunctival antibiotic administration is indicated for serious corneal as well as anterior segment infections (Table 2). Intravitreal antibiotic administration is potentially hazardous but indicated for bacterial endophthalmitis (see Table 2). Some cataract surgeons incorporate antibiotics into infusion fluid in phacoemulsification (Table 3).

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