Antimicrobial Agents in Ophthalmology

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2.1 Introduction

The US Food and Drug Administration has approved more new antibiotics in the past 20 years than all antibiotics discovered in the twentieth century. The recent proliferation of new antibiotics has made the selection more difficult [1–5]. The selection of an antibiotic depends on the clinical findings, the most likely causative organism, the laboratory confirmation, and the pharmacokinetics of the drug.

The purpose of this chapter is to put in the hands of the ophthalmologist a concise approach to the selection of topical or systemic antimicrobial agents in the management of infections of the eye. This would provide practical, concise, and objective information on antimicrobial agents used in the treatment of infections of the eye. The information is useful as a rapid reference for the eye care practitioner. The use of antibiotics in ocular infection can be preventive, preemptive, curative, or prophylaxis. The guidelines for the proper use of antimicrobial agents in ophthalmology are outlined (Table 2.1).

The dramatic decrease in the incidence of classic infectious diseases is due largely to, first, mass vaccination, which has eradicated certain infectious disease such as smallpox; second, the implementation of rigorous public health measures by many countries; and, third, the introduction of newly discovered antimicrobial agents. In the first decade of the twenty-first century, infectious diseases continue to be a serious cause of visual loss, mortality, and morbidity. We should not rest on the laurels we have won for overcoming the classic infections, but we should, rather, prepare ourselves to confront the microorganisms emerging from the degradation of our ecosystem as well as those bacteria that are becoming increasingly antibiotic resistant. Several new infectious agents have been recently identified as a cause of disease in man (Table 2.2).

Chemicals were used as early as the seventeenth century to treat infectious disease. Quinine was used for malaria, and emetine was used for amebiasis. Antibiotics, however, can cause harm as well as good. Erlich, in 1900 in Germany, introduced the concept of selective toxicity of chemicals, showing that it is possible to use an antibiotic that is toxic to the microorganism but does not harm the host. In 1929, Fleming recorded his observation that agar plates in his laboratory contaminated with *Penicillium* spp. were free of other bacteria such as staphylococci and went to discover penicillin. In 1935 in Germany, Domagk

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K. Tabbara et al. (eds.), *Ocular Infections*, Essentials in Ophthalmology,
DOI 10.1007/978-3-662-43981-4_2,

Table 2.1 Guidelines for the proper use of antibiotics for ocular infections

1. The use of antibiotics for treatment of ocular infections should be initiated whenever a patient has an infection which is microbial in nature and the organism is susceptible to the antibiotic prescribed
2. The patient's history and eye examination should be consistent with the diagnosis of microbial infection
3. Ocular specimens for stain, cultures, or molecular diagnosis (e.g., PCR) should be obtained before the initiation of therapy and sent immediately to the laboratory. The etiologic organism causing the infection should be identified
4. In serious infections, treatment may be started empirically before laboratory results are obtained
5. The selection of the antibiotic should be based on the susceptibility of the organisms, adverse effects, penetration into the affected tissue, and cost
6. Discrepancies between the results of the laboratory sensitivity tests and the patient clinical response should be carefully evaluated
7. Adverse effects from the use of the antibiotic (allergic or toxic) should be taken into account in the selection and administration of antibiotic agents' autotoxicity, nephrotoxicity, or hepatotoxicity. The antibiotic should be discontinued if an allergic or serious adverse reaction occurs after its use
8. Blood level monitoring of systemic antibiotics should be assessed whenever indicated
9. Duration of therapy is dependent on the nature of the infection and site of the infection but should not be less than 1 week
10. The route of antibiotics should be given at a dosage level that will allow penetration of the antibiotic into the desirable infected site within the safe margin and for the shortest period of time to eradicate the offending agent
11. The possibility of a superinfection should always be kept in mind when antibiotics are used for a prolonged period of time
12. The use of antibiotic combinations should be avoided unless the organism has not been cultured and the findings are highly suggestive of infectious etiology
13. Antibiotic prophylaxis in surgery should be used very carefully; the antibiotic used should cover both Gram-negative and Gram-positive organisms and be started just before surgery and discontinued immediately following surgery
14. Long-term use of antibiotics should be avoided

described sulfonamide, not only winning the Nobel Prize in 1939 but also launching a new era of antimicrobial agents. It was not until 1940, however, when Chain and Florey used penicillin in the treatment of *Streptococcus pneumoniae* infections, and that was the turning point in the management of infectious diseases.

Table 2.2 Newly discovered microbial pathogens

Disease	Cause
Cat scratch disease	*Bartonella henselae*
Pneumonia	Hanta virus
Kaposi's sarcoma	Human herpes simplex virus type 6
Autoimmune deficiency syndrome (AIDS)	Human immunodeficiency virus type 1 and type 2
T cell lymphoma	Human T cell lymphoma virus
Lyme disease	*Borrelia burgdorferi*
Whipple's disease	*Treponema whippelii*
Severe acute respiratory syndrome (SARS)	Corona virus
Middle East Respiratory Syndrome (MERS)	Corona virus
Avian influenza	H_5N_1 virus

Streptomycin was described in the late 1940s; tetracyclines were launched in the early 1950s, followed by chloramphenicol and later followed by lincomycin in the 1960s. Lincomycin was described from the systematic analysis of soil samples in Lincoln, Nebraska, in the United States and was named after the state's capital city, Lincoln. It was produced by a strain of *Streptomyces lincolnensis.* After this discovery, extensive soil sampling was conducted worldwide to isolate and identify antibiotic-producing organisms.

There are so many different types and generations of antibiotics. It is important, therefore, to identify those which are useful in ophthalmology and those that are not. It is of paramount importance to select the right antibiotic to treat ocular infection; fundamental to this is the identification of the organism responsible for the infection.

The initial selection of antibiotics for the treatment of ocular infections is based on the most frequently encountered organism, pharmacokinetics of the antibiotic, dosage, and cost.

The great stumbling blocks to safe and effective antibiotic therapy are resistance and toxicity, two factors which must always be taken into account when choosing an antibiotic. Cost is another factor and one that is often overlooked. It is important to be aware of the fact that some antibiotics are expensive. There have been

instances of patients receiving very expensive therapy when in fact the organism responsible for their infection was sensitive to much cheaper antibiotics. The combination of antibiotic agents may be used simultaneously in the following conditions:

(a) In a severe devastating vision-threatening ocular infection of unknown etiology and after lab tests have been initiated to determine a specific etiologic agent
(b) If an infection is caused by more than one organism
(c) The emergence of resistant strains of bacteria during the treatment
(d) In case of infections caused by organisms that are known to respond better to simultaneous use of more than one antibiotic such as *Toxoplasma* and *Acanthamoeba*
(e) Organisms not cultured and the clinical findings are highly suggestive of infectious etiology

2.2 Mechanism of Action

Although antibiotics can be described as being either bacteriostatic or bactericidal, this is a less useful classification than the one which is based on the drug mechanism of action, namely, how and where they affect the target organism. Under this system of classification, the first group of antibiotics inhibits synthesis of the cell wall, the second group inhibits the cell membrane, the third group affects ribosomal function and protein synthesis, and the fourth group affects nucleic acid synthesis.

Topical antimicrobial agents used in ocular infections are listed in Table 2.3. The antimicrobial agents that can be compounded for the treatment of ocular infections for topical, subconjunctival, intravitreal, and intravenous are summarized in Table 2.4. Antibiotics that are used for bacterial (Table 2.5), fungal (Table 2.6), viral infections (Table 2.7) are also listed.

Table 2.3 Commercially available topical ophthalmic antibacterial agents

Generic name	Trade name	Concentration	
		Ophthalmic solution	Ophthalmic ointment
Individual agents			
Bacitrin		Not available	500 units/g
Besifloxacin	Besivance	0.6 %	Not available
Ciprofloxacin hydrochloride	Ciloxan	0.3 %	0.3 %
Erythromycin		Not available	0.5 %
Gatifloxacin	Zymar, Tymer	0.3 %	Not available
Gentamicin sulfate	Genoptic, Garamycin	0.3 %	0.3 %
Lomefloxacin	Okacin		
Levofloxacin	Iquix	1.5 %	Not available
	Quixin	0.5 %	Not available
Moxifloxacin	Vigamox	0.5 %	Not available
Ofloxacin	Oflox, Optiflox	0.3 %	Not available
Sulfacetamide	Bleph-10	10 %	Not available
	Sulf-10 (15 mL) or preservative-free	10 %	Not available
	Generic	10 %	10 %
Tobramycin sulfate	Tobrex	0.3 %	0.3 %
	Generic	0.3 %	Not available
Tosufloxacin	Ozex	0.3 %	Not available
Mixtures			
Chloramphenicol eyedrops and ointment	Generic	0.5 %	
Polymyxin B/bacitracin zinc	AK-Poly-Bac Polysporin Polycin-B Generic	Not available	10,000 units – 500 units/g

(continued)

Table 2.3 (continued)

Generic name	Trade name	Concentration	
		Ophthalmic solution	Ophthalmic ointment
Polymyxin B/neomycin/bacitracin	Neosporin Generic	Not available	10,000 units – 3.5 mg – 400 units/g
Polymyxin B/neomycin/gramicidin	Neosporin Generic	10,000 units – 1.75 mg – 0.025 mg/mL	Not available
Polymyxin B/trimethoprim	Polytrim Generic	10,000 units – 1 mg/mL	Not available

Table 2.4 Compounding of major antibiotics for the treatment of ocular infections

		Route of administration		
Drug name[a]	Topical	Subconjunctival	Intravitreal	Intravenous[b]
Amikacin sulfate	10 mg/mL	25 mg	400 μgm	15 mg/kg daily in 2–3 doses
Ampicillin sodium	50 mg/mL	50–150 mg	5 mg	4–12 g daily in 4 doses
Bacitracin zinc	10,000 units/mL	5,000 units	–	–
Cefazolin sodium	50 mg/mL	100 mg	2,250 μgm	2–4 g daily in 3–4 doses
Ceftazidime	50 mg/mL	100 mg	2,000 μgm	1 g daily in 2–3 doses
Ceftriaxone	50 mg/mL	–	–	1–4 g daily in 1–2 doses
Clindamycin	50 mg/mL	15–50 mg	1,000 μgm	900–1,800 mg daily in 2–3 doses
Colistimethate sodium	10 mg/mL	15–25 mg	100 μgm	2.5–5 mg/kg daily in 2–4 doses
Erythromycin	50 mg/ml	100 mg	500 μgm	–
Gentamicin sulfate	8–15 mg/ml	10–20 mg	100–200 μgm	3–5 mg/kg daily in 2–3 doses
Imipenem/cilastatin sodium	5 mg/ml	–	–	2 g daily in 3–4 doses
Kanamycin sulfate	30–50 mg/ml	30 mg	500 mg	–
Neomycin sulfate	5–8 mg/ml	125–250 mg	–	–
Penicillin G	100,000 units/mL	0.5–1.0 million units	300 units	12–24 million units daily in 4–6 doses
Piperacillin	12.5 mg/mL	100 mg	–	–
Polymyxin B sulfate	10,000 units/mL	100,000 units	–	–
Ticarcillin disodium	6 mg/mL	100 mg	–	200–300 mg/kg daily 3 × in 4–6 doses
Tobramycin sulfate	8–15 mg/mL	10–20 mg	100–200 μgm	3–5 mg/kg daily in 2–3 doses
Vancomycin hydrochloride[c]	20–25 mg/mL	25 mg	1,000 μgm	15–30 mg/kg daily in 1–2 doses

[a]Most penicillins and cephalosporins are physically incompatible when combined in the same bottle with aminoglycosides such as amikacin, gentamicin, or tobramycin
[b]Adult doses
[c]Usage discouraged by CDC because of increased resistant organisms

2.3 Antibiotics That Inhibit Cell Wall Synthesis

Several antibiotics affect the cell wall of organisms including penicillins, cephalosporins, gramicidin, and bacitracin [6–17]. Bacterial survival can be compromised without a cell wall. The cell wall protects bacteria from the environmental noxious agents and maintains the intracellular milieu. The thickness of bacterial cell walls varies: Gram-positive bacteria have thick cell walls, and Gram-negative bacteria have thin cell walls. The internal osmotic pressure of Gram-positive organisms is higher than that in Gram-negative

Table 2.5 Bacterial keratitis therapy (initial therapy for bacterial keratitis)

Organism	Antibiotic	Topical dose	Subconjunctival dose
Gram(+) cocci	Cefazolin	50 mg/mL	100 mg in 0.5 mL
	Vancomycin[a]	50 mg/mL	25 mg in 0.5 ML
Gram(−) rods	Tobramycin	9–14 mg/mL	20 mg in 0.5 mL
	Ceftazidime	50 mg/mL	100 mg in 0.5 mL
	Fluoroquinolones	3 mg/mL	Not available
No organism or multiple types of organisms	Cefazolin with Tobramycin or Fluoroquinolones	50 mg/mL 9–14 mg/mL 3 mg/mL	100 mg in 0.5 mL 20 mg in 0.5 mL Not available
Gram(−) cocci	Ceftriaxone	50 mg/mL	100 mg in 0.5 mL
	Ceftazidime	50 mg/mL	
Mycobacteria	Amikacin	20 mg/mL	20 mg in 0.5 mL
	Azithromycin	1.5 mg/ml (0.15 %)	

[a]For resistant *Staphylococcus* species

Table 2.6 Antimicrobial agents for fungal keratitis

Generic (trade) name	Route	Dosage
Amphotericin B (Fungizone®)	Topical	0.1–0.5 % solution (most commonly 0.15 %); dilute with water for injection or dextrose 5 % in water
	Subconj.	0.8–1.0 mg
	Intravitreal	5 mcg
Liposomal amphotericin B	Intravenous	
Fluconazole (Diflucan®)	Oral	200 mg on day 1, then 100 mg daily in divided doses
		400 mg on day 1, then 200 mg daily in divided doses
Intravenous	IV	200–400 mg
Flucytosine (Ancobon®)	Oral	50–150 mg/kg daily 4 divided doses
Itraconazole (Sporanox®)	Oral	200–400 mg/kg daily
	Intravenous	200 mg IV twice a day for 4 doses, then 200 mg IV daily for 14 days
Ketoconazole (Nizoral®)	Oral	200–400 mg daily
Natamycin (Natacyn®)	Topical	5 % suspension
Voriconazole (Vfend®)	Oral	200 mg twice a day
	Intravenous	3–6 mg/kg every 12 h
	Intracorneal	25 µgm
	Topical	1 % eyedrops

Table 2.7 Antimicrobial agents for viral ocular infections

Generic (trade) name	Topical conc.	Intravit. dose	Systemic dosage
Trifluridine (Viroptic®)	1.0 %	–	–
Acyclovir sodium	–	24,000 µgm	Oral – *herpes simplex* keratitis: 200 mg 5 times daily for 7–10 days Oral – *herpes zoster ophthalmicus*: 600–800 mg 5 times daily for 10 days; IV therapy
Cidofovir (Vistide®)	–	–	IV – induction: 5 mg/kg constant infusion over 1 h administered once weekly for 2 consecutive weeks Maintenance: 5 mg/kg constant infusion over 1 h administered once every 2 weeks

(continued)

Table 2.7 (continued)

Generic (trade) name	Topical conc.	Intravit. dose	Systemic dosage
Famciclovir (Famvir®)	–	–	Oral – *herpes zoster ophthalmicus* 500 mg 3 times daily for 7 days
Fomivirsen (Vitravene®)	–	330 µgm	Every other week for 4 doses, then every 4 weeks. Contains 6.6 mg/mL, in a 0.25-ml vial
Foscarnet sodium (Foscavir®)	–	1 mg	IV – by controlled infusion only, either by central vein or by peripheral vein induction: 60 mg/kg (adjusted for renal function) given over 1 h every 8 h for 14–21 days Maintenance: 90–120 mg/kg given over 2 h once daily
Ganciclovir (gel) (Zirgan®, Virgan)	0.15 %		
Ganciclovir sodium (Cytovene®)	–	0.2 mg	IV – induction: 5 mg/kg every 12 h for 14–21 days Maintenance: 5 mg/kg daily for 7 days or 6 mg once daily for 5 days/week Oral – after IV induction: 1,000 mg 3 times daily with food or 500 mg 6 times daily every 3 h
Ganciclovir sodium (Vitrasert®)[a]	–	4.5 mg	
Valacyclovir (Valtrex®)	–	–	Oral – *herpes zoster ophthalmicus*: 1 g 3 times daily for 7 days Herpes simplex virus (types 1 & II): 1 g 2 times daily

[a]Sterile intravitreal insert designed to release the drug over a 5–8-month period

organisms. A Gram-positive organism, in particular, is under considerable risk of death when the cell wall is compromised.

Bacterial cell wall contains peptidoglycans and ligands of alternating pyranoside residues of two amino sugars, *N*-acetylglucosamine and *N*-acetylmuramic acid (the latter is not found in mammalian cells), and is cross-linked by pentapeptide chains. Pentapeptide cross-linking gives the cell wall its rigidity; consequently, the introduction of antimicrobial agents or antibiotics that interfere with cross-linking causes the cell wall to weaken and the organism to die.

Unlike bacteria, mammalian cells do not have cell walls a selective target and an example of selective toxicity.

2.3.1 Penicillins

Penicillins are beta-lactam antibiotics. There are four generations of penicillins. The first three are important in the treatment of ocular infections. The first-generation penicillins are penicillin G and penicillinase-resistant penicillins, of which there are two types, methicillin and nafcillin. Methicillin was used to treat beta-lactamase-producing organisms. Methicillin can cause interstitial nephritis and is no longer used in most centers. The penicillins are used specifically to treat ocular infections caused by *Streptococcus*, *Neisseria*, *Clostridium* spp., syphilis, and *Actinomyces*.

The second-generation penicillins include ampicillin and amoxicillin. These antibiotics have a slightly broader spectrum than those of the first generation. The second-generation penicillins are used to treat ocular infections caused by *Haemophilus* species and enterococci.

The third-generation penicillins are carbenicillin and ticarcillin. Ticarcillin has been combined with clavulanic acid as a suicide inhibitor of beta-lactamase. These antibiotics occupy receptor sites on Gram-negative bacteria making them more active against Gram-negative bacteria. Until recently, carbenicillin was used to treat *Pseudomonas* infections. Ticarcillin has replaced carbenicillin and may be used in combination

with aminoglycosides. The fourth group of penicillins comprises of mezlocillin, piperacillin and azlocillin which are derivatives of ampicillin and are similar to carbenicillin and ticarcillin. These antibiotics are also effective against Gram-negative organisms because they have a greater affinity to cell wall receptor sites in Gram-negative organisms than in Gram-positive organisms. The fourth-generation penicillins have limited role in ophthalmology. New generations of antibiotics are not necessarily better or more effective than earlier generations. Each generation of antibiotics plays a specific role and has specific indication and advantages in the treatment of infections caused by susceptible organisms.

Organisms become resistant by producing beta-lactamase. The enzyme disrupts the beta-lactam ring, rendering it ineffective. In order to counteract this, an antibiotic called clavulanic acid, produced by *Streptomyces* spp., has been introduced. Clavulanic acid has a very weak antibiotic effect and binds to beta-lactamase and inhibits its effects, "suicide inhibition." Clavulanic acid has unique affinity to beta-lactamase and leads to its deactivation. The combination of clavulanic acid to existing antibiotics does not constitute a new generation of antibiotics but is a new therapeutic strategy to improve the effectiveness of existing antibiotics.

A combination of 500 mg amoxicillin and 250 mg clavulanic acid (Augmentin®) is effective against beta-lactamase-producing organisms such as *Haemophilus* and streptococci. The drug is used for the treatment of preseptal cellulitis in young children where *Haemophilus* is a common cause. Similarly, a combination of ticarcillin and clavulanic acid (Timentin®).

Cloxacillin is similar to clavulanic acid (Timentin®) in that it has strong affinity for beta-lactamase and neutralizes its effects.

2.3.2 Monobactam Antibiotics

Several examples of monobactam antibiotics are available which are Impenem meropenen, ectapenem which have wide antimicrobial activity. Impenen is effective against anaerobes, Gram-positive and Gram-negative organisms, *Streptococcus pneumoniae*, *Streptococcus* Group A, *Staphylococcus aureus*, *Streptococcus faecalis*, and *Haemophilus influenzae*. The minimum inhibitory concentration of imipenem to *Haemophilus influenzae* and *Neisseria* spp. is less than 0.6 μg/ml. Imipenem is also effective against *Enterobacteriaceae*, *Pseudomonas*, and *Acinetobacter calcoaceticus.* Imipenem has been marketed in combination with silastin. Silastin inhibits hydropeptidase, an enzyme released by the brush border of the kidney which destroys imipenem. Consequently, cilastatin prolongs the half-life of imipenem and increases the concentration of imipenem in the urine. Imipenem should not be used in conjunction with cephalosporin because of potential antagonism.

2.3.3 Cephalosporins

Cephalosporins are an important group accounting for some 50 % of all antibiotics prescribed in hospitals (Tables 2.8a and 2.8b). Over 25 cephalosporins are available, and many more are under investigation. The advantages of cephalosporins include a broad-spectrum bactericidal with selective toxicity. Cephalosporins (first generation) are effective against penicillinase-producing *Staphylococcus aureus*. The disadvantages of cephalosporins include low CSF level, and therefore the agents are not recommended to treat meningitis. They have limited effects against enterococci, and they may potentiate nephrotoxicity if they are used intravenously in combination with aminoglycosides.

The first generation of cephalosporins was introduced in the 1970s. One of the antibiotics in this generation is cefazolin. As with other groups of antibiotics, each generation of cephalosporins has its own spectrum: the first-generation cephalosporins are more effective against Gram-positive cocci than the third- or fourth-generation cephalosporins.

The second-generation cephalosporins include cefuroxime and cefonicid. Cefuroxime

Table 2.8a The major cephalosporins

First generation	Second generation	Third generation
Parenteral	*Parenteral*	*Parenteral*
Cephalothin (Keflin)	Cefamandole (Mandol)	Cefotaxime (Claforan)
Cefazolin (Ancef, Kefzol)	Cefoxitin (Mefoxin)	Cefoperazone (Cefobid)
Cephapirin (Cefadyl)	Cefuroxime (Zinacef)	Ceftizoxime (Cefizox)
Cephradine (Velosef)	Cefotetan (Cefotan)	Ceftriaxone (Rocephin)
		Ceftazidime (Fortaz, Tazidime, or Tazicef)
		Cefepime (Maxipime)
Oral	*Oral*	*Oral*
Cephalexin (Keflex)	Cefuroxime axetil (Ceftin)	Cefixime (Suprax)
Cephradine (Velosef, Anspor)	Cefprozil (Cefzil)	Cefpodoxime (Vantin)
	Loracarbef (Lorabid)	Ceftibuten (Cedax)
Cefadroxil (Duricef)	Cefaclor (Ceclor)	Cefdinir (Omnicef)

Table 2.8b Selective oral cephalosporins for ocular and adnexal infections

Agent	Indication
First generation	
Cephalexin (Keflex) or	Eyelid minor soft tissue infections due to methicillin susceptible *S. aureus* and/or *S. pyogenes*
Cephradine (Anspor, Velosef)	Alternative in streptococcal pharyngitis
Second generation	
Cefuroxime (Ceftin), or	Alternative therapy in orbital cellulitis, otitis media, sinusitis, bronchitis
Cefprozil (Cefzil), or	Cefuroxime axetil has been used in Lyme disease
Loracarbef (Lorabid)	Alternate therapy in early selected cases of community-acquired pneumonia (CAP)
Cefaclor (Ceclor)	
Third generation	
Cefixime (Suprax)	Alternate therapy for *H. influenza* and *M. catarrhalis*
	Alternate for uncomplicated gonorrheal conjunctivitis
Ceftibuten (Cedax)	No unique role, possible alternative
Cefdinir (Omnicef)	No unique role
Ceftriaxone (Rocephin)	Lyme disease, leptospirosis, syphilis, gonorrheal conjunctivitis
Ceftazidime (Fortaz)	Endophthalmitis combined with vancomycin

is the treatment of choice for sinus infections. It has been used intracamerally in phacoemulsification for the prevention of postoperative endophthalmitis. Unfortunately, it has no effects against *Pseudomonas* or other enteric Gram-negative organisms. It is a good single drug for the treatment of patients with sinusitis or orbital cellulitis as it covers most of the Gram-positive cocci (staphylococci, streptococci) as well as non-enteric Gram-negative organisms; it is also effective against *Haemophilus*. In addition, cefuroxime has a long half-life and can be administered intravenously twice daily. Unlike cefamandole, cefuroxime does not cause bleeding tendencies and is well tolerated. The disadvantages of cefuroxime are as follows: (1) it is not active against *Pseudomonas* spp., enterococci, or *B. fragilis*, and (2) the drug is relatively expensive. Cefaclor is for oral administration.

The third-generation cephalosporins include ceftazidime, cefotaxime, and ceftriaxone. Ceftriaxone is the drug of choice for treating *Neisseria gonorrhoeae*. Most current strains of *N. gonorrhoeae* are resistant to penicillins, and many of them are resistant to other antimicrobial agents as well. Ceftriaxone is effective against infections caused by *Neisseria meningitidis.* Ceftriaxone is

used for the treatment of ocular infections caused by *Borrelia*, *Leptospira*, and *Treponema* and infections caused by *Haemophilus* and beta-lactamase-producing organisms. Other advantages of ceftriaxone include its long half-life and, therefore, can be used once or twice daily (unlike other cephalosporins which have to be administered three or four times daily) which makes it cost-effective. Ceftriaxone has certain disadvantages including its limited value in the treatment of infections caused by *Pseudomonas* spp. except when combined with aminoglycosides and has little or no effect against *Staphylococcus aureus* and may prolong the bleeding time.

The fourth and fifth generations of cephalosporins have so far limited use in ocular infections.

Teicoplanin (Targocid®, Sanofi Aventis Ltd.) is a glycopeptide antibiotic similar to vancomycin and is effective against Gram-positive cocci including methicillin-resistant staphylococci (MRSA) [18, 19]. The drug affects the cell wall synthesis of Gram-positive bacteria. Experience in ophthalmic infections is limited. Oral teicoplanin has been shown to be effective in the treatment of *Clostridium difficile*-associated pseudomembranous colitis [20].

Fumagillin is used for the treatment of corneal microsporidiosis [21]. It is compounded as eyedrops at a concentration level of 0.113 mg/ml (Leiter's Pharmacy Inc., 1700 Park Ave #30, San Jose CA, USA, Telephone No.: 800-292-6773). It has also been shown to inhibit angiogenesis.

2.4 Antibiotics That Inhibit Cell Membrane Function

Antibiotics that inhibit cell membrane function include polymyxin B, amphotericin B, colistin, imidazoles, and polyenes. Some of these antibiotics, such as amphotericin B and the polyenes, act against fungi and do not affect bacterial cell membranes.

Polyenes bind to ergosterol, a sterol moiety in the cell membrane of fungi. Ergosterol is not present in mammalian or bacterial cell membranes.

The imidazoles act against fungi but have different modes of action from the polyenes. Imidazoles act by inhibiting ergosterol synthesis leading to disruption of cell membrane function. In addition, imidazoles inhibit cytochrome C and peroxidase and allow the intracellular accumulation of hydrogen peroxidase leading to death of the fungus. Since ergosterol is the binding site for amphotericin B, the use of imidazoles may render amphotericin B less effective by competing ergosterol in the fungal cell membrane. Polymyxins bind to phosphatidylethanolamine-rich membranes, particularly in Gram-negative organisms. They have a detergent-like effect which disrupts the cell membrane, eventually causing death of the organism.

Polymyxins are effective in treating infections caused by species of *Pseudomonas* as well as certain other Gram-negative organisms. Polymyxins cannot be given systemically because of nephrotoxicity [22–26].

Daptomycin is a new lipopeptide antibiotic used for the treatment of resistant Gram-positive organisms. It is produced by the fungus *Streptomyces roseosporus.* The trade name is Cubicin®.

It binds to the bacterial cell membrane leading to depolarization and loss of membrane function. Daptomycin may also act by inhibiting protein synthesis.

Daptomycin is effective against Gram-positive cocci and shows significant corneal penetration following 1 % topical eyedrops in rabbits [27]. Daptomycin appears to be safe and effective when given intravitreally [28].

2.5 Antibiotics That Inhibit Protein Synthesis

The third group of antibiotics consists of compounds which inhibit protein synthesis and include chloramphenicol, tetracycline, lincomycin, clindamycin, aminoglycosides, and macrolides. They are used extensively in ocular infections [22]. Binding to bacterial ribosomes by erythromycin leads to inhibition of protein synthesis. Inhibition of protein synthesis is also

achieved when tetracyclines and aminoglycosides bind to 30S portion of the bacterial ribosome, while the chloramphenicols, lincomycins, and erythromycin bind to the 50S portion of the bacterial ribosome. The selectivity is partial and these antibiotics may have some toxic effect on human cells. Topical chloramphenicol, is widely used to treat ocular surface infections. There have been several reports of fatal aplastic anemia following topical administration of chloramphenicol. The incidence of idiosyncracy to chloramphenicol is not high; nonetheless, if large numbers of patients are given topical chloramphenicol, cases of fatal aplastic anemia will occur.

In other situations, the use of certain antibiotics is neither ideal nor appropriate. Approximately 30 % of staphylococci isolated from ocular infections are resistant to erythromycin. Erythromycin cannot be considered the drug of choice for the treatment of infections caused by these organisms. Fusidic acid is another antibiotic in this group and is helpful in the treatment of staphylococcal blepharitis [29, 30].

We recovered 163 staphylococcal isolates from ocular infection sites and assessed their sensitivity to different antibiotics [29]. Vancomycin was found to be the most effective antibiotic against all types of staphylococci, including *Staphylococcus epidermidis* and *Staphylococcus aureus.* The results showed that while 95 % of strains of *S. epidermidis* were sensitive to fusidic acid and 84 % were sensitive to bacitracin, only 45 % were sensitive to methicillin, 53 % to gentamicin, 56 % to erythromycin, and 33 % to chloramphenicol [29]. Unfortunately, resistant strains *of* staphylococci to fusidic acid started to appear. Currently, close to 52 % of ocular isolates of staphylococci are sensitive to fusidic acid. The topical use of antibiotics such as chloramphenicol is less effective and carries risks of systemic adverse effects. Chloramphenicol is an antibiotic which is considered to have a very narrow spectrum, with many organisms resistant to it, and carries the risk of aplastic anemia. It is vital that chloramphenicol be prescribed only when absolutely necessary, for example, treating strains of *Haemophilus* that are resistant to other antibiotics.

Vancomycin is a valuable antibiotic that should be used carefully. Wide or inappropriate use may lead to emergence of resistant strains. In addition, nephrotoxicity is likely to increase when systemic vancomycin is combined with gentamicin.

There is antagonism when tetracycline is used in combination with quinolone, erythromycin, and all the beta-lactam antibiotics. A beta-lactam antibiotic should not be used in combination with tetracyclines, erythromycin, or chloramphenicol; since the latter inhibit ribosomal function, they will interfere with the effects of beta-lactam antibiotics.

Azithromycin is a macrolide antibiotics belonging to the azalide group. It has been shown to be highly effective against chlamydial infections as well as against Gram-positive bacteria [31–33]. Azithromycin has a long elimination life reaching 68 h. Azithromycin has been found to be effective in the treatment of genital *Chlamydia*. A single, 1-g dose is sufficient to eradicate it. Azithromycin is also effective in the treatment of trachoma [34]. A 1-week course or repeated 3-day courses of azithromycin are required in chronic active cases of trachoma. The drug has high intracellular concentration in the macrophages and polymorphonuclear cells. Following a single oral dose of azithromycin, the drug remains in the conjunctiva above the minimum inhibitory concentration (MIC) of *Chlamydia* for up to 2 weeks [31]. The drug is currently available as eyedrops at a concentration of 1.5 % as Azyter® (Laboratoires Theá, Clermont-Ferrand, France) and 1.0 % concentration as Azasite (Inspire Pharmaceuticals Inc, NC, USA). The tear concentration of topical azithromycin was studied following topical administration of a single dose of azithromycin 1.0 and 1.5 % in healthy volunteers [32]. This study was a prospective, randomized double-masked study. A total of 91 healthy volunteers with normal tear functions were included. Twenty-three subjects received azithromycin 0.5 % eyedrops, 58 subjects received azithromycin 1.0 % eyedrops, and 38 subjects received azithromycin 1.5 % eyedrops. Tears were collected from each subject at seven time points over a 24-h period using the Schirmer strips that were weighed before and after tear sampling. The tear samples were analyzed for

azithromycin by high-performance liquid chromatography mass spectrometry (HPLC-MS). The peak of azithromycin was noted 10 min after instillation and the mean concentration remained above 7 mg/l for 24 h. A late-onset increase in the tear concentration of azithromycin was noted at 8–12 h and may be explained by the known azithromycin release from the tissues after storage in the cells [31, 35, 36].

In another study, Kuehne and coworkers [33] measured the concentration of azithromycin and clarithromycin in rabbit corneal tissue following topical application of 2 mg/ml (0.2 %) of azithromycin and 10 mg/ml (0.1 %) of clarithromycin. It was shown that topical azithromycin concentrations were higher in the corneal tissue than clarithromycin. Azithromycin is used for the treatment of chlamydial conjunctivitis, trachoma, keratitis due to *Mycobacterium chelonae*, and chronic blepharitis [31, 36–38].Topical azithromycin is used for the treatment of blepharitis [36–38]. Corneas exposed to desiccation showed significant increase in the azithromycin tissue level compared to normal eyes following topical application of azithromycin 1.5 % eyedrops [39]. It appears that dryness may increase the tissue absorption of the cornea [39].

Linezolid (Zyvox®) is a synthetic antibiotic, is a member of the oxazolidinones used for the treatment of serious infections caused by Gram-positive bacteria [40]. Linezolid inhibits protein synthesis and appears to work by disrupting the translation of messenger RNA into proteins in the ribosomes. Linezolid binds to 50S subunit of the ribosome. It has been shown that linezolid is most active against Gram-positive bacteria including streptococci, vancomycin-resistant-enterococci, and methicillin-resistant-*Staphylococcus aureus* (MRSA). The main indications of linezolid are infections of the skin and soft tissues and pneumonia. The drug is available in the United States and the United Kingdom under the name of Zyvox® and in European countries under the name of Zyvoxid®. On the other hand, in Canada and Mexico, the drug is known as Zyvixam®. Generics of these drugs are available in India under the name of Linospan by Cipla.

Linezolid is an oxazolidinone antibiotic which is a protein synthesis inhibitor. Resistance to linezolid by bacteria has remained low. Linezolid has proven to be safe and effective in infections due to susceptible organisms. The US Food and Drug Association approved linezolid in April 2000. It is considered a bacteriostatic agent, and the main indication of linezolid is the treatment of severe infections caused by Gram-positive bacteria that are resistant to other antibiotics. It has a narrow spectrum and, therefore, remains a reserved antibiotic for cases with severe infections due to resistant bacteria. Linezolid has been associated with *Clostridium difficile*-associated diarrhea and pseudomembranous colitis. The long-term use of linezolid may lead to bone marrow suppression and thrombocytopenia.

2.6 Antibiotics That Inhibit Nucleic Acid Synthesis

The fourth group of antibiotics, the quinolones, comprises antibiotics which inhibit nucleic acid synthesis [5, 41–66].

Pyrimethamine interferes with the synthesis of the hydrofolate which is an important building block of bacterial DNA. The drug is used for the treatment of *Toxoplasma*. Rifamycin interferes with nucleic acid synthesis by the inhibition of RNA-dependent DNA polymerase. Sulfonamides are synergistic with trimethoprim and, have been combined for systemic use.

Fluoroquinolones have a fluorine substitution at position 6 of the quinolone molecule. Additional substitutions at position 1 and position 7 markedly affect antimicrobial efficacy as well as penetration. These alterations have substantially improved the antimicrobial effects against Gram-positive as well as Gram-negative organisms in addition to improving solubility in ophthalmic solutions. Norfloxacin was the first fluoroquinolone to be used topically for ocular infections. It has primarily Gram-negative activity, including antipseudomonal activity as well as limited Gram-positive activity.

The regulation of DNA supercoiling is essential to DNA transcription and replication. In

supercoiling, the DNA molecule coils up and shortens the molecule. The DNA helix must unwind to permit the proper function of the enzymatic machinery involved in these processes. Topoisomerases serve to maintain both the transcription and replication of DNA. Type I and type II topoisomerases cut one strand or two strands of DNA, respectively.

The underlying mechanism of action is reversible trapping of DNA gyrase (topoisomerase II) and topoisomerase IV-DNA complexes. Complex formation is followed by reversible inhibition of DNA synthesis. As fluoroquinolone concentrations increase, cell death occurs as double-stranded DNA breaks releasing trapped gyrase and/or topoisomerase IV complexes. In many Gram-negative bacteria, resistance arises primarily from mutation of the gyrase A protein, while in some Gram-positive bacteria, primary resistance occurs via mutation in topoisomerase IV. In addition, efflux pumps that actively pump antibiotics out of the bacteria confer multidrug resistance via these membrane-associated efflux pumps. Gatifloxacin and moxifloxacin are more resistant to these efflux pumps. This change additionally confers added anaerobic activity. Gram-negative organisms may also exhibit decreased levels of outer membrane proteins that facilitate diffusion into the bacterial cell of drug, thereby conferring additional resistance, which can work in concert with the efflux pumps. These last two mechanisms confer a form of resistance and can be overwhelmed by higher concentrations of drug [65].

Fluoroquinolones include moxifloxacin, gatifloxacin, besifloxacin, ciprofloxacin, fleroxacin, lomefloxacin, norfloxacin, ofloxacin, perfloxacin, and temfloxacin, all of which are C-7 1-piperazinyl and C-7 fluoro-substituted quinolones. The drugs are more potent than the original nalidixic acid structure. Several quinolones are available in topical eyedrop form. These drugs have good in vitro actions against many Gram-negative and Gram-positive bacteria, while action against anaerobic bacteria remains poor. The mechanism of action of the quinolones is through inhibition of DNA gyrase. Lomefloxacin is effective against most Gram-negative and Gram-positive organisms. Studies on *Chlamydia trachomatis* show that this organism is moderately susceptible to lomefloxacin.

These susceptibilities are in contrast to the aminoglycosides and β-lactam antibiotics which have activity against bacterial cells in the growth phase, whereas fluoroquinolones are rapidly bactericidal in vitro and in vivo in both growth phase and secondary phase of cell growth.

Studies carried out on the rabbit model have revealed that lomefloxacin readily penetrates the cornea, iris, and ciliary body of the eye and reaches an appreciable concentration in the aqueous. Penetration occurs after both local and systemic administration and penetration have been shown to be increased in the presence of melanin.

The fluoroquinolones have two pKa values on each side of physiological pH with an isoelectric point at pH 7.4. Unionized fluoroquinolones are considered to be very lipophilic, a factor that is thought to influence considerably the mechanism by which these compounds penetrate bacterial cell membranes. Fluoroquinolones are approximately 20–30 % protein bound. This value has been found to be independent of the drug concentration. Following oral administration of lomefloxacin, 10 % of the drug is protein bound in the serum. Evidence from animal studies suggests that lomefloxacin is excreted unchanged by the kidney, although small concentrations of 5 metabolites have been described. The most notable drug interaction occurring is the effect of fluoroquinolones on the clearance of theophylline. Plasma concentrations of theophylline are raised by approximately 19 % during coadministration with perfloxacin as compared to 111 % for enoxacin and 23 % for ciprofloxacin. Ofloxacin and nalidixic acid do not increase the apparent plasma level of theophylline. The interaction is supposed to rise, not through the parent fluoroquinolone but through their 4-oxo metabolites. This interaction is produced through the effect on hepatic p450-related isoenzymes resulting in reduced capacity of *N*-demethylation of theophylline. No oxo-metabolite is produced in the metabolic elimination of lomefloxacin, and the drug is extensively excreted. Theophylline adjustment does not seem to be necessary in patients receiving concomitant lomefloxacin.

Quinolones are interesting in ophthalmology because several of them are available in topical forms. Levofloxacin, lomefloxacin, ciprofloxacin, ofloxacin, norfloxacin, moxifloxacin, gatifloxacin, besifloxacin, and temefloxacin are available for topical use. They are effective against Gram-negative organisms, and in topical form ciprofloxacin has a useful role in the treatment of bacterial keratitis caused by *Pseudomonas.* Certain fourth-generation quinolones, however, have limited efficacy against Gram-positive cocci.

Quinolones are highly effective against Gram-negative organisms and have intermediate activity against staphylococci. They are effective against group B streptococci but not useful against group A streptococci, *Streptococcus pneumonia*, and anaerobes. Clearly, these antibiotics have selective effects against microorganisms, making them unsuitable for "blind shot blanket" therapy. In addition, systemic fluoroquinolones may cause cartilage erosion in children. They should not be used in children or pregnant women. As the case with tetracyclines, antacids may decrease absorption of oral quinolones.

The antibiotics of choice for common ocular pathogens are shown in Table 2.9. The compounding dosages for intravitreal injections of antimicrobial agents are shown in Table 2.10. The antimicrobial therapy for tuberculosis (Table 2.11) and for ocular toxoplasmosis is also listed (Table 2.12).

Compliance with Ethical Requirements

Conflict of Interest The author declares that he has no conflict of interest.

Informed Consent No human studies were carried out by the authors for this article.

Animal Studies No animal studies were carried out by the authors for this article.

Table 2.9 Antibiotics of choice for common ocular pathogens

Pathogen	Antibiotic of first choice	Alternative agents
Viridans group		
S. pneumoniae	Penicillin G (with or without gentamicin)	Cefazolin, vancomycin
	Penicillin G	Cefazolin, vancomycin
Gram-negative cocci		
Neisseria gonorrhoeae	Ceftriaxone or cefixime or ofloxacin	Cefotaxime, spectinomycin, cefoxitin
N. meningitides	Penicillin G	Third-generation cephalosporin, chloramphenicol
Moraxella (*Branhamella*) *catarrhalis*	Trimethoprim-sulfamethoxazole	Amoxicillin-clavulanic acid, erythromycin, clarithromycin, azithromycin, cefixime, third-generation cephalosporin, tetracycline
Gram-positive bacilli		
Clostridium perfringens and *Clostridium* spp.	Penicillin G	Metronidazole, clindamycin, imipenem, meropenem, chloramphenicol
Listeria monocytogenes	Ampicillin with gentamicin	Trimethoprim-sulfamethoxazole (TMP-SMX)
Gram-negative bacilli		
Acinetobacter	Imipenem or meropenem	Tobramycin, gentamicin, or amikacin, usually with (or similar agent); TMP-SMX*; a ciprofloxacin
Enterobacter spp.	Imipenem or meropenem	An aminoglycoside and piperacillin or ticarcillin or mezlocillin; a third-generation cephalosporin; TMP-SMX*
		Aztreonam
		Ciprofloxacin

(continued)

Table 2.9 (continued)

Pathogen	Antibiotic of first choice	Alternative agents
Escherichia coli	TMP-SMX* or ciprofloxacin	A cephalosporin or a fluoroquinolones
Haemophilus influenzae	Cefotaxime or ceftriaxone	Chloramphenicol; cefuroxime, gatifloxacin, moxifloxacin, azithromycin
Gram-negative bacilli		
Klebsiella pneumoniae	Ceftriaxone or cefotaxime	Aminoglycoside, imipenem, or meropenem, TMP-SMX*, ticarcillin-clavulanic acid, ampicillin-sulbactam, piperacillin-tazobactam; aztreonam; a fluoroquinolone; amoxicillin-clavulanic acid
Proteus spp.		
Indole positive	Cefotaxime, ceftizoxime, ceftriaxone of cefepime	Aminoglycoside; ticarcillin or piperacillin or mezlocillin; TMP-SMX*; amoxicillin-clavulanic acid; ticarcillin-clavulanic acid, ampicillin-sulbactam, piperacillin-tazobactam; a fluoroquinolone; aztreonam; imipenem
Pseudomonas aeruginosa	Gentamicin or tobramycin or amikacin (combined with ticarcillin, piperacillin, etc., for serious infections)	Aminoglycoside and ceftazidime; imipenem or meropenem, or aztreonam plus an aminoglycoside; ciprofloxacin; trovafloxacin
	Ciprofloxacin, polymyxin B	Ticarcillin piperacillin, or ceftazidime; imipenem or meropenem; aztreonam, an aminoglycoside; cefepime
Gram-negative bacilli		
Serratia	Cefotaxime, ceftizoxime, or ceftriaxone	Gentamicin or amikacin; imipenem; TMP-SMX*; ticarcillin, piperacillin, or mezlocillin, which can be combined with an aminoglycoside; aztreonam; afluoroquinolones
Nocardia spp.	TMP-SMX* Amikacin Rifampin	Tetracycline
Acanthamoeba	Propamidine (0.1 %) Chlorhexidine (0.02 %) Aminoglycoside Voriconazole (1 %)	Polyhexamethylene biguanide
Microsporidia	Fumagillin 0.113 mg/ml Voriconazole 1 % Fluconazole 2 mg/ml	Ketaconazole Itraconazole Albendazole

**TMP-SMX* Trimethoprim-sulfamethazazole*

Table 2.10 Intravitreal injections of antimicrobial agents

Acyclovir	2.4 mg/0.1 ml
Amikacin sulfate	0.4 mg/0.1 ml
Ampicillin sodium	5 mg
Cefazolin sodium	2,250 µgm
Ceftazidime	2.25 mg/0.1 ml
Ceftriaxone	2 mg/0.1 ml
Clindamycin	1,000 µgm
Daptomycin	0.2 mg/.05 ml
Dexamethasone	0.4 mg/0.1 ml

Table 2.10 (continued)

Erythromycin	500 µgm
Foscarnet	2.4 mg/0.1 ml
Ganciclovir	0.2 mg/0.05 ml
Gentamicin sulfate	100–200 µgm
Tobramycin sulfate	100–200 µgm
Triamcinolone acetonide	4 mg/0.1 ml
Vancomycin hydrochloride	1 mg/0.1 ml
Voriconazole	0.2 mg/0.1 ml

Table 2.11 Antimicrobial therapy for tuberculosis (adult) [67]

Drug	Daily dose (mg)	Duration (months)	Adverse effects
Isoniazid	300	6	Peripheral neuropathy, hepatotoxicity
Rifampin	600	6	Hepatotoxicity, pink urine
Pyrazinamide	1,500–2,000	6	Liver toxicity, hyperuricemia
Ethambutol	800	2	Optic neuropathy, retinal ganglion cell loss

Table 2.12 Antimicrobial therapy for ocular toxoplasmosis

Treatment regimen (adult)
Pyrimethamine 200 mg orally on day 1, followed by 50 mg orally daily for 4 weeks
Sulfadiazine 2 g orally as a loading dose followed by 1 g orally 4 times daily for 4 weeks
Folinic acid 15 mg orally every other day twice a week
Force fluids and give sodium bicarbonate
Alternate regimen (adult)
Azithromycin, 500 mg orally twice daily for 4 weeks, or clindamycin 300–450 mg orally q 6 h for 4 weeks
Trimethoprim, 160 mg/sulfamethoxazole 800 mg twice daily for 4 weeks
Vision-threatening lesions
Corticosteroids to be used only when vision is threatened: prednisone, 1 mg to 1.5 mg/kg/day, gradually tapered over a period of 4 weeks, or periocular injection of triamcinolone acetonide 40 mg once
Give corticosteroids 3 days after initiation of antimicrobial agents
Congenital toxoplasmosis
Pyrimethamine, 1 mg/kg/day orally once every 3 days, and sulfadiazine, 50 mg to 100 mg/kg/day orally in two divided doses for 3 weeks
Corticosteroids for vision-threatening lesions: 1 mg/kg/day orally in two divided doses. The dosage should be tapered progressively and later discontinued
Folinic acid, 3 mg twice weekly during treatment with pyrimethamine

Adapted and modified from [1, 68]

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