CHAPTER 14

Antibacterials

Ankit Shah, *MD*
Thomas Mauger, *MD*

INTRODUCTION

Our antibiotic choices are not only critical to the well-being of our patients, but also have an impact on health care economics. Decisions as to whether antibiotics are needed at all and, if so, which particular antibiotic would be most appropriate equate to millions of dollars every day. Hospital administrators, pharmacists, insurance companies, and governmental agencies are concerned with our use of antibiotics. Cost containment committees and antibiotic usage review committees are in place in almost every hospital. Significant cost saving can be achieved. More importantly, choices on antimicrobial usage have profound effects on resistance patterns in the microbes that we are treating.

The US Joint Commission on Accreditation of Hospitals requires a regular review of clinical usage of antibiotics. This ruling is based on data indicating that physician prescribing habits are less than ideal and directly contribute to a large number of adverse reactions to antibiotics, excessive costs, and the development of resistant bacteria and infections. For example, yeast and fungal superinfections may follow antibiotic therapy (0.7% of 14,077 patients).[1]

ANTIBIOTIC PROPHYLAXIS

Should topical antibiotics be used prophylactically before intraocular surgery? To answer this question, the surgeon must know the origins and characteristics of the intraocular infection, as well as the antibacterial spectrum of the antibiotic being considered. This data is regularly provided by many health care organizations. (Table 14-1).

Exogenous infection should always be suspected when clusters appear. In a series of more than 23,000 cataract operations performed in India, nine separate clusters, accounting for 41% of all infections, occurred. Only one cluster was encountered in a second series of more than 25,000 cataract operations. The infection rate in the first series was 2.9:1,000; in the second series, it was 1.01:1,000.[2] The authors attributed this decrease in infection rate to prophylaxis with combined penicillin, chloramphenicol, and sulfadimidine treatment. Another interpretation of this information is that the earlier series (starting in 1963) differed from the second series (starting in 1973); facilities became available for better sterile technique during the second decade of the study. This is an illustration of the invalidity of comparing consecutive groups of cases. Of note, most of the advocates of prophylactic antibiotic therapy for eye surgery base their advice on such comparisons of series of before and after cases. Randomized, controlled studies with the endpoint being endophthalmitis are extremely difficult to perform due to the low incidence of this complication.

Nearly 40% of all antibiotic use is for prophylactic treatment.[3,4] On an individual basis, the cost of topical prophylactic antibiotic use for eye surgery is relatively low compared with systemic antibiotics. It is the scale of eye surgeries (> 2 M/year in the United States) that makes any decision regarding this of high magnitude. Our choices of prophylaxis for ophthalmic surgery are important in terms of cost, adverse reactions, and development of resistance because of the enormous numbers of patients involved.

Most investigations on the development of postsurgical infections and the role of prophylactic antibiotics are limited by the rarity of the event, the ancillary changes in perioperative management that may have occurred during the duration of the study, and the presence of retrospective controls in the study. For these reasons, the incidence of postoperative endophthalmitis after ophthalmic surgery in published studies over the past 100 years is highly variable (Fig. 14-1).[5-10] Among the known risk factors for endophthalmitis following cataract surgery are increased age of the patient, clear corneal incision, and communication with the vitreous during the surgery (broken posterior capsule or zonular dehiscence).[6,11]

TABLE 14-1. 2017 Antibiogram: Percent (%) Susceptibility. Reproduced from WVU Medicine: J.W. Ruby Memorial Hospital.

Gram-positive Bacteria	**# Isolates**	**Ampicillin**	**Cefazolin**	**Ceftriaxone**	**Clindamycin**	**Daptomycin[1]**	**Doxycycline[2]**	**Gentamicin[3]**	**Levofloxacin**	**Linezolid**	**Nafcillin**	**TMP/SMX**	**Vancomycin**
Enterococcus faecalis	721	98	*	*	*	100	*	73	*	99	*	*	98
Enterococcus faecium	224	13	*	*	*	91	*	80	*	100	*	*	25
Staph. aureus - MSSA	1113	*	100	*	73	100	95	99	*	100	100	99	100
Staph. aureus - MRSA	961	*	*	*	63	98	95	97	*	99	*	96	100
Staph, coagulase negative Frequently a contaminant	570	*	*	*	*	100	85	*	*	100	*	65	100
Streptococcus pneumoniae Non-meningitis	69	98	*	94	*	*	62	*	98	*	*	*	100
Gram-negative Bacteria	**# Isolates**	**Amox/Clav**	**Amikacin**	**Aztreonam[+]**	**Cefepime**	**Ceftazidime**	**Ceftriaxone**	**Ciprofloxacin**	**Gent/Tobra**	**Levofloxacin**	**Meropenem**	**Pip/tazo**	TMP/SMX
Enterobacter aerogenes	104	*	100	*	100	83	79	99	96	99	100	82	98
Enterobacter cloacae	232	*	97	*	83	59	58	90	88	90	90	66	87
Escherichia coli	3795	81	99	*	98	*	94	80	93	80	*	*	76
Klebsiella spp.	1022	92	99	*	97	96	95	*	95	*	*	*	88
Proteus mirabilis	319	98	100	*	99	99	99	74	87	76	*	*	74
Pseudomonas aeruginosa	736	*	94	72	87	86	*	74	G: 87 T: 96	74	86	89	*
Serratia marcescens	188	*	100	*	100	100	96	*	G: 97 T: 88	*	100	98	*
Stenotrophomonas spp.	91	*	*	*	*	55	*	*	*	83	*	*	90

[1] Not all isolates tested;
[2] Tetracycline is tested as the marker for doxycycline —susceptibility may be underestimated;
[3] Synergy-use combination therapy

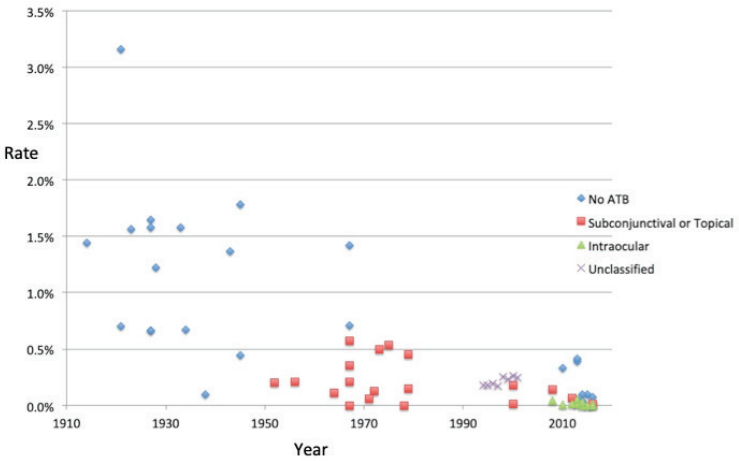

FIG 14-1. Incidence of endophthalmitis following cataract surgery by year of study. Adapted from: Starr *et al.*,[5] West *et al.*,[7] Huang *et al.*,[8] Gower *et al.*,[9] ESCRS Endophthalmitis Group.[10]

The goal of prophylaxis is to prevent postoperative infection. The sources of bacterial contamination are from the lids, lashes, and conjunctiva of the patient and also from insufficiently sterilized ophthalmic instruments. Conjunctival flora varies from day to day and week to week; therefore, preoperative cultures can be misleading and counterproductive in the selection of prophylactic antibiotics. Even the trauma of the culture itself can change the bacterial flora.[12] Organisms that may otherwise be considered normal flora or contaminants such as *Staphylococcus epidermidis* are potential pathogens to the eye. The use of preoperative topical antibiotics may decrease or eliminate bacterial flora from the conjunctiva;[13] however, such use will not prevent intraoperative contamination of the wound or anterior chamber. After uncomplicated cataract surgery, 43% of 30 patients were found to have culture-positive anterior chamber aspirates.[14] These patients were treated with topical gentamicin antibiotic as well as a chlorhexidine facial scrub the night before surgery. Immediately before surgery the eyelids were scrubbed with both hexachlorophene and 5% povidone-iodine (PI). PI was placed topically on the cornea, following which the eye and skin were irrigated with sterile saline solution. After surgery, aqueous humor was aspirated through the surgical wound and cultured. Thirteen of 30 (43%) eyes grew bacteria. Of 13 culture-positive eyes, *S. epidermidis* was found in eight. Despite the presence of organisms, no clinical infections were found, probably because of the small inoculant size and the presence of an intact posterior capsule. Subconjunctival gentamicin was placed in the inferior fornix after each operation. The aqueous humor provides a limited antimicrobial effect when small inoculants are involved. This is overwhelmed when large inoculants are presented. Unlike the aqueous, bacterial contamination of the vitreous appears to be relatively resistant to current prophylactic measures. All 25 rabbit eyes given subconjunctival gentamicin and cefazolin after vitreous injection of *Pseudomonas* still developed clinical endophthalmitis.[15]

The choice of antibiotic cannot be determined based on antibiotic sensitivities alone. Locatcher-Khorazo[13] showed that despite apparently good sensitivities of bacteria to chloramphenicol and terramycin, these medications had little effect on bacterial colony counts when applied to the eye. Intraocular antibiotic concentrations found when topical medications are used are usually insufficient to be bactericidal for possible pathogenic bacteria. Subconjunctival injections before or after surgery may give bactericidal levels of antibiotics in the anterior chamber for at least a short period. A prospective, controlled study investigating the role of subconjunctival antibiotic prophylaxis in 974 patients undergoing ocular surgery was performed.[16] Untreated controls had intraocular infections develop in 1.42% of cases compared with only 0.21% of the treated group. Treatment consisted of subconjunctival penicillin and streptomycin. The controls were given no antibiotics. Neither group of patients was given preoperative or postoperative topical or systemic antibiotics. The seven-fold decrease in the postoperative endophthalmitis rate was assumed to be the result of the subconjunctival penicillin and streptomycin used.

A small prospective study comparing topical and subconjunctival postoperative antibiotics with cataract surgery was reported in 1992. Sixty patients were randomized to receive either 2 mg of the corticosteroid betamethasone and 20 mg of gentamicin subconjunctival or 0.1% betamethasone and 0.5% neomycin topically. Increased conjunctival injection and anterior chamber reaction were found with subconjunctival injection. The small study numbers allow no conclusions concerning the prevention of postoperative endophthalmitis. Cultures were not performed from either the aqueous humor or the conjunctiva. The study did not differentiate between the effects of subconjunctival corticosteroids compared with antibiotics. This study simply reports the relative safety of both methods of prophylaxis and the increased tissue reaction associated with subconjunctival injections.[17]

Systemic antibiotic use has not been advocated because of the poor risk/benefit ratio. Oral ciprofloxacin has been found to produce vitreous levels in the bactericidal range for many bacteria. Doses of 750 mg of ciprofloxacin given as a single dose 4 to 8 hours before surgery or as multiple doses 24 and 12 hours before surgery were found to give bactericidal vitreous levels.[18] Cost effectiveness, risk/benefit ratio, and development of resistance to organisms have not been evaluated for the possible use of this modality of prophylaxis in routine ophthalmic surgery. It does seem to make clinical sense, for instance, in the case of an intraocular foreign body penetrating to the vitreal cavity. It may also have a role as a postoperative medication when the vitreous has been disturbed during ocular surgery; for example, after unplanned posterior capsule rent and anterior vitrectomy during cataract surgery. However, more

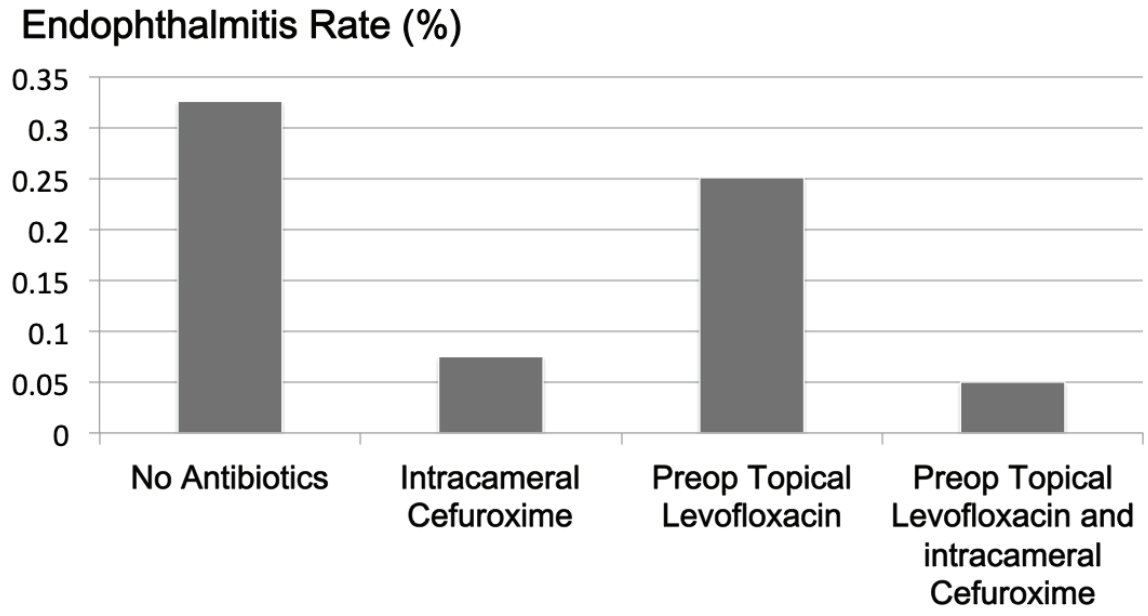

FIG. 14-2. Endophthalmitis rates: effect of intracameral antibiotics.

predictable intraocular drug levels will be achieved through direct intraocular injection.

Intraocular antibiotics have been used as prophylaxis in cataract surgery either as a single injection or as an infusion. Both modalities are rational in the sense that decreasing or eliminating intraocular organisms will probably reduce cases of endophthalmitis. The risk of intraocular toxicity is much higher than with topical or subconjunctival antibiotics, and this has not been properly evaluated in a large group of patients.[19] A number of agents have been used intracamerally as prophylaxis at the conclusion of surgery. These include the cephalosporins, moxifloxacin, and vancomycin. Intracameral vancomycin has been associated with hemorrhagic occlusive retinal vasculitis (HORV).[20]

The most commonly used agents for intraocular prophylaxis at the conclusion of cataract surgery are cefuroxime (or other cephalosporins) and moxifloxacin. The European Society of Cataract and Refractive Surgeons (ESCRS) conducted a randomized controlled trial of the use of intracameral cefuroxime and topical levofloxacin. Over 16,000 patients were recruited for this multicenter trial. The groups consisted of a control group that received no preoperative topical or intracameral antibiotic, a group that received only preoperative topical levofloxacin, another that received only intracameral cefuroxime, and a fourth group that received both. The endophthalmitis rates in each group are shown in Figure 14-2.[10]

The rate was significantly less in the two groups that were given intracameral cefuroxime and the relative risk of infection was 4.92 in eyes not given this antibiotic. The dose of cefuroxime used was 1 mg/0.1 ml. In Europe, there is a commercially available product (Aprokam) that contains 50 mg of cefuroxime powder that is diluted with 0.9% NaCl and a final concentration of 1 mg/0.1 ml is instilled into the eye. This is not available in the United States; therefore, cefuroxime must be compounded to achieve the proper dose.

Moxifloxacin has also been shown to be safely used intracamerally at the conclusion of cataract surgery.[21] A dose of 0.5 mg/0.1 ml (Auromox) was used in a series of patients in India without complication. The rate of endophthalmitis with this treatment was 0.02% compared with 0.07% when no intracameral antibiotic was used.[22] In the United States, this dose (0.5 mg/0.1 ml) may be obtained by drawing moxifloxacin from a bottle of non-preserved moxifloxacin 0.5% prepared for topical use (Vigamox). The solution has also been prepared in a concentration of 0.1 mg/0.1 ml with the intention of instilling 0.3 to 0.4 ml of the solution.[23]

In addition to antibiotic toxicity, another objection to prophylactic treatment is the possibility of development of resistant organisms. Most evidence indicates that resistant organisms occur with the systemic administration of antibiotics over long periods. There is little evidence indicating that topical antibiotics delivered over a short period contribute to development of resistant organisms. The magnitude of their use in ophthalmic surgery, however, demands attention to this possibility. It is not rational to

use the newest and most expensive antibiotics for prophylactic treatment in routine ocular surgery when a less expensive, established antibiotic will be equally effective. We must, however, remain cognizant of the development of resistant organisms with any antibiotic and evaluate the sensitivity of these organisms in our community so that our use of prophylaxis may be adjusted. Particular attention should be given to the development of resistance with *Staphylococcus* organisms, because these are a common cause of postoperative endophthalmitis.[5,24] Chronic or repeated use of an antibiotic over time does increase the chance for the development of resistant bacteria. A study of conjunctival flora with intermittent use of topical antibiotics associated with intravitreal injections demonstrated development of resistance of coagulase-negative *Staphylococcus* to the antibiotic used.[25]

Aseptic preparation of the eye before surgery is important in reducing endophthalmitis postoperatively. Caldwell *et al.*[26] reported a 9.6% postoperative positive-culture rate after the use of 5% PI solution applied to the lids, brows, and conjunctival cul-de-sac. This study also included an intensive use of gentamicin eye drops given every 2 hours for 36 hours prior to the surgery.[26]

Another study compared the effect of dilute PI preparation on mean colony counts.[27] The conjunctiva was cultured before and after conjunctival preparation. The study also compared ½-day *vs* 3-day antibiotic preparation. Although the PI preparation did eliminate all fungal growth in culture, the overall incidence of positive bacterial culture after preparation increased from 2.33 to 4.95 colonies per patient. This difference was not statistically significant. The authors believed the preparation and possibly the initial culturing freed bacteria from crevices in the conjunctival fornices, increasing the colony counts. The study did show a significant difference between 3-day gentamicin treatment and ½-day treatment, showing a 1.88 colony count per patient after 3-day treatment and a 5.42 colony count with ½-day treatment.[27] Reconciling these two studies into a rational preoperative preparation poses a difficult conundrum. One study indicates that PI conjunctival preparation decreases the incidence of postoperative cultures, and the other study indicates PI preparation of the eye increases conjunctival bacterial colony counts.

A third study reported in 1991 goes a long way in answering this question.[28] Two operating suites in the New York Eye Infirmary were used to compare a dilute PI preparation against silver protein solution during the 11-month period between April 1989 and February 1990. During a similar period before initiation of the study, 0.18% of cases from suite A and 0.16% cases from suite B developed culture-proven postoperative endophthalmitis. During the study, only 0.06% of patients from suite A, using PI preparation, had postoperative, culture-proven endophthalmitis develop compared with 0.24% cases from suite B using silver protein solution. During this time, 3,384 operations were performed in suite A and 3,289 were performed in suite B. It is interesting to note that in suite B (with the higher infection rate) a much higher percentage of cases were non-cataract ocular procedures. A similar percentage of non-cataract surgery procedures were performed during the retrospective control period before initiation of the study. Therefore, the difference in infection rates probably results from the different preparation regimens. Concomitant conjunctival culturing was not performed during this study. Nine of the 31 cases of postoperative endophthalmitis involved cases of cataract extraction with vitrectomy, suggesting that disturbance of the vitreous cavity increases the risk of endophthalmitis. Cataract cases involving disturbed vitreous may deserve special attention for prevention of endophthalmitis, such as the use of intravitreal antibiotic injections, antibiotics added to the infusion fluid, or systemic antibiotics (Table 14-2).

It would seem that an adequate preparation before ocular surgery should include preoperative topical antibiotics with a spectrum of action similar to the suspected pathogens. The topical antibiotic should be used 1 to 3 days before surgery to decrease colony counts. The skin preparation should be a meticulous scrub with 5% to 10% PI. This solution should be allowed to remain in contact with the skin for at least 2 to 3 minutes. Special attention should be directed to the lid margins and base of the cilia, removing all matter from these areas. A solution of 5% PI should be used as a conjunctival irrigation. The nasolacrimal systems can be a source of bacterial contamination, and these areas, including the caruncle, should be prepared at the same time as the conjunctiva. PI should be irrigated liberally from the conjunctiva so that intraocular instillation does not occur. The PI may then be reapplied to the skin surface to allow continued antimicrobial action. Over one-half of eyelids are still culture-positive following PI preparation.[29] If the eye is obviously infected at

TABLE 14-2. Systemic and Ophthalmic Dosage of Selected Antibiotics for Adults

Drug	Topical	Subconjunctival	Intracameral	Intravitreal	Systemic Daily Dose
Amikacin	10–50 mg/ml	25–50 mg		400 µg	15 mg/kg IM, IV
Gentamicin	8–20 mg/ml	20 mg		100–200 µg	3–5 mg/kg IM, IV
Tobramycin	8–20 mg/ml	20 mg		100–200 µg	3–5 mg/kg IM, IV
Ciprofloxacin	3 mg/ml	-		100 µg	0.5–1.5 g po/IV
Moxifloxacin	5 mg/ml	-	500 ug	50 ug	400 mg po/IV
Cefazolin	33–66 mg/ml	50–100 mg	1 mg	2.25 mg	1–6 g IM, IV
Cefuroxime	33–66 mg/ml		1 mg	2.25 mg	500–1,000 mg PO/IV
Cefamandole	50 mg/ml	50–100 mg		2.0 mg	1.5–12 g IM, IV
Clindamycin	10 mg/ml	15–40 mg		1.0 mg	0.6–3.6 g IM, IV
Vancomycin	50 mg/ml	25 mg		1.0 mg	0.5–2 g po 2 g IV
Penicillin G	100,000 units/ml	0.5–1 million units		-	1.2–24 million units IM, IV
Imipenem	5 mg/ml	-		-	1–4 g IV

IM; intramuscularly; IV: intravenously; po: orally

the time of elective surgery, the surgery should be delayed. It is virtually impossible to sterilize a clinically infected eye. The eye should be cultured, broad-spectrum topical antibiotics started, and the surgery delayed 2 to 4 weeks. Conjunctival cultures should be negative before surgery is considered after a recent ocular infection.

Much lower concentrations of PI have been used (0.25%) as an irrigation solution during eye surgery. This has been found to be well tolerated during the surgery. There appears to be significant antimicrobial effect with this concentration.[30] This concentration has also been instilled intraocularly in the treatment of endophthalmitis.[31] It is not known if this dilute PI has an advantage over the standard PI doses (5-10%) or as an additional step in endophthalmitis prophylaxis.

Several conclusions can be made in regard to the large body of literature on prophylaxis for ophthalmic surgeries. First, postoperative infections result from either periocular flora or contaminated surgical instrumentation. The reduction or elimination of periocular flora should reduce the incidence of postoperative endophthalmitis. Second, intensive preoperative topical treatment with antibiotics is an effective way to reduce the periocular flora. Preoperative cultures do not add significant information to antibiotic selection because of their variability. The antibiotic should be able to deliver bactericidal levels to the common causes of postsurgical infection (*e.g. Staphylococcus* species). Third, periocular and conjunctival preparation with dilute PI solution decreases the incidence of postoperative endophthalmitis. Fourth, subconjunctival antibiotics either immediately preoperatively or after closing of the incision can achieve bactericidal levels in the anterior chamber, presumably decreasing the bacterial colony counts. Fifth, the role of prophylactic systemic antibiotics is still unclear but probably unnecessary. Finally, intraocular antibiotics seemingly reduced the number of bacteria in the eye at the conclusion of surgery and reduce the rate of postoperative endophthalmitis with the increased risk of secondary side effects, including rare but potentially sight-threatening events such as HORV and toxic anterior segment syndrome (TASS). The risk/benefit ratio needs to be determined through study of large numbers of patients with appropriate controls.

Donor Cornea Management

Antibiotic treatment of donor eyes for corneal transplantation is a special kind of prophylaxis. Despite sterile technique in removal and handling, up to 100% of donor eyes are culture-positive after removal.[32] Current practice is to use 5% PI rinsing of the donor eye for at least 3 minutes before the tissue is removed for storage. The optimal duration of PI exposure is unknown and exposure time to PI must be balanced with the potential for ocular toxicity. Doubling the exposure time to 5% PI (from 5 to 10 minutes) resulted in a reduction of fungal (2.9% to 0.9%) and bacterial (6.5% to 4.0%) cultures. The incidence of postoperative fungal infections was also reduced (0.48% to 0). No ocular toxicity was observed.[33] Bacterial postoperative keratoplasty infections are rare despite positive

bacterial cultures from the corneal scleral rims.[34] A number of host infections have been reported that can be linked to donor disease. Among these are *Cryptococcus neoformans,*[35]*Streptococcus pneumoniae* in a patient with bronchial pneumonia, *Pseudomonas* in a patient with septicemia,[36] Creutzfeldt-Jakob disease,[37] and rabies.[38]

Streptococcal contamination of donor eyes is not uncommon. *Streptococcus viridans* was recovered in 2.3% of the cultures of 4,167 donor eyes.[39] *Propionibacterium acnes* has been cited as a cause of endophthalmitis after penetrating keratoplasty and also a source of contamination in donor corneas and corneal storage medium.[40] Both *P. acnes* and *Streptococcus* species are organisms that are frequently resistant to gentamicin, which is the one of the current antibiotic additives to corneal preservation solution. Gentamicin had little bactericidal effect at the low (4° C) storage temperature used with intermediate-term storage medium but becomes effective when the tissue is returned to room temperature during corneal transplantation. It is reasonable to assume that broadening the antimicrobial spectrum by adding another antibiotic to the corneal preservation solution will decrease the frequency of post-penetrating keratoplasty infections. Recent studies have indicated that vancomycin in a dosage of 100 µg/ml can be tolerated by the donor cornea for intermediate storage.[41] Other studies have indicated the efficacy of adding either vancomycin or streptomycin to intermediate corneal storage medium to enhance the antimicrobial spectrum of the solutions. These studies indicate that the addition of vancomycin does enhance the spectrum and increases the antimicrobial activity of the solution at 4° C.[42,43] Ciprofloxacin has also been found to be a useful adjuvant or alternative to gentamicin in the intermediate-storage solution, significantly increasing its antimicrobial spectrum, particularly against gentamicinresistant *Pseudomonas aeruginosa*.[43] Currently, the most commonly used media for storage and transportation is Optisol-GS, which incorporates both gentamicin and streptomycin to reduce donor corneal contamination. This solution contains no specific antifungal agents. The 4° C temperature of storage suppresses microbial growth but may not be cidal to more resistant species, such as many fungi.

These modifications of corneal storage solutions with antibiotics do not take the place of meticulous handling of tissue and evaluation of the tissue before its use. The use of tissue from donors with known sepsis or other systemic transmittable infections is contraindicated. Obvious ocular trauma or infection is also an absolute contraindication. Aseptic technique in surgery, just as in other ophthalmic operations, is essential in preventing postoperative endophthalmitis.

Contact Lens Management

The use of a "bandage" contact lens in the short-term management of an acute corneal defect may create a difficult situation. In a series of 278 patients wearing soft contact lenses for protective purposes, four developed corneal infections.[44] Frequent observation of such patients to permit early detection of an infection was advised. Several days of antibiotic usage when an infection is suspected is reasonable.

Both *P. aeruginosa* and *S. aureus* have been shown to adhere to soft and rigid contact lenses. This adherence is not related to protein deposits, and bacteria will adhere to new, unworn contact lenses.[45,46] A large percentage (34.5%)[47] of soft contact lens wearers do not adequately disinfect their lenses. Longer exposure (extended wear) and underlying disease (bullous keratopathy) increase the risk of infectious keratitis. Meticulous care, limited wearing time, attention to pre-existing problems (blepharitis), and maximizing fitting characteristics are keys to successful therapeutic contact lens wear.

Another circumstance in which prophylaxis might be considered is the continuous wearing of a hydrophilic contact lens on a normal eye. A drop of neomycin-polymyxin B-gramicidin solution is instilled four times daily for 3 months. This resulted in the development of bacterial resistance.[48] With *S. epidermidis* used as an indicator, resistance appeared in 2 weeks in the treated eyes and in 4 weeks in the opposite, untreated eyes. Prophylactic antibiotics are not indicated for routine use with continuous-wear cosmetic contact lenses. Prophylactic antibiotic use with therapeutic contact lens use will also lead to the development of resistant bacteria and should be used with caution.

Orbital Fractures

The use of prophylactic antibiotics in the treatment of orbital floor fractures is controversial. Historically, the use of oral broad-spectrum antibiotics (*e.g.* a cephalosporin) for 7 to 10 days was commonly employed to prevent sinus infection from spreading into the orbital and intracranial cavity. There are conflicting recommendations in the literature due to inadequate

case controls. Recent practice patterns of oculoplastic surgeons have reversed this trend and a majority of clinicians are not prescribing oral antibiotics following non-operative orbital fractures.[49]

Intraocular Foreign Body Management

There is controversy concerning the use of prophylactic antibiotics in the management of intraocular foreign bodies. There are no randomized controlled studies. One approach is to prophylactically treat every patient with an intraocular foreign body with intraocular antibiotics. Intraocular infections do develop in some cases and vision or the eye will be lost if an overt infection develops with a virulent species such as *Bacillus c.* Prophylactic intraocular antibiotics will reduce the risk of vision loss due to severe bacterial infections. Vitreous and aqueous taps, followed by intraocular injection of antibiotic have been recommended as prophylaxis in the case of an intraocular foreign body.[50] Not all injured eyes develop infection, and routine prophylaxis will certainly treat many eyes which would not have developed an infection without treatment. For instance, high-velocity metallic foreign bodies from metal-on-metal contact are thought to be sterilized from their formation and speed.[51] As previously mentioned, the instillation of medications intraocularly have associated complications and those must be considered in the choice of a treatment strategy.

Iatrogenic foreign bodies are often inserted around the eye at the time of retinal detachment surgery. If smooth, as in the case of silicon rubber, infection is unlikely. Silicone sponges, with thin multiple cavities, represent a greater hazard of infection. Saturating such a sponge with antibiotic before implantation can reduce the incidence of infection by seven-fold.[52] Meticulous preoperative disinfection and surgical technique contribute to a decreased incidence of scleral buckle infection independent from the effect of antibiotic soaking.[53] Extending the use of PI from preoperative to intraoperative use (0.25% solution) decreases bacterial contamination rate at the conclusion of surgery.[54]

Alteration of Microbial Flora

Severely burned patients provide an illustration of microflora alteration.[55] Burn patients combine susceptibility to infection with chronic antibiotic therapy. In a study of conjunctival skin flora of 53 severely burned patients, a dramatic change to gram-negative organisms occurred at about the fifth to sixth day. *Pseudomonas* was found in 34% of the eyes but remarkably caused no infection as long as the corneal epithelium was intact. Efforts should be made to protect against exposure keratopathy in such patients. Despite the prophylactic use of Neosporin ointment four times daily in 16 eyes, *Pseudomonas* was cultured from 62% of these treated eyes. Prophylactic antibiotic use should be avoided in these debilitated patients and reserved for use when active ocular infection is diagnosed. Otherwise, the topical antibiotic with its concomitant ocular toxicity will confuse the clinical picture and contribute to the development of resistance.

A report of an outbreak of methicillinresistant *S. aureus* (MRSA) infections in a burn unit is an excellent example of the impact of resistant organisms on a hospital. This study, conducted from 1979 through 1981, showed the development of a serious endemic of resistant *S. aureus*.[56] The infection appeared to be transmitted to the burn unit via the plastic surgery service. During the subsequent 2 years, colonization and infection rate with this tetracycline-resistant strain of MSRA rose from 0.03% and 0.2% to 0.16% and 0.28%, respectively. Hundreds of patients were colonized with this bacterium. By 1981, 53% of all *S. aureus* infections were caused by methicillin-resistant strains compared with a 16% rate in 1979. Twenty-four percent of 41 personnel caring for colonized or infected burn unit patients had transient carriage of MRSA compared with only 7% of personnel caring for non-burn patients. This outbreak of infections required permanent closure of the burn unit, resulting in decreased incidents of MRSA colonization and infection among non-burn unit patients. Burn units and intensive care units may serve as reservoirs for resistant organisms in a hospital. These organisms were likely transferred into this unit through hospital personnel. The authors point out the importance of hand washing in preventing transmission of resistant organisms. Hand washing is the single most important procedure in reducing the incidence of nosocomial infections. In the United States, 1.5 million suffer from nosocomial infections. Hand washing is not exercised in a consistent fashion in health care facilities.[56,57]

ADVERSE RESPONSES

The effect of topical antibiotics on the healing of corneal epithelial wounds is of practical importance because these drugs are commonly used in the pro-

phylactic treatment of eyes with epithelial defects. Even the preservatives in the antibiotic formulation can affect epithelial healing. Slight delays in corneal healing occur even with artificial tears containing polyvinyl alcohol, povidone, and chlorobutanol. In the absence of the masking effects of preservatives, significant delays in healing occurred with fortified gentamicin (10 mg/ml), neomycin (8 mg/ml), and bacitracin (10,000 units/ml) but not with the lower doses that are commercially available.[58,59]

The relative safety with which antibiotics can be prescribed for adults does not extend to treatment of the infant or fetus. As examples, colistimethate sodium causes abnormalities of infantile renal tubular cells, the eighth nerve of the newborn is particularly sensitive to streptomycin, tetracycline may cause pseudotumor cerebri and dental defects, pyrimethamine damages cerebral development, and novobiocin increases the chance of developing kernicterus. This means that the ophthalmologist should use systemic antibiotics in the treatment of pregnant women or infants with great care and in consultation with the primary care physician.[60]

Treatment of intraocular infection may consist of intensive use of intraocular as well as systemic and topical routes of antibiotic administration. Intracameral injection of antibiotics has the advantage of rapidly achieving a very high intraocular antibiotic concentration. The risks and benefits of such injection must be weighed in each case.

Irrigation of the anterior chamber with an excessive amount of antibiotic, even penicillin, can destroy the endothelium, result in dense corneal opacity, produce destructive iritis with neovascularization, and induce cataract. Care should be exercised regarding the dosage and formulation of any type of antibiotic injected into the eye. If endophthalmitis is clearly present, aqueous and vitreous taps for cultures should be followed by intravitreal antibiotic injection.

TOXIC CONJUNCTIVITIS

Chronic keratoconjunctivitis can develop after topical antibiotic treatment of a surface ocular infection. Although it is caused by the antibiotic, this inflammation is often misinterpreted as being a continuing infection. Neomycin is a particularly frequent cause of allergic reactions, as is the preservative thimerosal. This type of toxic keratoconjunctivitis may gradually become more severe during prolonged treatment. When this diagnosis is suspected, all medications should be discontinued and treatment limited to cold compresses. It will be often difficult to convince these patients that treatment should be stopped, particularly because a latent period of some days may precede improvement. Conjunctival scrapings of toxic keratoconjunctivitis characteristically show mononuclear cells with typical basophilic granules.[60]

MECHANISMS OF ACTION

Antibacterial drugs are historically designated as either bacteriostatic or bactericidal. This is inexact and dependent on the concentration of drug present. Many otherwise bacteriostatic drugs will become bactericidal when used in high concentrations, as may occur with ophthalmic topical application. Bacteriostatic drugs include erythromycin, tetracycline, chloramphenicol, and sulfonamides. Bactericidal agents include aminoglycosides, penicillins, fluroquinolones, and cephalosporins (Table 14-3).

Penicillins act through inhibition of peptidoglycan (mucopeptide) synthesis in the bacterial cell wall. Penicillins bind to target enzymes in the cell wall called penicillin-binding proteins (PBPs), which vary among bacterial species, accounting for a different spectrum of activity that cannot be predicted on the basis of β-lactamase production. Cephalosporins, imipenem, bacitracin, and vancomycin act through similar mechanisms. Polymyxin B and gramicidin affect the bacterial osmotic barrier through a detergent-like action.

Aminoglycosides are examples of action through inhibition of bacterial protein synthesis. Aminoglycosides *irreversibly* bind to the 30s ribosomal subunit. They are bactericidal to susceptible bacteria. Chloramphenicol, erythromycin, and clindamycin bind to the 50s ribosomal subunit. Tetracyclines *reversibly* bind to the 30s ribosomal subunit.

Sulfonamides interfere with the biosynthesis of the reduced form of folic acid (tetrahydrofolic acid) through interference with the utilization of *p*-aminobenzoic acid (PABA). Later stages of folic acid synthesis are inhibited by pyrimethamine and trimethoprim, which therefore act synergistically with sulfonamides.[61]

Fluoroquinolones bind DNA gyrase and topoisomerase IV. This results in breaks in the double-stranded DNA and cell death. Fluoroquinolones are bactericidal.

TABLE 14-3. Mechanisms of Action of Bactericidal Agents

Cell Wall Function	Inhibitors of Protein Synthesis
Inhibition of peptidoglycan synthesis	**Inhibition of 30s subunit of the ribosome**
Penicillins	Aminoglycosides
Bacitracin	Tetracyclines
Cephalosporins	**Inhibition of 50s subunit of the ribosome**
Vancomycin	Macrolides
Imipenem	Clindamycin
	Chloramphenicol
	Linezolid
	Streptogramins
	Inhibition of folic acid metabolism
	Sulfonamides
	Trimethoprim
	Pyrimethamine
	Inhibition of RNA polymerase
	Rifampin
	Inhibition of DNA gyrase
	Fluoroquinolones
	Destabilize liposaccharide outer membrane
	Polymyxin
	Creates pores in cell membranes
	Defensins
	Disrupt cell membranes
	Cecropins

MECHANISMS OF RESISTANCE

Bacteria may produce enzymes that destroy the antimicrobial drug. β-lactamases are the best-known enzymes in this category. β-lactamases are produced by a wide variety of organisms and effect a large spectrum of penicillin-like drugs. Penicillinase-resistant analogs have been created to overcome this form of resistance. Enzymatic resistance to other antimicrobials, including chloramphenicol and the aminoglycosides, has occurred. Bacterial resistance via enzymatic production may be transferred between organisms through plasmids (extrachromosomal DNA).

Absence of target enzymes in the cell wall will cause relative resistance to penicillins, whereas the lack of binding sites on the ribosomes induces resistance to aminoglycosides, erythromycin, and clindamycin. Permeability changes in the bacterial cell wall are yet another mechanism of resistance preventing buildup of bactericidal concentrations of antibiotics within the bacteria.

The development of antibiotic resistance with ophthalmic antimicrobial drug use is not well understood. Assuming that the enormous volume of topical antimicrobials in use has a commensurate impact, it is rational to follow these principles to limit the development of resistance. First, limit antimicrobial use to diagnosed infections caused by susceptible organisms. For instance, it is unnecessary to use a broad-spectrum antibiotic in the treatment of a viral conjunctivitis. Second, avoid chronic use of antibiotics. Third, use newer antibiotics only when necessary for treatment of infection resistant to traditional therapy. Finally, completely treat all clinical infections and consider using a second agent to prevent emergence of resistant organisms.

SPECIFIC AGENTS

Aminoglycosides

Aminoglycosides comprise a group of antibiotics and semisynthetic antibiotic derivatives including streptomycin, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, and tobramycin. They contain one or two amino sugars, glycosidically linked to an aminocyclitol. Aminoglycosides bind irreversibly to the 30s ribosomal subunit, inhibiting protein synthesis in susceptible bacteria and resulting in a bactericidal action. They are active against aerobic gram-negative and some gram-positive bacteria. They are inactive against anaerobic bacteria. Amikacin, gentamicin, netilmicin, and tobramycin are active against most strains of *P. aeruginosa*, while kanamycin, neomycin, paromomycin and streptomycin are generally inactive against this organism. Amikacin

has a slightly broader antimicrobial spectrum against some aerobic gram-negative bacteria than either gentamicin or tobramycin. However, there are some amikacin-resistant strains of bacteria that are susceptible to gentamicin and/or tobramycin. Aminoglycosides have little activity against *Streptococcus* but are active against many strains of *S. aureus* and *epidermidis*. Resistance may be conveyed to a bacterium to modify the drug enzymatically. Amikacin is resistant to many of these aminoglycoside-modifying enzymes. Resistance may also occur due to decreased permeability of the bacterial cell wall or alterations in the ribosomal binding site. This type of resistance is effective against all aminoglycosides and is fortunately rare. Streptomycin is active against *Microbacterium tuberculous*, *marinum*, and some strains of *Microbacterium kansasii*, *intracellulare*, and *avium*. Ototoxicity and renal toxicity are the most serious adverse reactions to aminoglycoside therapy. Renal toxicity is more likely in dehydrated patients or patients with pre-existing renal failure. Ototoxicity occurs by damage of the eighth cranial nerve and may include both auditory and vestibular dysfunction. Renal toxicity is usually reversible upon discontinuation of the drug, but chronic renal failure or uremia may rarely occur. Risks of toxicity increase with duration of therapy and in the elderly. Aminoglycosides can produce neuromuscular blockade, causing peripheral neuropathy or encephalopathy, including numbness, paresthesias, seizures, and myasthenia gravis-like syndromes. Optic neuritis has been reported with aminoglycoside use.

The antibacterial activity of aminoglycosides may be additive or synergistic with β-lactam antibiotics and vancomycin. It appears that penicillin, by inhibiting bacterial cell wall synthesis, allows the aminoglycosides to have greater access to the ribosomal binding site. Penicillins have been shown to inactivate aminoglycosides *in vitro* and may result in falsely low aminoglycoside concentrations on serum assays. Tobramycin is the most suspectable to *in vitro* inactivation by β-lactam antibiotics. Penicillinase may be added to serum prior to the drug assay to correct for this effect.[62]

Amikacin

Gentamicin, tobramycin, and kanamycin may be inactivated by at least nine distinct bacteria-produced enzymes, the presence of which confers resistance upon the organism. Amikacin is acetylated kanamycin. This semisynthetic additive prevents enzymatic destruction except by the acetyltransferase bacterial enzyme.

Systemic Use

Amikacin is ineffective orally and is given intravenously or intramuscularly in adults in a dosage of 15 mg/kg daily in divided doses every 8 to 12 hours. Doses should be adjusted in renal failure. Peak blood levels reach 18 to 25 μg/ml in ½ to 1 hour. The plasma half-life is 2 hours. After 8 hours, levels may fall below 2 μg/ml. More than 90% of sensitive microorganisms are inhibited by 2 to 4 μg/ml. Aqueous humor concentrations of amikacin were measured after a single intramuscular injection of 7.5 mg/kg given prior to cataract surgery. Aqueous humor concentrations ranged from 0.15 to 3.10 mg/l with an average value of 1 mg/l between 2 to 10 hours after injection. This level is approximately that which should be bactericidal for many bacteria. The systemic administration of this drug, however, does not seem to offer any distinct advantages over prophylaxis with subconjunctival aminoglycosides, such as gentamicin or tobramycin. The subconjunctival delivery gives bactericidal anterior chamber concentrations without subjecting the patient to systemic toxicity.[63] Patients receiving systemic aminoglycosides should be questioned daily about hearing loss, tinnitus, fullness in the ears, vertigo, and unsteadiness.

Penicillin derivatives and aminoglycosides act synergistically; therefore, carbenicillin and amikacin, for instance, may be combined in the treatment of resistant gram-negative organisms. These drugs should not be combined in a common injection, for this may physically inactivate the aminoglycoside. This physical inactivation may also contribute to artificially low measured serum levels of aminoglycosides. Penicillinase should be added to the serum prior to measurement of aminoglycoside levels if a penicillin derivative is given concurrently.

Ophthalmic Use

The most common ophthalmic use of amikacin is as an intravitreal antibiotic for the treatment of postoperative bacterial endophthalmitis. Intravitreal amikacin use is recommended in combination with vancomycin or a cephalosporin. Amikacin may be selected over gentamicin and tobramycin because of the possibility of the presence of a resistant organism, which if not covered could destroy the eye before cultures and antibiotic sensitivities were available. Intravitreal concentration of 400 μg in 0.1 cc of solution is

recommended. Animal studies have shown this to be non-toxic to the retina. Retinal toxicity is found with a dose of 1,500 µg of amikacin as compared with only 400 µg of gentamicin or 800 µg of tobramycin. Therefore, in the case of severe sight-threatening endophthalmitis, amikacin offers a broader spectrum of action along with lower toxicity.[64,65] However amikacin has been reported to cause macular toxicity with intravitreal injection of 200-400 µg.[66,67] Because the specific gravity of the intravitreal aminoglycosides is greater than one, the solution may concentrate in the posterior vitreous near the macula. Amikacin appears to be less toxic than similarly administered gentamicin or tobramycin.[15]

Topical use of amikacin in the treatment of bacterial keratitis should be limited to culture-proven organisms resistant to gentamicin or tobramycin. The recommended dose of amikacin is 10 to 50 mg/cc as compared to 8 to 20 mg/cc of gentamicin and tobramycin.[68] Corneal epithelial toxicity to this dosage is similar to that found with tobramycin. A combination of vancomycin (50 mg/ml) and amikacin (20 mg/ml) may be prepared that has equal efficacy to the solutions given separately.[69]

Gentamicin

Gentamicin is obtained from cultures of *Micromonospora purpurea*. Its mechanism of action is similar to the other aminoglycosides and seems to convey bactericidal activity via inhibition of protein synthesis through binding of the 30s subunit of the ribosomal protein. The recommended systemic dose is 3 mg/kg/day in divided doses at 8-hour intervals, given intramuscularly or intravenously. This dose may be increased to 5 mg/kg/day in life-threatening infections and raised to 6 to 7.5 mg/kg/day in children and 7.5 mg/kg for infants given intravenously. This recommended dose should be altered after obtaining serum levels of the drug. As with all aminoglycosides, the drug is nephrotoxic and renal function should be monitored during usage. Dosage in patients with renal failure should be decreased appropriately. Gentamicin is very active against many aerobic gram-negative, rod-shaped organisms. Diffusion of gentamicin through tissue may be limited due to its positive charge. Therefore, gentamicin and other aminoglycosides may be inactivated by such negatively charged polymers as heparin. They are inactive against anaerobes that lack oxidative phosphorylation and an active transport system, which is necessary for the aminoglycoside to penetrate into the bacteria. Resistance to gentamicin is produced by the presence of inactivating or modifying enzymes. This may be plasmid-mediated. A second type of resistance involves a decrease in the active transport system for the drug. This type of resistance affects all aminoglycosides non-specifically. Fortunately, this type of resistance is rare. Multiple drug therapy, combining an aminoglycoside with a penicillin derivative or a cephalosporin, is often recommended to prevent the emergence of resistant organisms. Synergism between β-lactam antibiotics and aminoglycosides has been demonstrated in the laboratory and this translates into clinical benefit by allowing greater penetration of the aminoglycoside into the bacteria. A semisynthetic aminoglycoside, plazomicin, shows superior activity to many organisms resistant to gentamicin, amikacin, and tobramycin.[70]

Ocular Penetration

Whether instilled topically as drops or ointment or given intramuscularly, gentamicin penetrates very poorly into normal eyes. Inhibitory aqueous levels may be obtained if the cornea is abraded.[71(71)] Inflamed eyes may achieve even higher levels with topical use.[72] No measurable vitreous levels of gentamicin can be achieved with topical use. Subconjunctival injection of 20 mg of gentamicin achieves therapeutic aqueous levels for several hours.[73,74]

Intravitreal antibiotics represent the most effective way of treating endophthalmitis caused by susceptible bacteria. Other routes of administration achieve ineffective intravitreal levels of antibiotic.[75,76] In most cases of bacterial endophthalmitis, a single injection of antibiotic is sufficient to sterilize the eye; however, in persistent infections, reinjection may be appropriate in 48 hours. Initial culturing is vitally important in these persistent cases in order to modify the antibiotic regimen for the second dose.

Topical Use

Topical gentamicin is clinically effective in the treatment of many external eye infections. Topical gentamicin sulfate is available in a concentration of 3 mg/ml. Fortified doses can be formulated from the intravenous preparation in doses of 8 to 20 mg/ml. These high doses of gentamicin are toxic to the corneal epithelium, delay corneal epithelial healing, and should be reserved for sight-threatening eye infections with susceptible organisms. Fortified gentamicin or tobramycin in combination with a cephalosporin or vancomycin are recommended

as the initial empiric treatment of bacterial corneal ulcers after culturing is performed. Initial treatment includes multiple dosing every 5 minutes during the first 30 minutes and then application every 30 to 60 minutes. Ophthalmic ointments are thought to be less effective than solutions from a theoretical standpoint due to binding of the drug to the ointment vehicle decreasing the available antibiotic. Gentamicin ointment and solution have been found to reduce bacterial colony counts equally well. Use of fortified ointments may allow extended dosing intervals and improved compliance.[77] Corneal levels of gentamicin associated with systemic administration do not compare with the high levels obtained with topical use.[78]

Hydrophilic contact lenses and collagen shields may be used to modify drug delivery in corneal ulcers. The amount of drug delivered by hydrogel lenses is dependent upon the initial concentration of the soaking solution and also the water content and thickness of the lens. Thicker, higher water content lenses will deliver more drug than thinner, lower water content lenses.[79] High antibiotic levels with constant exposure may lead to increased corneal epithelial toxicity.

Trans-scleral iontophoresis may offer a less invasive alternative to introduce intravitreal antibiotics compared with the currently accepted injection method.

Toxicity

Toxicity of aminoglycoside antibiotics can occur near their therapeutic range. Although a number of systemic dosing methods have been developed to initiate therapy, there is wide inter-patient variability in final serum concentrations after standard dosage with aminoglycosides in patients with similar renal function. This is most probably due to variable tissue retention of the aminoglycoside. Peak and trough serum concentrations are necessary to adjust systemic dosage. Nephrotoxicity and ototoxicity are the most serious side effects of aminoglycosides. These happen more commonly in elderly, dehydrated patients with renal impairment, and patients receiving high doses over long periods of time. Both auditory and vestibular symptoms may occur with aminoglycoside ototoxicity. The vestibular symptoms are more common with streptomycin, gentamicin and tobramycin, while auditory symptoms are more often associated with amikacin, kanamycin, neomycin, and paromomycin. Gentamicin accumulates selectively within lysosomes and causes a reduction of sphingomyelinase activity. As a result, phospholipid storage occurs within the cells in the form of concentric, lamellar structures, similar to the whirl inclusions of Niemann-Pick disease. Nephrotoxicity includes tubular necrosis, increase in blood urea nitrogen (BUN) and serum creatinine and decreases in urine specific gravity and creatinine clearance. Proteinuria and metabolic acidosis may also occur. Aminoglycosides may produce neuromuscular blockade resulting in respiratory paralysis or a myasthenia gravis-type syndrome. Peripheral neuropathy and encephalopathy may occur. Pupillary mydriasis and conjunctival paresthesias have been reported after topical and subconjunctival use of gentamicin.[80]

The corneal and conjunctival epithelium can show characteristic concentric lamellar structures associated with gentamicin use. These are due to accumulation of the drug in lysosomes causing phospholipid storage but do not seem to have clinical significance.

Neomycin

Neomycin is an aminoglycoside antibiotic obtained from *Streptomyces fadiae*. It is a complex of neamine and neomycin B and C. The commercially available drug is the sulfated form of neomycin B. Its antibacterial spectrum is broader than that of bacitracin, penicillin, or streptomycin. The drug is very stable at room temperature and is not inactivated by body fluids.

Systemic Use

Neomycin is used clinically either orally or topically. Intramuscular and intravenous use are contraindicated due to nephro- and ototoxicity. Approximately 3% of an oral dose is absorbed from the normal gastrointestinal (GI) tract; however, increased absorption may occur with abnormal GI motility. It is indicated in the treatment of hepatic encephalopathy and preoperative intestinal antisepsis. It is also useful in the treatment of diarrhea caused by *Escherichia coli*.

Ophthalmic Use

Its ophthalmic use is primarily in combination with other medications as a topical antibiotic. It is used in combination with polymyxin B and gramicidin as a broad-spectrum antibacterial combination solution. Its spectrum encompasses most causes of bacterial eye infections. Neomycin is bactericidal for many gram-positive and gram-negative organisms.

Neomycin is used in combination with polymyxin B and bacitracin as an ointment.

Patients who use a combination antibiotic containing neomycin for long periods of time for treatment of chronic infections will frequently develop an allergic reaction. Long-term use of any antibiotic is usually not recommended and may result in colonization with resistant microorganisms.

Streptomycin

Streptomycin is obtained from cultures of *Streptomyces griseus*. Because of its limited bacterial spectrum when compared to other aminoglycosides, its use in bacterial infections has largely been supplanted by gentamicin, tobramycin, and amikacin. Streptomycin is used in combination with at least one other agent in the treatment of tuberculosis (TB). It may also be used in the treatment of tularemia, plague, brucellosis, glanders, lymphogranuloma inguinale, and chancroid.

Aminoglycosides should be used with caution in patients with myasthenia gravis, Parkinson's syndrome, or other neuromuscular disorders. These drugs may aggravate muscular weakness due to neuromuscular blockade and cause respiratory paralysis. This effect can even occur in individuals handling the drug and proper precautions should be taken. Streptomycin should not be given alone in the treatment of TB. It is usually used for resistant TB in combination treatment with other agents.

Tobramycin

Tobramycin is obtained from cultures of *Streptomyces tenebrarius*. Like other aminoglycosides, it is bactericidal through inhibition of protein synthesis and susceptible bacteria due to binding of the 30s subunit of the ribosome. Its bacterial spectrum is similar to gentamicin. It is active against 96% of *P. aeruginosa* compared with only 77% activity of gentamicin. (67) Tobramycin use should be restricted to those infections not responding to gentamicin or with antibacterial sensitivity showing resistance to gentamicin. It may also be used in the case of a life-threatening or sight-threatening infection that has a high probability of being caused by *P. aeruginosa* because of the differential sensitivities of the two drugs and the importance of optimum initial empiric drug selection.

Systemic Use

The usual dosage is 3 mg/kg daily given in three divided doses at 8-hour intervals. This dosage may be increased to 5 mg/kg for life-threatening infections. Peak serum concentrations are vital in adjusting the dosage to maintain optimum levels and limit toxicity. This is particularly important in patients with renal impairment. Renal function should be monitored throughout the course of treatment (BUN and serum creatinine).

Ophthalmic Use

Topical tobramycin sulfate is available commercially in a 0.3% solution. This solution does contain a preservative and is not appropriate for intraocular injection. Fortified topical preparations may be prepared from the intravenous solution. Sterile parental tobramycin can be obtained in concentrations of 10 mg/ml, 20 mg/ml, 40 mg/ml, 60 mg/ml, and 80 mg/ml. Fortified concentrations for topical use in severe keratitis range from 8 to 20 mg/cc.[81] Subconjunctival injection of 20 mg in 0.5 cc may be used. Tobramycin 0.1 to 0.4 mg in 0.1 ml may be used intravitreally and in the vitreous infusion fluid at a dose of 10 µg/cc.[82] Tobramycin may be applied via a collagen shield. Care must be taken in the concentration used because prolonged corneal epithelial toxicity and sloughing may result if the highest fortified dosage is used.

Very low levels of aqueous and vitreous tobramycin are detected after systemic administration and these peak at 1 to 2 hours after administration. Cornea and tear levels are even lower.[83] Inhibitory levels of tobramycin are found in the aqueous after subconjunctival injection.[81] Adequate tear and corneal levels may be sustained over 1 hour with fortified topical solutions. A corneal and conjunctival reservoir of solution appears to be present, allowing the persistence of tear drug levels. The tear levels of the drug may be increased by occlusion of the lacrimal puncta with intracanalicular collagen plugs.[84] Multiple applications of the drug result in dramatic increases of corneal tear levels. Drops given every 15 minutes will increase initial tear levels from 20 µg/ml to over 50 µg/ml in 4 hours. Similarly, corneal levels will increase from 10 to 50 µg/ml. One must remember with these frequent topical instillations and also with subconjunctival injections that significant serum levels may be obtained.[81,85] Iontophoresis has been used experimentally to provide vitreous levels of tobramycin without injection.[86]

Penicillins

Penicillin is a generic term often used without the realization that a number of natural and synthetic

derivatives of 6-aminopenicillanic acid exist. All of the clinically useful penicillins effectively inhibit certain bacteria, resist inactivation by human tissues, and are remarkably non-toxic. Considerable variations exist in solubility, stability, and resistance to destruction by penicillinase.[87]

Types

Potassium penicillin G is very water-soluble and is ideal for attaining high plasma concentrations rapidly. This form of penicillin is absorbed and excreted rapidly; therefore, it must be administered intramuscularly at least every six hours to maintain satisfactory blood levels. As much as 100 million units/day may be given intravenously for overwhelming or resistant infections. Intramuscular doses greater than 500,000 units may be very painful.

Although potassium penicillin G may be given orally, its absorption is limited because of its instability in gastric acid. Approximately only 15% of the orally administered drug can be recovered in urine. To avoid destruction of the drug, oral doses should always be given at least 1 hour before or 2 hours after meals. For treatment of infections caused by sensitive bacteria, the minimal recommended oral dose is 400,000 units four times a day.

Procaine penicillin G is less soluble in water and is therefore absorbed more slowly than potassium penicillin G. Intramuscular doses of 600,000 units every 24 hours will maintain demonstrable plasma concentrations, comparable to those attained by oral administration of 250 mg four times a day of phenoxymethyl penicillin or potassium phenethicillin. If higher blood levels are desired, large injections of potassium penicillin G should be used. Giving doses of procaine penicillin G larger than 600,000 units and more often than every 12 hours is an inefficient method of achieving high plasma concentrations.

Benzathine penicillin G is only slightly water-soluble and produces very low blood levels, which may last for several weeks. A single injection of 2,400,000 units intramuscularly will cure early syphilis in most cases. The longer acting forms of penicillin are more likely to produce hypersensitivity reactions.

Phenoxymethyl penicillin (penicillin V) is much more acid-stable than is penicillin G; hence, it is well suited for oral use. As much as 75% of an oral dose may be recovered in the urine, indicating absorption two to five times that of oral penicillin G. Phenoxymethyl penicillin may be given without regard to the time of meals. An oral dose of 250 mg four times a day is adequate for most infections. The oral route may be considerably more economical than the parenteral route. Phenoxyethyl penicillin is pharmacologically comparable to phenoxymethyl penicillin.[88]

All types of penicillin described to this point differ in solubility and stability. Their antibacterial effect, however, is essentially the same, as all are effective against most gram-positive cocci (with the noteworthy exception of penicillinase-producing and therefore resistant staphylococci), gonococci, enterococci, *Haemophilus*, *Clostridium*, and spirochetes. Most gram-negative bacteria (specifically, *Pseudomonas*) are resistant to these forms of penicillin.

Penicillinase-Resistant Agents

Sodium methicillin (sodium dimethoxyphenyl penicillin) is resistant to destruction of penicillinase and is a first-choice agent against resistant staphylococci (unless the patient is allergic to penicillin). Minimal dosage is 1 g intramuscularly every 6 hours. Serious infections may require 2 g every 4 hours, given by continuous intravenous drip. The renal excretion of methicillin is rapid, half being excreted within 2 hours after intramuscular injection and 1 hour after intravenous administration.

Methicillin is extremely unstable in even slightly acid solutions and therefore should be dissolved just before use. When added to infusion fluids, it may be inactivated within several hours.

Sodium oxacillin is pharmacologically comparable to methicillin, except that it is more acid-stable and may therefore be given orally (500 mg every 2 hours). Frequent dosage is necessary because of the rapid excretion of the drug.[89] Oxacillin is not excreted in sweat and therefore is not effective against skin surface infections.

Broad-Spectrum Agents

Ampicillin is an acid-stable, orally absorbed synthetic penicillin with broad-spectrum antibacterial activity. It is effective against a variety of gram-negative bacteria, particularly *E. coli* and *Proteus*.[90] The drug is administered orally, 0.75 g every 6 hours. It is chiefly indicated for the treatment of infections caused by tetracycline-resistant, gram-negative bacteria. Being inactivated by penicillinase, ampicillin is ineffective against penicillin G-resistant staphylococci. Amoxicillin is comparable to ampicillin. Azocillin is an acylaminopenicillin with expanded gram-negative activity. It is comparable to piperacillin and mezlocillin. Carbenicillin is a semisynthetic penicillin

that acts against gram-negative pathogens. Inhibition of most strains of *Pseudomonas* requires doses of up to 50 µg/ml. *Proteus* and *E. coli* may respond to carbenicillin therapy. Penicillinase-producing staphylococci are resistant. Gentamicin and carbenicillin are incompatible in solution; however, they are synergistic against gram-negative microorganisms. The drug has low toxicity and may be used in doses of 20 to 40 g/day. Because of acid instability, carbenicillin must be given parenterally. The intravenous route is ordinarily used. Ticarcillin is comparable to carbenicillin.

Ocular Penetration

The blood-aqueous and blood-vitreous barriers severely limit passage of non-lipid-soluble drugs such as penicillin into the vitreous, aqueous, and lens. A comparable barrier separates the healthy vitreous from the aqueous. A common error is to think of the entire eye as being within the blood-aqueous barrier; this is not correct. The uveal tract is freely accessible to blood-borne medications.

The semisynthetic penicillin derivatives vary considerably in their intraocular penetration. Methicillin, carbenicillin, cloxacillin, and amoxicillin do not penetrate nearly as well as does ampicillin.[91-93]

An active transport system removes organic anions from the vitreous. This mechanism can be blocked by probenecid, in the same manner as renal excretion is blocked.

Clinical Uses

The use of penicillin in the treatment of eye infections is limited by several factors. Most important is the susceptibility of the offending microorganism, for, of course, there will be no therapeutic response to penicillin if the organism is resistant. A very practical limitation is the 5% incidence of allergy after topical ocular use of penicillin. Because of this, other antibiotics and antibacterials have completely replaced penicillin in the local treatment of minor surface ocular infections. The most complex limiting factor is the resistance of the blood-aqueous barrier to the passage of penicillin, which persists to a certain degree even in an infected eye.

Treatment of syphilitic optic neuritis, a manifestation of central nervous system infection, is not easily accomplished because of the blood-brain barrier. Even after 10,800,000 units of benzathine penicillin are given over a period of weeks, *Treponema pallidum* can be recovered from cerebrospinal fluid. Similarly, procaine penicillin G and penicillin in aluminum monostearate fail to produce treponemicidal levels in cerebrospinal fluid (CSF). A reliable way of achieving treponemicidal CSF levels of penicillin is to give 500,000 units of penicillin G every 6 hours together with 500 mg of probenecid by mouth every 6 hours.[94] Official recommendations of the US Centers for Disease Control for treatment of neurosyphilis advise use of intravenous aqueous crystalline penicillin G 18-24 million units per day given as 3–4 million units every 4 hours for 10 to 14 days. Alternatively, the penicillin G can be given as a single intramuscular dose of 2.4 million units and probenecid 500 mg orally for 10 to 14 days.

The incidence of penicillinase-producing strains of gonococcus is increasing. Initial therapy should be aqueous crystalline penicillin G, 50,000–100,000 units/kg/day. The therapy may be modified when susceptibility data is available. In areas with high incidence of penicillinase-producing organisms, treatment with a penicillamine-resistant drug (nafcillin, cephalosporins) is rational.[95]

Topical therapy is penicillin 100,000 units/ml, alternately. *Chlamydia trachomatis* in neonatal conjunctivitis has been successfully treated with 25 mg/kg oral erythromycin ethylsuccinate twice daily for 14 days.[96]

Benzathine penicillin (900,000 units intramuscularly every 2 weeks for 4 months) has been used for the treatment of trachoma,[97] in which 12 patients were completely cured and 2 showed great improvement at the end of 4 months. Two years later, all but one of the 18 were cured. Whether penicillin acts directly on the chlamydia or merely arrests secondary bacterial infection is not clear. Tetracycline or doxycycline is currently recommended in the treatment of trachoma and inclusion conjunctivitis in adults. Erythromycin is the alternate choice in adults and first choice in children under 8 years of age and in pregnant women.

Toxic Effects

External application of penicillin in any concentration is non-toxic to the eye. The anterior chamber will tolerate irrigation with potassium penicillin G, 5,000 units/ml.

Penicillin Allergy

Five percent of the population in the United States is said to be allergic to penicillin.[98] This is presumably related to the enormous amount of penicillin used (350 tons/year or 3,000,000 units/inhabitant). Eighty percent of all drug rashes are caused by penicillin.

With the advent of benzathine and the other types of repository penicillin, allergic reactions have become even more severe and prolonged.

The most common type of penicillin allergy is the delayed response that simulates serum sickness. After an incubation period, usually lasting 1 to 2 weeks, urticaria, fever, and joint pains appear. This response is a result of the development of antibodies after the injection, and therefore skin tests and past history will not reveal penicillin sensitivity.

The local ocular use of penicillin may result in as high as a 16% incidence of allergic blepharitis.[99] For this reason, topical ocular use has fallen out of favor.

Cephalosporins

Cephalosporins are derivatives of cephalosporin C produced by the fungus *Cephalosporium acremonium*. The drugs are related to penicillin through their common β-lactam structure. They are also related to cephamycins and 1-oxa-β-lactams. Instead of the five-membered thiazolidine ring of penicillin, cephalosporins are composed of the β-lactam ring fused with a six-membered dihydrothiazine ring. Cleavage of the β-lactam ring at any point destroys the antibacterial activity. Once mixed in solution, cephalosporins are not stable unless frozen. They are bactericidal in action through the inhibition of mucopeptide synthesis in the bacterial cell wall. Cephalosporins are active against many gram-positive aerobic bacteria and some gram-negative aerobic bacteria as well as some anaerobic bacteria. Cephalosporins are classified based on the spectra of their activity. First-generation cephalosporins are active *in vitro* against gram-positive cocci including penicillinase-producing *S. aureus* and *S. epidermidis*, group A β-hemolytic streptococci, group B streptococci and *S. pneumonia*. First-generation cephalosporins are not active against enterococci, MRSA, *Bacteroides fragilis*, *Citrobacter*, *Enterobacter*, *Listeria*, *Monocytogenes*, *Proteus* (other than *Proteus mirabilis*), *Providencia*, *Pseudomonas*, and *Serratia*. Second-generation cephalosporins are noted for their increased activity against *Haemophilus influenzae* and may also show some activity against *Acinetobacter*, *Citrobacter*, *Enterobacter*, *E. coli*, *Serratia*, *Providencia*, *Proteus*, *Neisseria*, and *Klebsiella*. Third-generation cephalosporins show less activity against *Staphylococcus*, but much greater activity against gram-negative bacteria.

Bacterial resistance may occur due to decreased permeability of the bacterial cell wall to the antibiotic or due to resistant metabolic pathways. β-lactamase inactivates the β-lactam ring in the antibiotic, neutralizing its action.

Subconjunctival Cephalosporins

Intraocular levels peak 60–90 minutes after subconjunctival injection.[100,101] Subconjunctival cephalosporins may be useful in enhancing surgical prophylaxis as an adjunct to subconjunctival aminoglycosides. Their spectrum of action is variable and, in most cases, would not be appropriate as a single agent.

Intravitreal Cephalosporins

Intravitreal cephalosporins provide an excellent adjunct to aminoglycosides in the treatment of postoperative endophthalmitis and the prophylaxis of endophthalmitis in intraocular foreign body management. Vancomycin used in a concentration of 1 mg/0.1 ml is a good substitute for a cephalosporin intraocularly when used in combination with aminoglycosides and may provide somewhat better gram-positive coverage. Ceftazidime may be used intravitreally with vancomycin as an alternative to aminoglycosides in the treatment of endophthalmitis. The dosage for intravitreal ceftazidime is 2.0 mg in 0.1 cc.[102]

Topical Cephalosporins

Cephalosporins may be used in combination with topical aminoglycosides in the treatment of severe infectious keratitis. Solutions should be mixed in concentrations ranging from 33 to 66 mg/cc. Cefazolin is a commonly used drug for this purpose in a dosage of 50 mg/cc alternating with an aminoglycoside every ½ hour around the clock for a severe bacterial corneal ulcer. Vancomycin may be substituted for the cephalosporin to achieve better gram-positive coverage. The vancomycin concentration is also 50 mg/cc. Ciprofloxacin, with good gram-positive and gram-negative coverage, has been advocated as a single agent in the treatment of corneal ulcers. Streptococcal coverage is not as effective with ciprofloxacin compared with the cephalosporins.

Toxicity

Pseudomembranous colitis resulting from clostridial overgrowth occurs most often with clindamycin but also occurs with cephalosporins, ampicillin, chloramphenicol, and tetracyclines. Diarrhea occurs in 20% to 30% of patients receiving cephalosporins, but usually resolves spontaneously when treatment is stopped.

By killing intestinal flora, cephalosporins may

induce vitamin K deficiency.[103] Replacement therapy with vitamin K is effective.

Disulfiram-like (Antabuse) reactions may occur when alcohol is ingested even two days later. This is due to inhibition of acetaldehyde dehydrogenase and the consequent increase in acetaldehyde concentrations. Moxalactam, cefamandole, and cefoperazone have this effect due to a specific side chain.[104]

Mild allergic reactions and rarely fatal anaphylaxis may occur with cephalosporins. Between 1-10% of patients with penicillin allergy may be cross-allergic to cephalosporins. This is most common with first-generation cephalosporins and very rare with third- or fourth-generation cephalosporins.

Summary

The cephalosporins are useful adjuvants to other antibiotics (aminoglycosides) in the treatment of severe ocular infections, including infectious keratitis and endophthalmitis. Their spectrum of action limits their use as a single agent for most ophthalmic purposes. Ceftazidime may be used as a substitute for aminoglycosides along with intravitreal vancomycin for treatment of infectious endophthalmitis. Therapeutic intraocular levels have been obtained with several modes of delivery, notably subconjunctival and intravitreal injections.

Carbapenem β-Lactams

Imipenem

Imipenem is a carbapenem β-lactam antibiotic with the broadest antimicrobial spectrum of any other β-lactam antibiotic. Its action is through inhibition of mucopeptide production in the bacterial cell wall. It is bactericidal against many organisms. Imipenem is combined with cilastatin (Primaxin, MSD) for systemic use. Cilastatin inhibits *in vivo* metabolism of imipenem by dehydropeptidase I in the brush border of the proximal renal tubular cells, increasing urinary concentration of imipenem.

Uses and Dosages

Imipenem and cilastatin is recommended in treatment of lower respiratory tract, skin, intra-abdominal, gynecologic, bone or joint, and urinary tract infections as well as septicemia and endocarditis caused by susceptible organisms. Mild infections are treated with 250-500 mg every 6 hours intravenously and severe infections 500 mg–1 g every 6 hours depending upon the susceptibility of the organisms. Aqueous and vitreous levels well above the minimum inhibitory concentration (MIC) (90) for streptococci are achieved 2 to 3 hours following a single 1 g injection of imipenem, but levels do not exceed the MIC (90) of *Pseudomonas* and *Proteus*.[105]

Imipenem's use in ophthalmology is primarily in the treatment of bacterial keratitis and endophthalmitis resistant to conventional therapy. Topical imipenem (5 mg/ml) is effective in the treatment of aminoglycoside-resistant *P. aeruginosa* keratitis. Concentrations higher than 5 mg/ml are difficult to achieve due to its solubility characteristics. Aqueous humor concentrations increased ten-fold with removal of the corneal epithelium exceeding the MIC for *P. aeruginosa*.[106]

Intravitreal infusion of imipenem in concentrations of 16 µg/ml or less was found to be non-toxic in the rabbit eye. The authors recommended imipenem infusion in the treatment of endophthalmitis in a concentration of 5 µg/ml.[107] Dave *et al.* described the management of 139 cases of gram-negative endophthalmitis.[108] Resistance ranged from 29% to 40% for ciprofloxacin, amikacin, gentamicin, and ceftazidime, respectively. There were no resistant cases found for imipenem. Of the 56 cases 40%) resistant to ceftazidime over half were also resistant to ciprofloxacin, amikacin, or gentamicin but none to imipenem. The authors recommend a treatment dose of 50 micrograms/0.1ml for intravitreal injection. Topical imipenem (50 mg/ml) was used to successfully treat a case of methicillin-resistant *S. epidermidis* (MRSE) keratitis.[109]

Toxicity

Cilastatin apparently decreases the inherent nephrotoxicity of imipenem and significant renal dysfunction is rarely reported. Transient increases in serum creatinine and BUN occur in only 2% of patients. Among the most frequently reported adverse reactions include nausea, diarrhea, and vomiting in 4% of patients. Pseudomembranous colitis (*Clostridium difficile*) has occurred in less than 0.2% of patients.

Meropenem

Meropenem is another carbapenem with a mechanism of action similar to imipenem. Unlike imipenem, it is stable to mammalian dehydropeptidases and does not require co-administration of cilastatin to prevent nephrotoxicity. Compared to imipenem, meropenem has increased bactericidal activity to gram-negative aerobic organisms. Meropenem 10 mg/ml was applied

to a human cornea in an artificial anterior chamber.[110] The authors found low levels of toxicity and good penetration into the cornea and anterior chamber. Meropenem (50 mg/ml) was used to successfully treat a corneal ulcer caused by *Achromobacter xylosoxidans* resistant to multiple antibiotics.[111] Meropenem (1 mg/0.1 ml) has been used in the treatment of a case of endogenous bacterial endophthalmitis.[112]

Bacitracin

Bacitracin is a bactericidal antibiotic with a range of activity closely resembling that of penicillin. Its mechanism of action is interference with bacterial cell wall synthesis. It is active chiefly against gram-positive organisms but also affects spirochetes, gonococci, *Entamoeba histolytica*, and *Actinomyces*. Bacitracin is ineffective against gram-negative bacilli. Most gram-positive organisms are inhibited by 0.001 to 0.5 unit/ml of the drug. Strains of bacteria resistant to bacitracin are much less frequently encountered than with penicillin. Bacitracin is not inactivated by blood, pus, necrotic tissue, or bacterial enzymes such as penicillinase.

Clinical Use

Concentrations of 500 to 1,000 units/g are non-irritating to the eye and other tissues and cause no undesirable systemic effects. Bacitracin does not penetrate the cornea in therapeutic amounts. Use of bacitracin is ordinarily confined to topical application because of significant renal toxicity with systemic use. Topical bacitracin is quite effective in the treatment of surface ocular infections and is commonly used for this purpose.[113]

Although the antibacterial spectrum of bacitracin is comparable to that of penicillin for topical ocular use, bacitracin is preferable to penicillin because fewer strains of organisms are resistant, allergy is less frequent, and sensitization that prevents future use of penicillin is avoided.

Gramicidin

Gramicidin has a spectrum of activity similar to bacitracin. It acts through altering cell wall permeability. Like bacitracin, its role is limited to topical use due to systemic toxicity. Gramicidin causes hemolytic anemia when given systemically. It is used in combination with polymyxin B and neomycin in solution to treat bacterial conjunctivitis and blepharitis. Bacitracin is substituted for gramicidin in the combination ointment. These combination topical antibiotics are uniquely suited for ophthalmic use because resistance to systemic drugs will not develop as a result of their use.

Chloramphenicol

Antimicrobial Spectrum

Chloramphenicol is a synthetic antibiotic that was initially isolated from the bacteria *Streptomyces venezuelae* and has a broad antimicrobial spectrum against a wide variety of gram-positive and gram-negative organisms, *Chlamydia*, *Mycoplasma*, *Rickettsia*,[114] and spirochetes.

Mechanism of Action

Chloramphenicol acts by reversible binding to bacterial 50s ribosome and the inhibition of protein synthesis. Because of this reversibility, the drug is bacteriostatic rather than bactericidal. Chloramphenicol binding is inhibited by erythromycin, lincomycin, and clindamycin. The drug is primarily (90%) inactivated by the liver and thus is tolerated in patients with renal insufficiency.[115]

Intraocular Penetration

The ether/water partition coefficient indicates the relative solubility of a drug in lipids or water. The ether/water coefficient of penicillin is 0.0004, whereas that of chloramphenicol is 4.25. In other words, chloramphenicol is 10,000 times more fat-soluble than penicillin. Its high differential solubility results in a superior intraocular penetration of chloramphenicol.[116]

Systemic Dosage

Blood levels of chloramphenicol in excess of 15 µg/ml are easily attained in humans. The usual dosage for adults is 3 to 5 g/day, administered in divided doses every four hours. Chloramphenicol is readily absorbed from the GI tract, producing a peak blood level at 2 hours and declining to insignificant levels by 8 hours. Rapid renal excretion and hepatic metabolism occurs.

Aplastic Anemia

The most serious side effect of chloramphenicol is the development of aplastic anemia. The incidence is in the range of 1 in 24,500–40,800 with systemic use.[117] The effects on bone marrow may be reversible, dose-related, or idiosyncratic and irreversible, leading to death in half of cases. There appears to

be a genetic predisposition to blood dyscrasias with systemic chloramphenicol. There are case reports of reversible and irreversible (fatal) blood dyscrasias associated with the use of topical chloramphenicol.[118] Should topical chloramphenicol be used for routine conjunctivitis and surgical prophylaxis? Use of topical chloramphenicol in the United States virtually stopped following the case report in 1982;[119] use elsewhere in the world continues.[120] Due to the infrequency of the complication, it is not possible to determine the incidence or the probability of the link to topical use. The clinician must make an assessment of the benefits of the drug with the potential risks. Certainly, patients with a history (or family) history of bone marrow suppression with chloramphenicol use should not be treated with medication — either systemically or topically — unless no other alternative exists.

Early recognition and proper care of drug-induced agranulocytosis demands careful observation of patients receiving drugs known to cause this condition. The mechanism of agranulocytosis may be the formation of antibodies that agglutinate leukocytes in the presence of the drug. The mortality rate is very low if agranulocytosis is discovered by routine white cell count before the development of an infection. The sudden onset of a severe infection (usually a sore throat) during treatment with chloramphenicol requires immediate evaluation of the possibility of agranulocytosis. Aplastic anemia of delayed onset, not necessarily dose-related, is the most serious complication of chloramphenicol therapy.

Prolonged use of chloramphenicol has been suspected to cause optic atrophy in children. Recognizable bilateral optic neuritis has been reported in only six of 200 chloramphenicol-treated patients with cystic fibrosis.

Clinical Use

Systemic and topical chloramphenicol has been supplanted by the cephalosporins, vancomycin, aminoglycosides, and quinolones in the treatment of severe ocular infections in the United States. Because of the potential toxicity of chloramphenicol, it should not be used systemically for trivial infections, nor should it be used for serious infections in which less toxic antibacterial drugs are equally effective. Chloramphenicol should usually be employed only after the causative organism has been isolated and determined to be sensitive to the drug.

Clindamycin

Clindamycin is a chlorinated analog of lincomycin. It is effective against gram-positive, gram-negative, and anaerobic microorganisms. Clindamycin is effective against toxoplasmosis. Topical 0.2% clindamycin hydrochloride is well tolerated.[121]

Clindamycin is available as a hydrochloride, phosphate, or palmitate. The hydrochloride form is a biologically active antibiotic. The phosphate or palmitate forms are prodrugs, requiring enzymatic breakdown in the body before becoming active. The hydrochloride is extremely bitter to taste and excessively irritating on parenteral use. The phosphate may be dispensed as flavored granules for oral use. Clindamycin hydrochloride is the most lipid-soluble form and therefore penetrates the cornea better than the phosphate, achieving aqueous levels twice as high. The eye possesses the enzymes required to activate the phosphate to the hydrochloride form.[122] Fortunately for the patient with ocular toxoplasmic retinochoroiditis, clindamycin is selectively concentrated in the choroid and retina.

Clinical Use

Subconjunctival injection of 15–50 mg every other day for 4 weeks has been used successfully in the treatment toxoplasmosis retinochoroiditis in humans.[123] Oral clindamycin 300 mg four times a day for 4 weeks may also be used. A subconjunctival injection may be used to initiate therapy followed by oral dosing. Intravitreal clindamycin has also been effectively used to treat post-traumatic endophthalmitis caused by *Bacillus* species, as well as delayed postsurgical endophthalmitis from *P. acnes*.

Side Effects

Diarrhea is a common side effect of clindamycin. Systemic administration of this drug may modify intestinal microflora sufficiently to permit overgrowth of *C. difficile*, the cause of pseudomembranous colitis, which may be life-threatening. It requires treatment with either metronidazole or vancomycin.

Lincomycin

Lincomycin is the parent compound from which clindamycin is derived by chlorination. Clindamycin is better absorbed, less toxic, and more potent than lincomycin and is the preferred drug. Cross-resistance between these drugs and erythromycin can develop.[115]

Lincomycin is bactericidal against a wide range of gram-positive organisms but is ineffective against most gram-negative microorganisms. It may be given orally or parenterally in a dosage of 500 mg, which will result in effective serum levels lasting for as long as 6 hours (oral) or 20 hours (intramuscular).[124]

Side Effects

As with clindamycin, overgrowth of *C. difficile* may lead to diarrhea and pseudomembranous colitis. The onset of severe diarrhea is an indication for stopping the antibiotic and starting treatment with vancomycin (500 mg every 6 hours), to which *C. difficile* is highly sensitive.

Erythromycin

Erythromycin is quite similar to penicillin in its effect against gram-positive microorganisms. Staphylococcal resistance to erythromycin develops as readily as it does to penicillin and is related to the frequency of use.[125] Many species of *Chlamydia*, an organism of particular ocular importance, are susceptible to erythromycin. It is also effective against *Rickettsia*, *Treponema*, *Actinomyces*, *Mycoplasma*, and *Legionella pneumophila*. Inhibition of protein synthesis by binding to the 50s ribosomal complex is the mechanism of action.[115]

Erythromycin is well tolerated in oral dosage of 200 to 600 mg every 6 hours. The 0.5% ophthalmic ointment is non-irritating. Jaundice and abnormal liver function may occasionally occur during or after erythromycin therapy. GI irritation with nausea and vomiting may be caused by large doses.[126]

Clinical Use

Erythromycin alone has a much more limited antibacterial spectrum than most combination topical antibiotics now in common use for eye infections. It is certainly not the drug of choice for treatment of an ocular infection of unknown etiology. Early trachoma responds well to treatment with oral erythromycin. At least 2 weeks of therapy is recommended.

Non-gonococcal urethritis occurs in at least 2.5 million US citizens annually.[127] *Chlamydia trachomatis* is recovered from two-thirds of these cases. Newborn infants from these mothers develop chlamydial conjunctivitis, pneumonia, and enteritis. Traditional treatment of this form of ophthalmia neonatorum has been topical erythromycin or tetracycline. Such management is inadequate to remedy the associated relatively asymptomatic but potentially serious pulmonary and enteric infections, which require systemic treatment with erythromycin or tetracycline. It should be noted that tetracyclines cause permanent discoloration of developing teeth. The pediatric oral dose of erythromycin is 30 to 50 mg/kg daily in four divided doses. The adult dose is 4 g daily in divided doses.

Azithromycin (AzaSite)

Azithromycin is another bacteriostatic macrolide that shares a similar mechanism of action to erythromycin. It binds to the 50s ribosomal subunit of susceptible bacteria, thereby interrupting translation, and inhibiting protein synthesis. Its benefits over erythromycin include once-daily dosing, less GI side effects, and an ability to have higher intracellular concentrations.[128] It is used commonly to treat community-acquired pneumonia, skin, and soft-tissue infections. The ophthalmic variant of azithromycin (AzaSite 1%) was approved by the FDA in 2007 to treat bacterial conjunctivitis and blepharitis. Dosing for AzaSite is one drop used twice daily for 2 days, followed by one drop once daily for the next 5 days for a total of 7 days.

Isoniazid

Isoniazid (isonicotinic acid hydrazide) has proved to be an effective anti-tuberculous agent without significant toxicity. Oral dosage is 4 to 5 mg/kg/day (100 mg every 6 hours for an average adult). Peak plasma levels appear within 1.5 hours after oral administration of isoniazid. Excretion is mainly renal and is usually complete within 24 hours. Topical ocular application of a 10% solution or ointment is well tolerated, as is subconjunctival injection of 10 to 20 mg.

Isoniazid is completely ineffective against the common bacteria and viruses, but concentrations as low as 0.02 µg/ml are bacteriostatic for *Mycobacterium tuberculosis*. Corneal penetration of isoniazid is good, and aqueous concentrations are adequate for bacteriostasis by any route of administration.[129] All ocular tissues, including the sclera, are penetrated rapidly by isoniazid. Posterior segment concentrations obtained by systemic routes are higher than those achieved by topical administration.

Clinical Use

Combination therapy with isoniazid, streptomycin, and p-aminosalicylic acid is more effective than use of any one of these drugs alone. Combination therapy

with isoniazid and rifampin may be bactericidal instead of merely bacteriostatic.[115] Topical cortisone may be helpful in combination with isoniazid in the treatment of tuberculous uveitis.[130]

Unfortunately, resistance of tubercle bacilli to isoniazid develops rapidly. The development of resistant strains is significantly delayed by the use of combinations of anti-tuberculous drugs; hence, such combined use is strongly recommended (for example, streptomycin, 1 g twice weekly; p-aminosalicylic acid, 12 to 15 g/day; and isoniazid, 4 mg/kg/day).

Toxicity

Isoniazid can cause severe hepatic damage that may result in chronic scarring of the liver or may even be fatal. The combination of isoniazid and ethambutol is not uncommonly used in anti-tuberculous treatment. Both drugs interfere with enzyme functions. A case of bilateral retrobulbar neuropathy with central scotomata has been reported as a complication of such combined therapy.[131] This is most likely related to ethambutol, which is well known to cause optic atrophy. Visual fields and color vision should be monitored if the patient is on lengthy ethambutol treatment.

Isoniazid increases the excretion of pyridoxine, which is an essential coenzyme for glutamic acid decarboxylase and gamma aminobutyric acid transaminase. Malfunctioning of these enzymes causes peripheral neuritis and convulsions. Such convulsions are not responsive to diazepam, phenobarbital, or phenytoin but can be stopped within 2 hours by pyridoxine treatment. The pyridoxine is given in a dosage of equal weight to the isoniazid.[132]

Peripheral neuritis occurs in 10% of patients receiving 10 mg/kg of isoniazid and may not be completely reversible. Prophylactic dosage of 50 mg pyridoxine daily may prevent this complication.[115]

Polymyxin B

Polymyxin B is bactericidal against most gram-negative microorganisms. The mechanism of action of polymyxin B (as well as polymyxin E, Colistin) is a detergent-like effect destabilizing the outer lipopolysaccharide membrane of gram-negative bacteria. For example, *E. coli*, *P. aeruginosa*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, and *H. influenzae* may be sensitive to polymyxin B. Sensitive organisms are unlikely to develop resistance. *Proteus vulgaris, Neisseria* sp.*, Moraxella catarrhalis, Helicobacter pylori, Vibrio* sp., *and Brucella sp.* are usually resistant to polymyxin B. Combining polymyxin B with rifampin, azithromycin, and/or imipenem produces significant synergism.[133]

Polymyxin B is not absorbed from the GI tract, will not readily pass the blood-brain and blood-aqueous barriers, and does not penetrate the intact cornea after topical application. Renal tubular epithelial damage and neurotoxicity are caused by parenteral dosage in excess of 2.5 mg/kg/day. If systemic use is indicated, 1.5 to 2.5 mg/kg/day is the recommended dose. Laboratory tests subsequent to the administration of polymyxin B should include BUN and albuminuria determinations.

Ocular Tolerance

Concentrations of 0.25% (2.5 mg/ml) are non-irritating and may be used for topical application. Concentrations as high as 1% cause ocular irritation.[134] Subconjunctival injection of 0.5 mg is fairly well tolerated. Currently available ophthalmic ointments contain 0.2% polymyxin B (1 mg of purified drug contains 10,000 units).

Ocular Penetration

Although the intact corneal epithelium prevents penetration of polymyxin B into the corneal stroma, therapeutic concentrations do enter the stroma after epithelial damage.[135] Good stromal penetration occurs after epithelial abrasion whether drug application is by topical instillation or subconjunctival injection.

Polymyxin B/Trimethoprim Combination

Polymyxin B and trimethoprim ophthalmic solution (Polytrim) is approved for the treatment of bacterial conjunctivitis and blepharitis. Trimethoprim inhibits bacterial dihydrofolate reductase, necessary for folate synthesis in bacteria. This combination covers most gram-negative organisms via polymyxin B while the gram-positive organisms are covered via trimethoprim. This alternative avoids the development of resistance, which can affect the therapeutic spectrum of important systemic antibiotics such as the aminoglycosides.

Quinolones

Quinolone antibiotics exert their activity by inhibiting DNA gyrase in susceptible organisms, thereby preventing DNA replication. They are valuable antibiotics due to their unique mechanism of action

and are an effective substitute to treat organisms resistant to aminoglycosides and cephalosporins. The original quinolone antibiotic was nalidixic acid, synthesized in the early 1960s. Fluoroquinolones were created by the presence of fluorine at position six on the molecule. The fluoroquinolone antibiotics have a greater spectrum of action than nalidixic acid.

Nalidixic Acid

Nalidixic acid has a limited activity, including some *Proteus* species, *E. coli*, *Enterobacter*, *Klebsiella*, and some strains of *Salmonella* and *Shigella*. Notably, nalidixic acid is not active against *Pseudomonas* or *S. aureus*. Nalidixic acid has limited clinical use, reserved mainly for urinary tract infections resistant to other standard antibiotics. Other non-fluorinated quinolones include cinoxacin and oxolinic acid, which also have a limited spectrum of antibacterial activity.

Fluoroquinolones

Fluoroquinolones have an expanded antibacterial spectrum. This group of antibiotics is characterized by a fluorine at position six of the four-quinolone nucleus. This generally conveys both improved gram-negative and gram-positive spectrum; however, as a group they are not as effective against anaerobic bacteria.

Ciprofloxacin

Ciprofloxacin hydrochloride is a second-generation fluoroquinolone. It may be used either orally or topically, and ciprofloxacin lactate may be used in intravenous infusion. Ciprofloxacin inhibits DNA gyrase necessary for bacterial DNA replication and also certain aspects of transcription, repair, recombination, and transposition in susceptible bacteria. Ciprofloxacin has been approved by the FDA for use as a single agent in treatment of bacterial corneal ulcers and conjunctivitis (Ciloxan 0.3%, Alcon). Its spectrum of action includes most aerobic gram-negative organisms as well as *S. aureus* and *S. epidermidis*. It has variable activity against streptococcal organisms including *Streptococcus pyogenes*; hemolytic *Streptococcus* groups B, C, F, and G; *S. pneumoniae*; and *Streptococcus faecalias*. Resistant organisms include anaerobic cocci, *Clostridia* species, and *Bacteroides* species. Ciprofloxacin was found to be more potent compared to ofloxacin and norfloxacin in the treatment of susceptible *Pseudomonas* keratitis in a rabbit model.[136]

In the routine treatment of bacterial conjunctivitis, other broad-spectrum antibiotics — such as sulfacetamide and erythromycin — and combination antibiotics — such as polymyxin B/trimethoprim and neomycin-polymyxin B-gramicidin — may be better choices due to better streptococcal coverage.[137]

Ciprofloxacin may be used as single agent in the treatment of bacterial keratitis. Treatment failure may occur and require aminoglycoside, another fluoroquinolone, cephalosporin, and/or vancomycin therapy.

The benefits of substituting a commercially prepared single agent, such as a fluoroquinolone, for the currently used dual-fortified antibiotic regimen for the treatment of bacterial corneal ulcers includes decreased chance of contamination compared with non-preserved solutions as well as miscalculation of concentrations. Use of a single agent may also increase patient compliance. The potential disadvantages include the possibility of insufficient antibacterial coverage, allergic reaction, and direct toxicity to the preservative (if it contains one) in the commercially prepared antibiotic.

Corneal Precipitates

A white precipitate in the anterior cornea developed in 16.6% of patients on topical ciprofloxacin. These opacities appear to be granular or crystalline in nature and are more frequent in elderly patients. The precipitate appears to be crystallized ciprofloxacin.[138] The precipitates are likely related to ciprofloxacin's acidic composition (pH of 4.5) and its reaction to the more alkaline ocular surface.[139] These precipitates clear when the drug is stopped and do not interfere with its antimicrobial properties.

Intraocular Levels

Therapeutic aqueous levels can be obtained following the intravenous administration of 200 mg ciprofloxacin. These levels peaked within 1 hour after administration and dropped quickly during the subsequent 9 hours in non-inflamed eyes. The levels obtained with inflamed eyes may be somewhat higher compared to a normal blood-ocular barrier.[140] As with other antibiotics, the systemic administration of ciprofloxacin does not substitute for intravitreal antibiotic administration in the face of a bacterial endophthalmitis. It may, however, be an adjuvant to intravitreal antibiotic use in selected patients.[18] Ciprofloxacin has been found to be safe when administered intravitreally in doses of 100 µg or less in phakic or aphakic

rabbit eyes. Disorganization of outer rod segments was found with transmission electron microscopy after intravitreal injection with ciprofloxacin doses higher than 100 µg. Similarly, increases in corneal thickness occurred with intravitreal injections of greater than 100 µg of ciprofloxacin.[141]

Norfloxacin

Norfloxacin has a spectrum of activity similar to that of other fluoroquinolones, including ciprofloxacin. It is active against most gram-negative aerobic bacteria and many gram-positive aerobic bacteria. Like ciprofloxacin, the MIC for streptococci are poor when compared to the other gram-positive aerobic bacteria. It is approved by the FDA for use in the treatment of bacterial conjunctivitis. Quinolones such as norfloxacin (Chibroxin, MSD) and ciprofloxacin have been shown to cause arthropathy in immature animals with systemic administration. Topical quinolones have not been shown to have any effect on weight-bearing joints. Norfloxacin has been used successfully in the treatment of *Pseudomonas* corneal ulceration and would seem to have similar clinical usage as ciprofloxacin.[142] Norfloxacin was discontinued in the United States in 2014.

Ofloxacin

Another fluoroquinolone, ofloxacin, is approved for topical use. Its spectrum of activity is similar to that of norfloxacin and ciprofloxacin.[143]

Topical ofloxacin (0.3%) has been found to produce peak aqueous levels of 0.338 µg/ml compared with 0.072 and 0.057 for ciprofloxacin and norfloxacin, respectively.[144] Ofloxacin has greater aqueous solubility than either ciprofloxacin or norfloxacin, attributed to its more basic pH composition of 6.4.[145]

Levofloxacin

Levofloxacin 0.5% is the L-isomer of ofloxacin and has a similar therapeutic index against gram-negative organisms with that of ofloxacin. It has improved activity against gram-positive organisms over ciprofloxacin and ofloxacin. Due to its enhanced solubility, higher concentration, and lower cytotoxicity, it is approved as a first-line treatment of corneal ulcers.[146]

Topical levofloxacin has been approved for use topically in children 1 year and older. Adverse reactions to its use include transient decline in visual acuity, headaches, and photophobia. Topical levofloxacin drops have been suggested as a cause of lung injury.[147]

Gatifloxacin

Gatifloxacin is a fourth-generation fluoroquinolone that is indicated for the treatment of bacterial conjunctivitis. It has excellent gram-negative coverage like its counterpart fluoroquinolones; however, because of its dual binding mechanism through its 8-methoxy group, it provides a broader therapeutic effect against new susceptible microbes. Its mechanism of action includes inhibition of both DNA gyrase as well as DNA topoisomerase IV.[148] Specifically, it not only provides additional gram-positive coverage, but it has improved activity against atypical bacteria and some anaerobic coverage.

Moxifloxacin

Moxifloxacin is another fourth-generation fluoroquinolone that is available for topical, oral, and intravenous formulations. Structurally, like gatifloxacin, it is part of the 8-methoxy fluoroquinolones and has excellent gram-positive and gram-negative coverage. It is bactericidal by binding to both the DNA gyrase and topoisomerase IV, which helps to decreases the chance of developing resistance. The oral and intravenous formulations are commonly used to treat skin and soft-tissue infections, respiratory infections including sinusitis and bronchitis, and intra-abdominal infections.[149] Unlike gatifloxacin, it can be made to not contain any preservatives. This non-preserved solution has been used for antibiotic prophylaxis at the conclusion of cataract surgery. Its pH is closer to the physiological pH and thus does not precipitate on the ocular surface. This medication has become the popular choice as a first-line treatment for corneal ulcer and is commonly employed for dual (in addition to an aminoglycoside) coverage for *Pseudomonas* keratitis. Adverse reactions are similar to the other fluoroquinolones and include tendinitis, arthropathy, neuropathy, and prolongation of the QT interval.

Besifloxacin

Besifloxacin (0.6%) is the newest generation of fluoroquinolone and is only available for ophthalmic use. It is currently approved for the treatment of bacterial conjunctivitis. Compared to the other fluoroquinolones, it has the greatest gram-positive coverage and has been shown to be effective in the treatment of MRSA. It is the only fluoroquinolone that does not have a systemic formulation and, as a result, systemic toxicity and resistance is negligible. Adverse reactions to besifloxacin are limited to local

allergic reaction, eye pain, and photophobia, and it is well tolerated for use in patients older than 1 year.[150]

Rifampin

Although primarily used in treatment of mycobacteria, rifampin has a broad spectrum of antimicrobial activity, being effective against *Pseudomonas*, *Proteus*, *Neisseria*, and *Haemophilus*, for example. It causes cytoplasmic and ribosomal damage to cells. Rifampin diffuses freely within body tissues and traverses the blood-brain barrier. Rifampin and amphotericin B exhibit marked synergism (more than 100-fold enhancement of activity) against various fungi. The synergistic effect of amphotericin B occurs because it increases cell wall permeability, thereby permitting entry of the second antibiotic. Such synergism also occurs with 5-fluorocytosine and amphotericin but is less predictable. Natamycin-rifampin combination also shows synergism, but of a lesser amount.[151]

Dosage

In the treatment of TB, rifampin is given 10 mg/kg/day for adults and 15 mg/kg/day for children.

Toxicity

Rifampin commonly causes aching of muscles, joints, and abdomen and a transient jaundice (1%). In management of TB, this drug is used for long periods of time and is usually tolerated well. It may cause elevation of liver enzymes and is potentially hepatotoxic. The most serious problem with rifampin is an immunologic reaction encountered with intermittent use of large doses. Hematologic, pulmonary, and renal anaphylactic reactions can occur, but such reactions are very uncommon despite widespread use of rifampin in tuberculotherapy.[115]

Rifabutin

Rifabutin is a semisynthetic derivative of rifamycin. Its mechanism of action is inhibition of DNA-dependent RNA polymerase. Its primary use is in the treatment of *Mycobacterium avium* complex (MAC) in patients with advanced HIV infection. Dosage is 300 mg orally daily in combination with other drugs. Systemic side effects include rash, GI intolerance, and neutropenia.

Acute Uveitis Associated with Rifabutin

Acute hypopyon uveitis has been reported in patients receiving rifabutin for MAC. These patients were also receiving other systemic medications for MAC (clarithromycin, fluconazole, and ethambutol). These eyes responded well to topical corticosteroids.[152,153]

Sulfonamides

The sulfonamide drugs are bacteriostatic by virtue of their ability to competitively inhibit p-aminobenzoic acid. Knowledge that many local anesthetics are esters of p-aminobenzoic acid is of practical value, since such drugs (procaine and tetracaine) will interfere with sulfonamide action. Purulent exudate also contains p-aminobenzoic acid and therefore interferes with the action of sulfonamides.

Toxic effects

Sulfonamides cause a variety of undesirable reactions. Renal complications are among the most common problems and include crystalluria, hematuria, and anuria. A fluid intake sufficient to produce at least 1,000 ml of urine daily will help to avoid renal problems. Since sulfonamides are considerably more soluble in an alkaline pH, sodium bicarbonate greatly reduces the possibility of crystalluria.

Other complications include agranulocytosis, hemolytic anemia, toxic hepatitis, erythema multiforme major (Stevens-Johnson syndrome), skin rashes, photosensitization, peripheral neuritis, drug fever, acute psychoses, transient myopia, and allergic reactions.

One case of erythema multiforme major (Stevens-Johnson syndrome) has been convincingly linked to the use of topical 10% sulfacetamide solution with no history of sulfa allergy. The patient had been previously sensitized with systemic sulfa.[154] Transient myopia may occur with systemic and topical sulfonamide use. This results from ciliary body edema and concomitant zonular relaxation and anterior lens movement. Intravenous sulfonamide preparations are irritating and may cause local thrombophlebitis.

When sulfonamide ointments are applied in the treatment of marginal blepharitis, local photosensitization may result in circumscribed sunburn of the lid margin. The mistaken diagnosis of allergic response is commonly made.[155]

Sulfacetamide may crystallize, forming white plaques on a dry surface. White corneal plaques have been reported in a patient with severe dry eye syndrome treated for a conjunctivitis with 10% sulfacetamide drops. The plaques were superficial and were removed with simple excision.[156]

Clinical Use

Although sulfonamides have largely been replaced by other antibacterials, topical use of sulfacetamide (a 30% solution or a 10% ointment) is still a highly effective prophylaxis against corneal infection after abrasions or the entry of superficial foreign bodies and in the treatment of pre-existing infections caused by susceptible organisms.[157]

Sulfonamide therapy is an important supplement to pyrimethamine in the treatment of retinochoroiditis presumably caused by toxoplasmosis. The amount of pyrimethamine needed is greatly reduced by the synergistic effect of sulfonamides, thereby decreasing the risk of toxic effects.[158] A total of 2 g is administered daily in four divided doses. Use of triple sulfonamides (sulfadiazine, sulfamerazine, and sulfamethazine) is said to reduce the danger of crystalluria but is not readily available. Folinic acid supplementation (4 mg every other day) is required in order to prevent thrombocytopenia and leukopenia that may result.[159]

The combination of trimethoprim and sulfamethoxazole has been found to be useful in the treatment of otherwise resistant microbial keratitis. Nocardia keratitis is typically a slowly progressive corneal infection resistant to intensive broad-spectrum topical antibiotic therapy. The synergistic effect of trimethoprim (16 mg/ml) and sulfamethoxazole (80 mg/ml) has been reported to allow more rapid resolution of a nocardia keratitis than would be expected with sulfacetamide alone.[160]

The trimethoprim-sulfamethoxazole combination has been used successfully in the treatment of *Toxoplasma gondii* posterior uveitis. Trimethoprim (160 mg) and sulfamethoxazole (300 mg) given orally twice per day may be used with adjuvant prednisone and clindamycin. Because pyrimethamine is not used, bone marrow suppression is not encountered.[161]

Sulfacetamide is antagonistic to the inhibition of *Pseudomonas* by gentamicin.

Tetracyclines

Tetracyclines are bacteriostatic through inhibition of protein synthesis through binding to the 30s subunit of ribosomes. They may be bactericidal at high concentrations. Tetracycline absorption in the GI tract is reduced with concomitant food ingestion, particularly milk and milk products. Aluminum hydroxide, calcium, magnesium salts, and iron preparations bind to tetracycline, chelating it and decreasing absorption.

The tetracycline group includes the short-acting class: chlortetracycline, oxytetracycline, and tetracycline used 1–2 grams/day with four divided doses; the intermediate-acting class: methacycline and demeclocycline (300 mg BID); and the long-acting class: doxycycline and minocycline (100–200 mg used once or twice a day). Doxycycline causes the least change in the intestinal flora. Minocycline achieves the highest levels in the tears. Both doxycycline and minocycline absorption are unaffected by food ingestion. The tetracyclines are termed broad-spectrum antibiotics because of their ability to inhibit the activity of a wide variety of gram-positive organisms, many gram-negative organisms (including *E. coli*, *Aerobacter, Klebsiella*, *Bacillus subtilis*, and *Neisseria gonorrhoeae*), *Rickettsia*, *Actinomyces*, *Spirochaeta*, and *Chlamydia*. *Lymphogranuloma venereum*, psittacosis, *molluscum contagiosum*, trichomonads, organisms causing tularemia, amoebas, pinworms, and anthrax bacilli also respond to tetracycline therapy. Not all strains of these organisms are susceptible; for example, one-third or more of staphylococcal strains may be highly resistant. *P. aeruginosa* and *Proteus vulgaris* are rarely responsive to tetracycline.[162]

Dosage

From 1 to 4 g may be given daily in divided doses every 6 to 8 hours. Comparable amounts may be given intravenously if necessary, but therapy should be changed to the oral route as soon as practicable because of the possibility of phlebitis. For topical ocular use, 0.5% ointment is prescribed and the frequency of application is determined by the severity of the infection.

Significant serum concentrations are reached within an hour after oral dosage, reach a maximum level at 4 to 6 hours, and persist to some degree for as long as 24 hours. Dosage of 1 g every 6 hours will achieve minimal, sustained serum levels as high as 5 µg/ml.

Toxicity

Nausea, vomiting, and diarrhea may complicate oral dosage. Tetracycline may cause an irritated diarrhea which must be differentiated from the enterocolitis caused by *Staphylococcus* and the life-threatening pseudomembranous colitis caused by *C. difficile*. Aluminum hydroxide gels markedly reduce absorption and therefore should not be used to relieve GI symptoms. Thrombophlebitis may occur at the site of intravenous injection. Photosensitivi-

ty reactions manifested by marked erythema after exposure to sunlight have been reported. Vestibular damage, hearing loss, and esophagitis are also rare but serious complications associated with tetracycline use. Overgrowth of non-susceptible organisms (such as *C. albicans*) may follow prolonged tetracycline therapy.

In nine reported instances, death occurred late in pregnancy after prolonged intravenous use of high doses (up to 6 g/day) of tetracyclines. Autopsy revealed extensive fatty degeneration of the liver in all cases.[163]

Tetracycline that has deteriorated from aging in a moist environment may be highly nephrotoxic. Acute necrosis of the renal convoluted tubules may follow use of only a few such outdated capsules.[164,165]

Tetracycline inhibits mineralization of bone in the chicken embryo. A 40% reduction of growth of the fibula results from tetracycline administration to premature infants. This probably results from the strong chelation of tetracycline to cations such as calcium. Even in an adult, 3% to 11% of a dose of tetracycline becomes incorporated in bony structures and remains there cumulatively (except as 10% of the skeleton is remodeled annually). Presence of tetracycline in adult bone has no known adverse circumstances, except that it causes a yellow discoloration.[166]

Tooth development occurs during the last half of in utero development and continues to the age of 8 years. Tetracyclines permanently discolor developing teeth yellow and brown and also cause enamel hypoplasia. Bone growth is slowed. The "bulging fontanel syndrome" is due to tetracycline-induced intracranial hypertension. No reports document discoloration of the teeth or any other adverse effects arising from use of topical ocular tetracycline preparations.

Therapy of Ocular Infections

Surface ocular infections caused by susceptible microorganisms respond well to topical tetracycline application. The incidence of allergy and irritation is insignificant. Although intraocular penetration of tetracyclines is poor, large oral doses (6 to 8 g/day) produce demonstrable aqueous concentrations.

Ocular rosacea

Tetracycline has been advocated in the treatment of acne and ocular rosacea. This is an underdiagnosed chronic skin disease affecting the forehead, cheeks, and nose causing erythema, telangiectasia, papules, pustules, hyperemia, and enlargement of the sebaceous glands. Ocular involvement includes the entire ocular surface: lids, conjunctiva, and cornea. Associated conditions include blepharitis, chalazia, hordeolum, conjunctivitis, and keratitis. Treatment involves 1 g tetracycline per day for 4 to 6 weeks followed by a slow taper to 250 mg every 1 to 2 days depending upon the clinical response. This clinical improvement may, in part, be due to reduced lipase production by *Staphylococcus* organisms as well as a reduction in microflora.[167] Doxycycline may also be used in the treatment of rosacea. A starting dose of 100 mg once or twice per day may be tapered depending upon response to as low as 20–40 mg per day.

Over half of patients with recurrent or persistent chalazion have acne rosacea. Since tetracycline therapy is highly effective in eliminating the findings of rosacea, such treatment would be expected to be helpful in cases of recurrent chalazia.

Gastric hypochlorhydria is characteristically associated with rosacea. A similar pH change affects the tears and may be responsible for the severe symptomatic burning and irritation of the eyes. Determination of tear pH in 44 normal patients and 20 patients with various inflammatory conditions other than rosacea showed all these to have a pH of 7.0. In seven patients with rosacea, all had much more alkaline tears, measuring 8.0. Five patients with inactive tetracycline-treated rosacea measured 7.0.[168]

Phlyctenular Keratoconjunctivitis

Phlyctenular keratoconjunctivitis is characterized by peripheral corneal nodular lesions associated with a hypersensitivity response to *Staphylococcus*. Rosacea-like skin features occur secondary to staphylococcal hypersensitivity reaction and are improved with tetracycline.

Chlamydial Disease

Adult inclusion conjunctivitis is a chronic follicular conjunctivitis acquired from genital contact. Systemic therapy is recommended for the patient and sexual partners to eliminate reinfection from untreated reservoirs of disease. A 3-week course of tetracycline or minocycline is recommended. Erythromycin is an alternative when tetracycline is contraindicated (pregnancy).

Neonatal inclusion conjunctivitis is best treated with systemic and topical erythromycin or sulfa.

Untreated neonatal inclusion conjunctivitis will spontaneously resolve but may leave corneal micropannus and conjunctival scarring.[169] Topical erythromycin ointment prophylaxis will prevent inclusion conjunctivitis but not pneumonitis. Prompt diagnosis and thorough systemic treatment is essential for successful resolution without sequelae.[170]

The prophylactic use of topical tetracycline antibiotics in the eyes of newborn infants has been effective in several thousand patients.[171-173] The eyes of antibiotic-treated infants were open, clean, and non-inflamed, in contrast to the reddened, irritated, closed eyes that characteristically persist for 3 to 4 days after use of silver nitrate. Secondary bacterial conjunctivitis (75% staphylococcal) was reported in 17% to 26% of eyes treated with silver nitrate in contrast to 2.3% to 5% of the eyes treated with tetracyclines.

Acute trachoma may be cured by topical application of tetracyclines. An ointment vehicle is most effective. Treatment must be continued for 2 to 4 weeks.[174-177]

Spirochetal Infection

Tetracycline or doxycycline is recommended for the treatment of Lyme disease caused by *Borrelia burgdorferi*. Patients 9 years of age or older are treated with 250–500 mg four times/day for 10 to 30 days until clinical symptoms resolve. Tetracycline or doxycycline are acceptable alternatives to erythromycin in the treatment of syphilis in patients with penicillin allergy. They are not recommended in the treatment of pregnant women due to fetal effects. Tetracyclines are the drugs of choice in tick-borne (epidemic) and louse-borne (epidemic) relapsing fever caused by *Borrelia* species.

Persistent Epithelial Defects

Epithelial defects of the cornea may be persistent in the presence of chronic ocular or systemic inflammation or following chemical trauma. Tissue- and leukocytic-produced collagenase may be responsible for this, as well as stromal melting and perforation. Tetracyclines have an anti-collagenolytic effect independent of their antimicrobial properties and thus are commonly employed as adjunct therapy in cases with severe corneal thinning, descemetocele formation, and early corneal perforations from infectious keratitis. Systemic tetracyclines have also been useful in healing refractory epithelial defects.[178] Tetracycline has been found to be effective in chronic gingival disease through similar mechanisms.[179] Tetracycline may not be as effective in the treatment of persistent epithelial defects not associated with ocular or systemic inflammation such as occur with diabetes or neurotrophic disease.

Summary

The tetracycline derivatives are remarkably non-toxic antibiotics, highly effective against a wide variety of microorganisms. Unfortunately, they penetrate poorly into the eye. At least 6 to 8 g/day should be given orally if these antibiotics are indicated for the treatment of an infection within the eye. *Pseudomonas*, *Proteus*, and many strains of *Staphylococcus* are resistant to the tetracyclines.

Vancomycin

Vancomycin is derived from cultures of *Nocardia orientalis*. It is a tricyclic glycopeptide that is bactericidal through inhibition of glycopeptide polymerization in the cell wall. It is bactericidal for most gram-positive organisms. It is useful in the treatment of staphylococcal infections in patients who are allergic to or have failed to respond to the penicillins and cephalosporins. It is recommended in the treatment of methicillin-resistant streptococci and also *Bacillus cereus*. Vancomycin is used in combination with an aminoglycoside to treat *Streptococcus viridans* (or *S. bovis*) endocarditis. Vancomycin is indicated in the treatment of pseudomembranous colitis caused by *C. difficile*.[62]

Resistance

Vancomycin-resistant strains of enterococci (VRE) are beginning to emerge. These enterococci are often resistant to all other antibiotics; therefore, systemic use of vancomycin should be limited to reduce selective pressures for the emergence of resistance.

Ophthalmic uses

Vancomycin may be used topically or intraocularly to treat sight-threatening eye infections. These include infectious keratitis and endophthalmitis caused by methicillin-resistant staphylococci or streptococci.[180] It is an acceptable substitute for a cephalosporin used in combination with an aminoglycoside in the empiric treatment of infectious keratitis and endophthalmitis.[181,182] Additionally, vancomycin is very effective in the treatment of infected filtering blebs in trabeculectomy patients.

Dosage

Intravenous dosing of vancomycin in adults with normal renal function is 500 mg every 6 hours or 1 g every 12 hours. Dosing must be adjusted in children and with renal impairment. Dosing with renal impairment should be based on actual serum concentrations after initial empiric administration.

Topical vancomycin may be given in a concentration of 50 mg/cc in the treatment of infectious keratitis. Lower concentrations (5 mg/cc) have been used successfully in the treatment of susceptible staphylococcal blepharoconjunctivitis. Solutions mixed in sterile water have uncomfortably low pH levels. Mixing vancomycin in a buffered tear solution is better tolerated. The drug may precipitate out in solution and should be shaken prior to administration. Vancomycin solution remains stable up to 21 days at either 4° C or 25° C.[182]

Intravitreal vancomycin with an aminoglycoside has been recommended as initial, empiric therapy for exogenous bacterial endophthalmitis. Doses up to 2 mg were found to be non-toxic in phakic and aphakic vitrectomized rabbit eyes by clinical histological and electrophysiologic measures. A dose of 1 mg in 0.1 cc establishes intraocular levels significantly higher than the MIC for most gram-positive organisms.[183,184]

Adverse Reactions

Nephrotoxicity and ototoxicity are the most important side effects of intravenous vancomycin. These occur more frequently in patients with pre-existing renal insufficiency. Deafness may be preceded by tinnitus and may progress despite cessation of the drug. Serum creatinine and BUN concentrations should be monitored while on systemic vancomycin. Vancomycin may cause the “red man’s syndrome”, with flushing and/or rash with hypotension. This reaction is attributed to a large efflux of histamine from mast cells and basophils due to rapid infusion of vancomycin. It may be prevented by slowing the rate of vancomycin infusion or pre-medicating patients with systemic antihistamines.[185]

Topical and intraocular vancomycin have not been associated with nephro- or ototoxicity. Hourly use of 50 mg/ml vancomycin (30 µl drops) could deliver a dose of only 36 mg/day, well under the recommended systemic dose.

Intraocular use of vancomycin has been associated with the development of HORV.[186] The incidence of this is still unclear, but it seems there is a relationship between intracameral or intravitreal administration and the development of HORV. This should not preclude the use of intraocular vancomycin in the face of gram-positive endophthalmitis sensitive to vancomycin when alternatives are not available.

Oxazolidinones

Linezolid is the most common synthetic oxazolidinone antibiotic and is a drug of choice for treating gram-positive bacteria. It is efficient in treating MRSA and VRE and works by inhibiting protein synthesis through inhibition of the 50s ribosomal subunit. It is commonly employed in the treatment of skin and soft-tissue infections as well as nosocomial pneumonia. Although available through intravenous administration, linezolid is unique in that it has 100% oral bioavailability. This benefit allows patients to be easily transitioned from parenteral to oral medication.[187] Adverse reactions are significant for bone marrow suppression and include thrombocytopenia, anemia, and neutropenia. Documented cases of retinopathy and linezolid-induced optic neuropathy have been described and should be considered as a cause of painless vision loss in patients receiving treatment with linezolid.[188] Additionally, because linezolid is a reversible inhibitor of monoamine oxidase, it can potentiate serotonin syndrome in patients taking concurrent selective serotonin reuptake inhibitor antidepressants.

Daptomycin

Daptomycin is a subtype of cyclic lipopeptide which functions by binding to bacterial cell membranes, inducing rapid depolarization of the membrane potential and subsequently interfering with protein, RNA, and DNA synthesis.[189] It is only available for intravenous use. This bactericidal medication is extremely effective against gram-positive agents including MRSA, methicillin-susceptible *S. aureus*, and enterococcus. Indications for daptomycin use include the treatment of septic arthritis, osteomyelitis, and endocarditis. Current studies investigating the use of intravitreal daptomycin in rabbit eyes for treatment of gram-positive endophthalmitis have shown some promise.[190]

Streptogramins

Streptogramins are a class of antibiotics isolated from the bacteria *Streptomyces pristinaespiralis* introduced to target superbugs including MRSA and VRE. Quinupristin/dalfopristin (Synercid) is a combination of synergistically active synthetic streptogramins that

function by inhibiting protein synthesis through irreversible binding of both the 50s and 70s ribosomal subunit. This class of antibiotics is only available for intravenous use in the treatment of severe, life-threatening gram-positive bacteremia and sepsis. Currently, there are no ophthalmologic indications for the use of this antibiotic. Adverse reactions for streptogramins include severe hematologic dysfunction, including spontaneous cerebral hemorrhage, cerebrovascular accidents, and hyperbilirubinemia.[191]

Defensins

Defensins are antimicrobial peptides derived from granules of alveolar macrophages and neutrophils. This group of naturally occurring molecules create pores in the cell membrane of susceptible bacteria to promote phagocytosis.[192] They also appear to have activity through changes in macromolecular synthesis. Rabbit defensing neutrophil peptide-1 (NP-1) had potent bactericidal activity against *Morganella morganii, P. aeruginosa, S. pneumoniae*, α-hemolytic *Streptococcus*, and *C. albicans* with a concentration of 10 µg/ml. Rabbit defensin NP-5 demonstrated minimal bacterial activity at a concentration of 50 µg/ml. These unique molecules are not yet available for clinical use but have an attractive spectrum of action, which would be desirable for ophthalmic use.[193] Defensins have also been recognized to be important contributors to both the tear film and the ocular surface.[192]

Defensin NP-1 has been evaluated as a microbicide in corneal storage media.[194] *S. aureus, S. pneumoniae,* and *P. aeruginosa* were grown in solutions of Optisol (Chiron) without antibiotics and supplemented with rabbit NP-1 at concentrations of 1, 10, 100, and 200 µg/ml. Concentrations of 200 µg/ml killed the bacteria tested at temperatures of 4°, 23°, and 37° C. Defensins (particularly NP-1) may provide an attractive alternative to traditional agents (gentamicin) in the preservation of corneal storage solutions.

Cecropins

Cecropins are a group of small (< 36 amino acids) cationic antimicrobial peptides isolated from the hemolymph of the cecropia moth. They are a natural antimicrobial defense for the moth. These peptides have lytic properties and can disrupt cell membranes.

Shiva-11 is a synthetic cecropin analog, which has been found to have good broad spectrum-activity measured *in vitro*. This activity extends to bacteria and fungi as well as certain viruses and protozoa.[195] There is also some *in vitro* evidence of growth factor activity.[196]

In addition to their antimicrobial effects, certain cecropins have been found to have significant anti-inflammatory properties.[197,198]

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