Conferences and Reviews

Antibiotic Therapy for Ocular Infection

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Infections of the eye can rapidly damage important functional structures and lead to permanent vision loss or blindness. Broad-spectrum antibiotics should be administered to the appropriate site of infection as soon as a diagnosis is made. Topical drops are preferred for corneal and conjunctival infections. Intravitreal antibiotics, and possibly subconjunctival and parenteral antibiotics, are preferred for endophthalmitis. Parenteral antibiotics are recommended for infection in deep adnexal structures. We review specific aspects of antibiotic therapy for ocular and periocular infection.

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The appropriate use of antibiotics to treat ocular infection requires an understanding of the disease processes being treated and a knowledge of the pharmacology and pharmacokinetics of the drugs used. The prompt use of the appropriate antibiotics is essential to preserving vision in the presence of severe eye infection such as bacterial keratitis or endophthalmitis. We will review antibiotic therapy for various ocular infections. Commonly used antibiotics are shown in Table 1.*

General Principles of Antibiotic Therapy

Antibiotic therapy may result in killing the microorganism (bactericidal drugs) or inhibiting bacterial growth (bacteriostatic drugs). When bacteriostatic drugs are used to treat ocular infection, the host defense mechanisms are ultimately responsible for clearing and eradicating the infective organism. In bacterial keratitis, the infection develops in the avascular cornea, and in endophthalmitis it develops in the fluid-filled aqueous or vitreous cavity. In either case, the immune system may be unable to control the organism fast enough to prevent sight-threatening sequelae. Within the first 24 hours pathogens may multiply and release toxins and degradative enzymes that destroy the function and integrity of ocular tissues. Thus, bactericidal drugs are preferred for the treatment of severe ocular infection. The penicillins, cephalosporins, aminoglycosides, and fluoroquinolones are bactericidal agents and are generally used to treat ocular infection. Tetracycline, erythromycin, chloramphenicol, and sulfonamide are bacteriostatic and are often reserved for less severe infections or where there is a specific benefit such as tetracycline in the treatment of ocular rosacea.

Antimicrobial resistance is a constant concern to physicians, and resistance is found to ampicillin, gentamicin, tobramycin, newer cephalosporins, and fluoroquinolones.[1-4] In general, it is thought that with frequent and persistent long-term use of a given antibiotic, there is a greater chance of bacterial strains developing with resistance to that drug. To date, there have been no studies documenting increased resistance of bacteria following the treatment of acute bacterial conjunctivitis or following the short-term use of prophylactic topical antibiotics. It may be that increased antibiotic resistance for a given drug is related to the total area of the body treated or the systemic concentrations of the drug. Thus, antibiotics administered topically to the eye may not affect bacterial resistance to a substantial degree. On the other hand, there remains legitimate concern that drug resistance will occur when topical antibiotics (particularly bacteriostatic agents) are used for prolonged periods.

Topically applied antibiotics are capable of delivering high concentrations of antibiotics to the site of infection in most cases. With conjunctivitis and keratitis, the antibiotic is directly applied (by topical drops or ointments) to the area of infection. With endophthalmitis, topical antibiotics must transit the cornea, and therapeutic concentrations may not be achieved within the eye.[5,6] The factors that influence the intraocular penetration of antibiotics include the charge of the drug, the status of the corneal epithelium, the degree of ocular inflammation, the formulation and concentration of the drug, and the dosage regimen employed.[7] The chemical properties of a drug influence its intraocular penetration through its ability to diffuse across the layers of the cornea. The outer epithelial layer is rich in lipids, whereas the inner stroma of the cornea is composed primarily of water (about 70%). Biphasic solubility is necessary for a molecule to diffuse across both the epithelium and the stroma. The pH and buffering system of an antibiotic's formulation can profoundly influence its ocular penetration, as can the molecular size of the drug.[5,6] Most commonly used ophthalmic antibiotics are molecu-

*See also the editorial by J. P. Whitcher, MD, MPH, "Ocular Infections—A Rational Approach to Antibiotic Therapy," on pages 615-617 of this issue.

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TABLE 1.—*Antibiotics Commonly Used for Eye Infection*

Diagnosis	*Antibiotic*	*Dosage*
Bacterial conjunctivitis	Trimethoprim sulfate and polymyxin B sulfate (Polytrim)	q 1-2 hr while awake
	Ciprofloxacin HCl 0.3%	q 1-2 hr while awake
	Gentamicin sulfate or tobramycin 0.3%	q 1-2 hr while awake
	Sulfacetamide sodium 10%	q 1-2 hr while awake
Bacterial keratitis	Cefamandole nafate 5% *plus* Tobramycin 2% *or*	q ½-1 hr around the clock
	Ciprofloxacin HCl 0.3%	q ½-1 hr around the clock
	Ofloxacin 0.3%	q ½-1 hr around the clock
Endophthalmitis		
Intravitreal	Vancomycin HCl *plus*	1 mg
	Amikacin sulfate	0.4 mg
Subconjunctival	Vancomycin HCl	25 mg 2×/day
	Ceftazidime	100 mg 2×/day
Topical	Vancomycin HCl 5% *plus* Amikacin sulfate 2%	q ½-1 hr around the clock
Parenteral	Amikacin sulfate *plus* Ceftazidime	Per manufacturer's recommendations
Orbital cellulitis		
Children	Cefuroxime sodium	100 mg/kg/day in divided doses IV
Adults	Ceftizoxime sodium	2 grams q 8 hr IV

HCl = hydrochloride, IV = intravenous, q = every

larly small enough to diffuse through biologic membranes without difficulty, but bacitracin and colistin and other polymyxins are higher-molecular-weight antibiotics that penetrate the cornea poorly.[5]

Some drug formulations can cause microdisruption of the corneal epithelium, and this "microtoxicity" enhances drug penetration because the epithelium is the principal barrier to drug penetration. This is thought to occur when ethylenediaminetetra-acetate (EDTA) or sodium benzoate are used as preservatives. Ocular inflammation may also result in damage to the corneal epithelial barrier and enhance penetration.[5-7] The turnover of the tear film is relatively rapid, and formulations that increase the persistence of the drug in the tear film may enhance drug concentrations. This can be accomplished by making the preparation more viscous or by placing it in an ointment form. In theory, ointments have superior bioavailability to solutions because of the increased contact time on the eye. Hydrophilic antibiotics, however, may crystallize within the ointment base, which then prevents their release and subsequent penetration, with the net effect of decreasing their bioavailability.

Increasing the concentration of the antibiotic will increase the diffusion gradient across the cornea and enhance its penetration.[5,8] The formulation of topical antibiotics in "fortified" strengths may be limited by the solubility or toxicity of an individual antibiotic. Fortified preparations produce substantially higher drug concentrations in the cornea and aqueous humor and are more effective in killing microorganisms in experimental models of bacterial keratitis than are standard-strength solutions.[9-12] Fortified antibiotics are therefore frequently used to treat bacterial keratitis. The newer fluoroquinolones are an exception and have not been formulated in fortified antibiotic preparations. Ciprofloxacin in the commercially available concentration of 0.3% (3 mg per ml) has been shown to yield therapeutic corneal levels, and more recently, ofloxacin has been shown to produce both therapeutic cornea and aqueous levels when a commercial-strength 0.3% solution is used for dosing.[13,14]

Specific dosing techniques can also be used to advantage in topical therapy for serious ocular infection. A loading regimen of one drop every minute for 5 minutes, repeated 60 minutes later, is capable of producing high concentrations of antibiotic within the cornea (well above 100 μg per gram of tissue).[15] The sustained administration of an antibiotic—one drop of 0.3% gentamicin sulfate every 30 to 60 minutes—appears optimal.[16,17] When more than one antibiotic is used, five minutes should elapse between installations to prevent a "washout" of the first antibiotic.

Toxicity of topically applied antimicrobials may be related to the antibiotic or to the preservatives and vehicles

used in the formulation. Antibiotics may retard epithelial healing, and this may occur to a greater extent with fortified solutions.[17,18] Thimerosal, a mercurial compound with relatively weak antimicrobial activity, can cause hypersensitivity reactions, keratoconjunctivitis with coarse corneal epithelial changes, giant papillary conjunctivitis, corneal stromal infiltrates, and calcific band keratopathy.[19-23]

Benzalkonium chloride is known to inhibit epithelial adhesion, cause a loss of superficial epithelial cells, and delay healing of the epithelium. These epithelial toxic effects and the surfactant properties of benzalkonium may enhance the penetration of topically applied antibiotics.[24,25]

The administration of antibiotics into the vitreous cavity is advocated for the treatment of endophthalmitis. This disease has a poor prognosis despite aggressive treatment with topical, parenteral, and periocular antibiotics.[26] Conventional routes of antibiotic administration (topical and parenteral) are unable to produce sustained therapeutic antibiotic concentrations in the vitreous, thereby mandating direct intravitreal administration whereby therapeutic antibiotic levels may be maintained for relatively long periods of time (gentamicin has a half-life of 33 hours in the primate vitreous).[27] Retinal toxicity of antibiotics administered to the vitreous cavity is the main problem with intraocular therapy. In animal and clinical trials in humans, it is thought that the maximum tolerable doses are 100 to 400 μg for gentamicin, 2 mg for cefazolin or methicillin, 400 μg for amikacin, and 1 mg for vancomycin.[26-31] Because of the narrow range between the therapeutic dose and toxicity of the aminoglycosides, it is essential that the medications are carefully and properly prepared and that injections are made into the anterior or mid-vitreous to avoid excessively high concentrations near the retina.

Parenteral antibiotics are indicated in patients with preseptal cellulitis, orbital cellulitis, dacryocystitis, and as an adjunct in the treatment of endophthalmitis or keratitis with scleral extension or impending or actual corneal perforation. In addition, corneal or conjunctival infections with *Neisseria gonorrhoeae* at any age or *Pseudomonas*, *Haemophilus*, and *Chlamydia* species in neonates should be treated with parenteral antibiotics.

Topical antibiotics are effective and safe when used as prophylaxis against endophthalmitis after surgical therapy and to decrease the risk following penetrating trauma.[32-37] Antibiotics may best be administered at least 24 hours before an operation to effectively minimize the bacterial counts in the conjunctival cul-de-sac.[38] The subconjunctival administration of antibiotic following an intraocular operation has been shown effective in animal models and is commonly used.[39,40] On rare occasions, severe retinal toxic reactions have occurred with the postoperative administration of subconjunctival aminoglycoside, and cephalosporin administration may be preferred. Most of these reactions have been associated with inadvertent scleral perforation during the drug administration.[41] Visualization of the needle tip during administration will reduce this risk.

Severe ocular infections such as bacterial keratitis, endophthalmitis, or orbital cellulitis are clear indications for aggressive antibiotic therapy with broad-spectrum drugs. In most cases, the initial choice of antibiotic must be made without knowing the identity or susceptibility of the infecting organism. In bacterial keratitis and endophthalmitis, specimens from the infected site should be obtained for culture and smear before the antimicrobial therapy is administered, and this should be done promptly so as to avoid any delay in treatment.[42]

Bacterial Keratitis

Bacterial keratitis refers to bacterial infection of the cornea. The surface epithelium, the mechanical properties of the lids, and bioactive components of the tear film provide an effective barrier to infection. Infection may occur when these barriers are compromised and may then lead rapidly to ulceration of the cornea with resultant surface irregularity or corneal scarring, with associated loss in visual function. The early treatment of bacterial keratitis with adequate doses of the appropriate antibiotic is essential to minimize the loss of vision.

Because the invading organism is usually not immediately known, broad-spectrum antibiotics are chosen as the initial therapy for severe infections so that all possible gram-positive and gram-negative pathogens are covered. In the treatment of bacterial keratitis, this typical "shotgun" approach to treatment is begun with a combination of cephalosporin and aminoglycoside. The antibiotics are also formulated in fortified concentrations to provide the highest possible concentrations of antibiotic before toxicity is attained, so that bactericidal levels can be quickly established in the cornea. In a typical regimen, 2% tobramycin and 5% cefamandole nafate may be used. After a loading regimen, the antibiotic administration is continued every half hour around the clock for the first 24 hours, with a gradual tapering of this dosage over the ensuing days as therapeutic effect is observed. Once the results of cultures and antibiotic sensitivity patterns are reported, the therapy can be modified to single-drug coverage as indicated.

A second alternative is to use the newer fluoroquinolones as single-drug coverage for bacterial keratitis. This single-drug regimen is probably much easier for the patient or care giver to administer and thus has the theoretical advantage of enhanced compliance. There has been some controversy over the single use of the fluoroquinolones because of concern that perhaps some of the organisms, such as *Streptococcus pneumoniae*, may not be covered adequately. With the corneal drug concentrations that are obtainable with topical ciprofloxacin therapy (3.1 μg per gram of tissue), this may not be a legitimate concern.[43] Ciprofloxacin hydrochloride in a 0.3% solution as a single agent and given every hour has been shown to be efficacious in a prospective multicenter study of the treatment of bacterial keratitis.[44] More recently, ofloxacin has been formulated for topical ocular antibiotic therapy and may also prove efficacious because higher aqueous levels of ofloxacin can be attained with comparative dosing regimens.[14]

Subconjunctival and intravenous antibiotics are traditionally reserved for cases of impending ocular perforation or when the infectious process appears to extend into

TABLE 2.—*Initial Therapy for Endophthalmitis*

Route of Administration	Traumatic Infection	Postoperative Infection Protocols	
		Endophthalmitis Vitrectomy Study*	Bascom Palmer Eye Institute†
Intravitreal (in 0.1 ml).....	Vancomycin HCl, 1 mg Amikacin sulfate, 0.4 mg‡	Vancomycin HCl, 1 mg Amikacin sulfate, 0.4 mg	Vancomycin HCl, 1 mg Ceftazidime, 2.25 mg Dexamethasone, 0.4 mg
Subconjunctival (in 0.5 ml)	Vancomycin HCl, 25 mg Gentamicin sulfate, 20 mg	Vancomycin HCl, 25 mg Ceftazidime, 100 mg	Vancomycin HCl, 25 mg Ceftazidime, 25-50 mg Dexamethasone, 12-24 mg
Topical.....	Vancomycin HCl, 5% Gentamicin sulfate, 0.14%	Vancomycin HCl, 5% Amikacin sulfate	Vancomycin HCl, 5% Ceftazidime, 5% Corticosteroids
Parenteral	Clindamycin phosphate Amikacin sulfate Ciprofloxacin HCl	Amikacin sulfate Ceftazidime	Vancomycin HCl Ceftazidime

HCl = hydrochloride

*From the National Eye Institute ("Manual of Operations," Data Coordinating Center, University of Pittsburgh, Pittsburgh, Pennsylvania, 1990).
†From H. W. Flynn, MD, and T. G. Murray, MD, Bascom Palmer Eye Institute, Miami, Florida, written communication, November 1994.
‡For *Bacillus* species, add clindamycin phosphate, 0.25 mg.

the sclera. Administering drugs subconjunctivally is painful and causes scarring of the conjunctiva. The concentration of antibiotic obtained is greater than can be obtained with frequent topical dosing, but the concentrations are not typically maintained beyond a few hours.[45]

There has been recent interest in using collagen shields (contact lenses fashioned out of animal collagen) soaked in various antibiotics. When placed in the eye, they may result in high corneal or aqueous levels of antibiotic; however, they prevent the cleansing or toileting action of the lids and tear film and may sequester bacterial toxins and enzymes at the site of a corneal or scleral infection.

Endophthalmitis

Endophthalmitis or infection within the eye is potentially the most devastating of ocular infections and a vision-threatening ocular emergency that mandates immediate and aggressive antibiotic therapy. Endophthalmitis occurs most frequently following penetrating trauma, but may also occur after an intraocular operation. Rare cases occur by spread from the bloodstream. Any pathogenic organism can cause endophthalmitis following a penetrating injury. Bacilli are seen more frequently than in nontraumatic endophthalmitis. The organisms most commonly associated with endophthalmitis after surgical therapy are the same as those that colonize the lids, namely, *Staphylococcus aureus*, *S epidermidis*, several *Streptococcus* species, and assorted gram-negative rods. The bacteria themselves may release toxins and enzymes that destroy the retina, and the host inflammation can also compromise delicate intraocular structures. Antibiotic therapy for endophthalmitis is most effective in preserving visual function if initiated during the first few hours following early clinical detection and before there is substantial tissue destruction. The eye is first cultured with specimens taken from the conjunctival cul-de-sac, and then intravitreal aspirates are obtained either with a cutting vitrectomy instrument or by a 23-gauge needle passed through the sclera at the pars plana. Intravitreal antibiotics are then administered. Subconjunctival antibiotics, fortified drops, and intravenous therapy are begun. The antibiotics chosen should provide an initial broad spectrum. The antibiotics and their dosages are given in Table 2.

Conjunctivitis

Conjunctivitis is often synonymous with red eye and is simply an inflammation of the conjunctiva. It may be caused by allergic or toxic stimuli, bacteria, or viruses. Allergic conjunctivitis is typically seasonal, with the main symptom of itching, and may present with a ropy mucin-like discharge or minimal discharge and an inflamed conjunctiva. Viral conjunctivitis usually affects first one eye and then, in about a third of the cases, the fellow eye. Patients have irritation and possible photophobia and present with a clear watery discharge, preauricular lymphadenopathy, and occasionally an associated pharyngitis. The hallmark of bacterial conjunctivitis is ocular irritation, inflamed conjunctivae, and a purulent discharge. The most common organisms identified in adult patients with bacterial conjunctivitis are *S aureus*; *S epidermidis*; *Streptococcus*, *Haemophilus*, *Acinetobacter*, and *Corynebacterium* species; *S pneumoniae*; and *Proteus* or *Morganella morganii*.[46] Because bacterial conjunctivitis is common and infection is generally not severe, physicians often do not consider it a serious disease and specimens are not taken for culture; rather, empiric topical antibiotic therapy is started. Broad-spectrum antibiotics such as the combination of trimethoprim sulfate and polymyxin B sulfate (Polytrim, Allergan Pharmaceutical Corporation) provide coverage against both gram-positive and gram-negative organisms, are well tol-

erated on the eye, and may be an excellent choice for the treatment of conjunctivitis.[47] Ciprofloxacin hydrochloride (Ciloxan, Alcon Laboratories, Inc) has also been shown to be effective in treating bacterial conjunctivitis.[48] The aminoglycosides gentamicin sulfate and tobramycin have also been widely used with good results. Sulfacetamide sodium in a 10% solution is also commonly used to treat bacterial conjunctivitis, but produces some stinging, particularly in younger patients.[49]

In conjunctivitis in children, the bacterial organisms identified are somewhat different from those seen in adults. In a study by Gigliotti and co-workers, *H influenzae* and *S pneumoniae* were found to be the most common bacteria isolated rather than the *Staphylococcus* species.[50] Polytrim again seems to be a reasonable choice because of the coverage of both the *Streptococcus* and *Haemophilus* species.

Some patients will have a hyperacute conjunctivitis with prominent chemosis and purulent discharge from the eye. Cultures and Gram's stain should be done because *N gonorrhoeae* may be identified. If the gonococcus is identified, then these patients should also be treated with parenteral antibiotics.

Orbital Cellulitis

Orbital and periorbital infections may be caused by a variety of organisms including bacteria, fungi, and parasites. Infection may be initiated from both surgical and nonsurgical trauma or by a retained foreign body. An infecting organism may also extend into the orbit or periorbital tissue from the conjunctiva, the globe itself, the lacrimal sac, or from the paranasal sinuses. Less frequently, orbital involvement may follow hematogenous spread from other sites in the body. Ophthalmologists generally separate orbital and periorbital infection into subgroups that include preseptal cellulitis, orbital cellulitis, and subperiosteal or intraorbital abscess. Cavernous sinus thrombosis occurs less frequently. Preseptal (outside the orbital septum) cellulitis requires parenteral antibiotic therapy, and the drug of choice will depend on the postulated overlying cause of the disease. Orbital involvement mandates not only parenteral antibiotic therapy but also consideration of the surgical drainage of an infectious focus. This is particularly the case for a subperiosteal abscess where the growing abscess is within the closed space of the orbital mass and may cause increased pressure on the globe, compromising blood flow to the eye. A more thorough description of the medical and surgical management of infections of the orbit is presented by Gonnering and Harris.[51]

Dacryocystitis

Infections of the lacrimal sac are common. They may occur at any age and are usually the result of either an acquired or congenital obstruction of the nasolacrimal duct. Definitive treatment depends on reestablishing a patent drainage system. Acute dacryocystitis with signs of overlying inflammation and cellulitis should initially be treated with parenteral antibiotics—1 gram of oral dicloxacillin sodium per day in divided doses for 10 to 14 days—and topical antibiotics until the infection is controlled. Antibiotic therapy can be changed based on the patient's response and results of culture and sensitivity tests. Before antibiotic treatment, any discharge material should be cultured. Hot compresses to the skin overlying the inflamed lacrimal sac may assist in drainage, and the ophthalmologist may also attempt to drain the swollen sac with nasolacrimal probing or external fistulization if the sac is excessively swollen and tender. Once the acute infection is controlled, the antibiotic doses are tapered and the patient's condition reevaluated. Persistent obstruction of the nasolacrimal duct usually requires surgical intervention to prevent recurrent infection or persistent epiphora.

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