CHAPTER

14

New Anti-Infectives for Ophthalmology

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I. INTRODUCTION

The eye is amazing. It is open to the environment, but rarely gets infected. Nevertheless, when it does become infected, gram-positive bacteria, like *Staphylococcus aureus*, are the usual cause. Fungi and viruses are also culprits, but infections by these organisms occur less frequently. Anti-infective agents, like aminoglycosides, fluoroquinolones, tetracyclines, and macrolides, have been useful in treating ocular infections, but microbial resistance to these agents has challenged the pharmaceutical research community to create better and more effective anti-infective agents for prophylaxis and therapy. Classical antibiotic families and approaches still have merit, and families like the fluoroquinolones still offer some fruitful candidates. Although antibiotic research is drying up in Big Pharma companies, other smaller companies are taking up the gauntlet and creating novel ways to handle these ocular pathogens. This chapter reviews the approaches taken and some of the more recent new entities that might prove useful for preventing or treating ophthalmic infections.

II. THE OCULAR ASSAULT

Although the eye rarely gets infected, the ocular environment is warm, moist, and rich in proteins and sugars, and offers a good opportunity for invasion by microorganisms. Microorganisms can enter the eye through ocular injury, trauma, through contact lens use, or even during surgery. Successful invasions yield bacterial, viral, fungal or protozoan infections of the eye (e.g. conjunctivitis, blepharitis, keratitis, endophthalmitis).

III. THE ENEMY

Microorganisms have been terrorizing humankind for generations. Our eyes are not immune to these assaults. It is probable that Moses of the Book of Genesis (Figure 14.1) suffered with bacterial conjunctivitis or keratitis during his wanderings in the desert. He was surrounded by sandy irritants and microbial opportunists like *Staphylococcus aureus* (Figure 14.2). The types of organisms invading his eyes haven't changed much over the years. Microbial taxonomists since Carl Linnaeus (1707–1778) have named and renamed organisms based on the technology of the times and what they knew about their physical, nutritional, and pathogenic characteristics. Today, the genetic make-up of microorganisms is the primary basis for nomenclature and microbial taxonomy. The list of potential microbial enemies is long: there are over 4400 published and approved bacterial species, over 100,000 species of fungi, over 12 genera of protozoa that infect the human body, and over 80 virus families representing over 270 genera of viruses. Nevertheless, we are lucky – the array of microorganisms successfully infecting the eyes is limited and finite (Table 14.1). Currently, there are only antibacterials, antifungals, antiprotozoans or antivirals, and no topical "broadest possible spectrum" antimicrobials for therapy against bacteria, fungi, protozoa, and viruses. Gram-positive bacteria still predominate as the most common enemy of our eyes today (Table 14.2).

IV. AVOIDING OCULAR INFECTIONS

The strategy is fairly simple – keep microorganisms out of and away from the tissues of the eye. Preventing infection involves the concept of prophylaxis (from the Greek meaning "to guard against beforehand") that involves keeping the eyes clean and free of microbes by good hygiene, disinfection, antisepsis or antibiotic treatment. If this approach is not successful and infection occurs, then the strategy is refocused on killing or eliminating the offending microbe through therapeutic

FIGURE 14.1 Michelangelo's *Moses* in Rome, Italy. Photolink/Getty Images

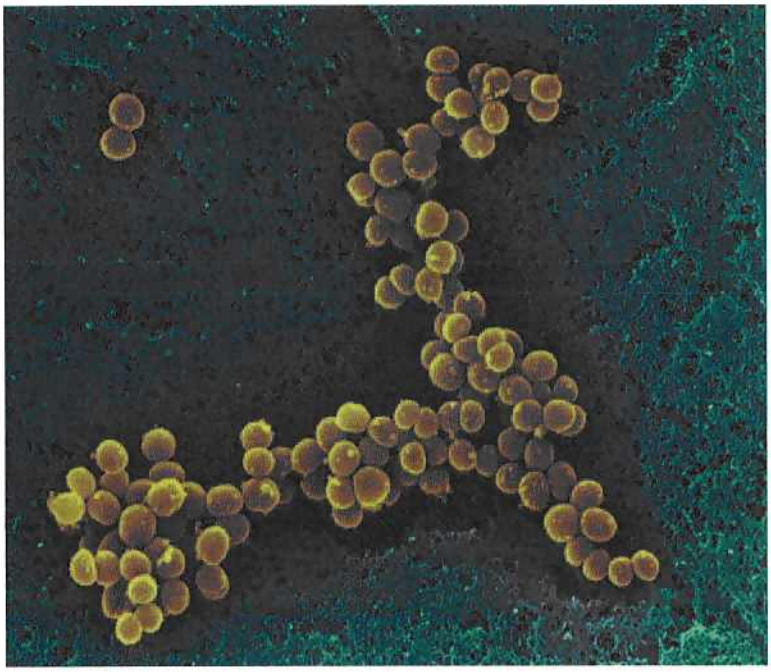

FIGURE 14.2 *Staphylococcus aureus* (SEM). S. Lowry/Univ. Ulster/Getty Images

TABLE 14.1 Microbes that cause ocular infections

Bacteria		
Gram-positives	**Gram-negatives**	**Fungi**
The old bad guys		
Staphylococcus aureus	*Pseudomonas aeruginosa*	*Aspergillus fumigatus*
Staphylococcus epidermidis	*Serratia marcescens*	*Fusarium solani*
Other coag neg staphylococci	*Moraxella* sp.	*Candida albicans*
Streptococcus pneumoniae	*Acinetobacter*	**Viruses**
Streptococcus viridans	*Proteus/Morganella*	*Herpesvirus*
Corynebacterium	*Haemophilus influenzae*	*Adenovirus*
Propionibacterium acnes	*Neisseria gonorrhoeae*	*Cytomegalovirus*
	Chlamydia trachomatis	**Protozoa**
		Acanthamoeba

The new bad guys

- Atypical mycobacteria
- MRSA: Methicillin resistant *Staphylococcus aureus*
- VRSA: Vancomycin resistant *Staphylococcus aureus*
- VRE: Vancomycin resistant Enterococci
- PRSP: Penicillin resistant *Streptococcus pneumoniae*
- FQRP: Fluoroquinolone resistant *Pseudomonas*
- Multi-drug resistant organisms, e.g. *Staphylococcus aureus*, which are resistant to methicillin, erythromycin, ciprofloxacin, aminoglycosides, fluoroquinolones AND clindamycin
- *Enteroviruses*

TABLE 14.2 Incidence of gram-positive or gram-negative bacteria in ocular infections

	Gram-positive bacteria	Gram-negative bacteria
Bacterial corneal ulcers	74%	26%
Bacterial blepharitis	93%	7%
Bacterial conjunctivitis – mostly adults	70%	30%
Bacterial conjunctivitis – children	43%	57%
Bacterial conjunctivitis – neonates	85%	15%

Based on over 7000 ocular infections (data from Alcon).

means, i.e. treating the eye with antibiotics or antimicrobial products.

V. EVOLUTION OF ANTI-INFECTIVE AGENTS

The treatment of ocular infections over the centuries has ranged from hot and cold packs, ocular massages and eye washes with stream water, frankincense gum, and boric acid solutions, mixtures of tortoise brain and honey, freshly disemboweled frog mixed with raw onion, plant extracts and minerals, milk, wine, oils, mercuric salts and acupuncture (Astbury, 2001). Sulfas and antibiotics became available in the 1930s and 1940s, and opened up the golden age of antibiotics. Ophthalmic antibiotics available from the 1950s to 1980s were effective,

but sometimes toxic, limited in spectrum, and usually bacteriostatic. Today, these have been replaced by significantly broader spectrum, more effective and safer therapies. In general, eye care practitioners no longer use sulfonamides, chloramphenicol, polymyxin, or bacitracin to treat ophthalmic infections. Aminoglycosides (e.g. neomycin, gentamicin, tobramycin) had their heyday, but their use is waning as better agents, like the fluoroquinolones, have become available and preferred.

VI. PHARMACEUTICAL RESEARCH

The grandparents of most of today's antibiotics were agents discovered in the 1940s and 1950s, that interfered with the synthesis of the bacteria's cell wall, its protein or its DNA, so that they could not reproduce themselves. The molecular structures of earlier antibiotics were tweaked to keep them working against resistant bacteria, but new approaches and families are constantly needed.

A. Big Pharma vs. Small Biotech

Some major pharmaceutical companies have discontinued antibiotic drug research and focused on chronic diseases, like Alzheimer's, cancer, or cardiovascular diseases, because of cost of development and the rapid development of antibiotic resistance. Even though the worldwide anti-infective market is the second largest pharmaceutical market, with sales equal to $25 billion in 2005, there have been few new antibiotic launches or new antibiotic classes. Anti-infectives usually provide short-term treatment, so there are no "patients for life". Infections are becoming increasingly resistant to existing antimicrobial agents (perhaps most alarming) and the pharmaceutical pipeline of new antimicrobials, particularly antibacterial drugs, is drying up (Livermore, 2004; Bosso, 2005). Smaller biotech firms have taken up the R&D challenge. Nevertheless, Big Pharma is now being enticed back into anti-infective research and development business because of the lack of candidates that overcome resistance. The recent launch of a glycylcycline, Wyeth's tigecycline, represents one of the first new antibiotic classes to be introduced in years. The need for effective antimicrobial products for ophthalmic use continues as the ocular antimicrobial market continues to grow and expand. The worldwide ocular anti-infective market in 2005 was over US$900 million. Considering the threat of bioterrorism, much research has been focused on targets like smallpox, anthrax, plague, botulism, tularemia, viral hemorrhagic fevers (i.e. Ebola, Lassa, Arena viruses) – infections that present greater morbidity than ocular infections. While the Big Pharma companies are funneling their research funds into anti-hypertensive, arthritis, sexual dysfunction, Alzheimer's or diabetes research, companies dedicated to ophthalmic research, like Alcon, plus a few "Small Pharma" or start-up biotech companies focusing on a limited number of antimicrobial candidates or "one-trick ponies" will be the future source of antimicrobials for ophthalmology.

B. Japanese Antibiotics

Japan was the third country, after the US and the UK, to become self-sufficient in penicillin manufacture, as early as 1948. Besides the production of penicillin, much effort was made nationwide in exploratory research on anti-infective products. One of my professors at the University of Texas at Austin, Jackson W. Foster, was acclaimed as the "father of Japanese antibiotics" during the 1940s–1950s through his participation in the post-war development of this industry. There are currently over 100 useful antibiotics and related agents of Japanese origin, and over 40 have been licensed around the world. The first antibiotic from Japan was colistin (discovered in 1950), followed

TABLE 14.3 Topical ophthalmic anti-infective properties

The agent
- Antimicrobial activity broad enough to be used prophylactically (pre- and post-operatively), and strong enough to be used as therapy to cure serious ocular infections.
- Active *in vitro* (MICs), *in vivo* (animal infections), and effective in human clinical trials.
- Safe in animals and humans with minimum side effects.
- Has rapid antimicrobial action as demonstrated by kill curve studies (i.e. kills quickly or sterilizes or decontaminates the surgical eye area effectively).
- Penetrates deep into ocular tissues upon topical instillation.
- Chemically and microbiologically stable for delivery to patient.
- Compatible with other concurrent medications or therapies.

The product
- Contains only necessary ingredients.
- Is comfortable and nontoxic upon topical instillation.
- Is effective with simple dosage regimens and short duration of therapy.
- Is effective in treating or preventing an array of clinical ocular infections.
- In an acceptable dosage form and package for product administration.
- Easy to use for practitioners, surgeons, nurses, patients or care-givers.
- Effective in a wide variety and special populations of patients (e.g. neonates, children, adults, geriatric patients).
- Is useful in treating or preventing a wide range of ocular infections (e.g. conjunctivitis, keratitis, endophthalmitis, blepharitis, and dacryocystitis).

by well-known agents such as kanamycin (1957), cefazolin (1969), amikacin (1972), piperacillin (1976), norfloxacin (1977), cefoperazone (1978), ofloxacin (1980), clarithromycin (1984), and meropenem (1987). The major groups include the beta-lactam and fluoroquinolone antibiotics. In Japan, fluoroquinolones are the most widely prescribed antibiotics in ophthalmic solutions and all are benzalkonium chloride-free products.

VII. OCULAR ANTI-INFECTIVE RESEARCH

Whether a company is developing an antibiotic for systemic or ophthalmic usage, the process is similar and involves an *in vitro* screening step, an *in vivo* infection step and finally clinical trials. Many ophthalmic antibiotics today were first assessed for treating systemic or non-ophthalmic infections. The future challenges for ophthalmic anti-infective research are daunting. Every new product must have its unique uses and advantages over the existing products. We demand more and more from our topical antibiotic products for ophthalmology (Table 14.3).

VIII. THE SCOURGE OF ANTIBIOTIC RESISTANCE

Antibiotic resistance developed quickly in the past, starting with resistance to sulfonamides in the 1930s and to penicillin, streptomycin, tetracycline and erythromycin in the 1940s and 1950s. In the 1960s, microbes developed resistance to nalidixic acid, the great-grandmother of the fluoroquinolones. Significant resistance to vancomycin developed in the 1970s, and to the early fluoroquinolones (i.e. norfloxacin) in the 1980s. These events have focused on more potent agents effective against resistant strains of bacteria. Fluoroquinolones have become the dominant family of ophthalmic antibiotics. But even the older fluoroquinolones (e.g. ofloxacin, ciprofloxacin) have lost much of their effectiveness against some important ocular isolates. Considering

all of the characteristics for an ideal ophthalmic antibiotic product, moxifloxacin ophthalmic solution 0.5% represents one of the best antibiotic products of choice for treating and preventing ophthalmic infections today (Schlech and Blondeau, 2005). Growing microbial resistance to current antibacterial agents, and widening gaps in antibiotic coverage create a need for more potent and genetically smart fluoroquinolones. When the first ocular fluoroquinolone, ciprofloxacin, became available for treating bacterial conjunctivitis and keratitis roughly a decade and a half ago, there was tremendous excitement. This product was also used to prevent and treat ocular bacterial infections, especially before, during, and after cataract and refractive surgery. Today, however, this most impressive weapon has lost some of its punch (Goldstein *et al.*, 1999; Hwang, 2004; Thompson, 1999). Several groups of microorganisms have developed resistance to ciprofloxacin and its sister fluoroquinolones, ofloxacin and levofloxacin, more quickly than imagined, and the levels of resistance are increasing each year (Alfonso, 2003). The bacteria hold most of the cards for the future. They will evolve and respond to their environment, and produce progeny that will be resistant to today's antibiotics. Humans can only try to keep ahead of these clever creatures. Abandoning the old antibiotics and creating new entities are the only ways to keep up with these resistant trends. Continuing to use older, previous-generation antibiotics will only facilitate the continued development of resistant strains (Dahlhoff and Schmitz, 2003). Although investigations are ongoing, to the author's knowledge there is no substantial study that proves that any topical ocular application of antibiotics induces microbial antibiotic resistance distal to the site of instillation. Conjunctivitis occurs worldwide and affects people of all ages, all social strata, and both sexes. It has been cited as one of the most frequent causes of self-referral in the practice of comprehensive ophthalmology (Chou *et al.*, 2004). According to the American Academy of Ophthalmology (AAO, 2003) "conjunctivitis infrequently causes permanent visual loss or structural damage, but the economic impact of the disease in terms of lost work time, although undocumented, is doubtless considerable". The annual worldwide sales of anti-MRSA agents are projected to be in excess of $2 billion in 2007. The prevalence of MRSA in hospitals and communities is about 64–68% (Kowalski *et al.*, 2003; Armstrong, 2000). Gaynor *et al.* (2005) have reported that the topical use of 1% ophthalmic tetracycline ointment may increase the antibiotic resistance of *Streptococcus pneumoniae* in the nasopharynx.

IX. THE ATTACK STRATEGIES – ANTIMICROBIAL TARGETS

Unlike glaucoma, cataracts, or AMD, infectious diseases involve the host being attacked by another organism, the pathogen. Strategies for therapy focus on the unique differences between the microorganism, its metabolism and its pathogenic process, and those of the host. An ideal or successful target is one that involves a process unique to the pathogen, but not found in the human host. The following are the major targets:

- **Interfering with protein synthesis** – e.g. aminoglycosides, sulfonamides, tetracyclines, macrolides, chloramphenicol, clindamycin, clotrimazole, erythromycin, rifampicin, rifamycins, ansamycins, oxazolidinones, pleuromutilin, lincosamides, proteases, specific inhibitors of 23S, 30S and 50S ribosomal subunits, muramoyl pentapeptide carboxypeptidase, polypeptide deformylase (PDF), methionyl-tRNA synthetase, matrix metalloproteinase, glutamate racemase, metallo-enzyme/metalloprotease.
- **Interfering with DNA and RNA synthesis** – e.g. fluoroquinolones,

rifamycins, mitomycin, sulfonamides, trimethoprim, triazoles, echinocandins, and specific inhibitors of glucan synthase, topoisomerase ATP hydrolyzing, nucleoside analogue reverse transcriptase (NRTI), DNA polymerase.

- **Interfering with cell wall synthesis** – e.g. penicillins, beta-lactams, carbapenems, penems, cephalosporins, glycopeptides, vancomycin, monobactams, bacitracin, lysostaphin, dihydrofolate reductase inhibitors (DHFR).
- **Interfering with membrane integrity** – e.g. Cationic peptides, cationic steroids, LpxC inhibitor, ceragenans, polymyxin, polyenes such as amphotericin, triazoles, gramicidin, nystatin, cyclic peptides, bacteriocins, lantibiotics.
- **Interfering with fatty acid synthesis** – e.g. Fab inhibitors, unsaturated fatty acids including palmitoleic acid, oleic acid, linolenic acid, arachidonic acid, other plant alkaloids.
- **Interfering with bacterial efflux mechanisms** – the efflux systems of bacteria protect bacteria against antibiotics by actively transporting these potentially toxic compounds out of the cytoplasm and preventing their accumulation within the bacterial cell (Lomovskaya and Bostian, 2006). This intrinsic capability is responsible for numerous examples of antibiotic resistance especially in *Pseudomonas aeruginosa*. Efflux pump inhibitors (EPIs) include newer macrolides and tetracyclines, plant and natural alkaloids, or peptidomimetics. Most of these agents target resistant gram-negative and gram-positive bacteria including *Pseudomonas* and MRSAs. A number of tetracycline derivatives have been created that are not sensitive to bacterial efflux mechanisms and are more likely to be bactericidal than the earlier bacteriostatic tetracyclines. EPIs are also being evaluated as adjuncts to antibiotic therapy, especially with fluoroquinolones. No EPIs have been successfully marketed today, but they do represent a significantly new target for anti-infective research.
- **Non-traditional approaches for ophthalmic anti-infectives** – there are a number of untapped approaches for anti-infective therapy being researched and several novel areas include: vaccines, bacteriophage, biomimetics, defensins, lipopeptides, halogen generators (e.g. Aganocide™ compounds), cationic peptides or steroids, monoclonal antibodies, and quorum sensing blockers.

X. OPHTHALMIC USAGE

A. Therapeutic Usage

Topical therapy to treat ocular infections remains an important and convenient avenue for the physician. In most situations, a single pathogen is the target. The ability of an antibiotic or antimicrobial product to eradicate this pathogen, cure an ocular infection quickly and prevent serious vision loss is a paramount consideration for judging the effectiveness of these products. "Limited spectrum" antibiotic products have a role only if the pathogen is identified and covered by the antibiotic. The ability of the antibiotic to penetrate the ocular tissues and eradicate the pathogens at the site of the infection is also an important goal. At this time, moxifloxacin has better ocular penetration qualities than earlier fluoroquinolones, such as ciprofloxacin or ofloxacin (Hariprasad *et al.*, 2005; Robertson *et al.*, 2005). Future antimicrobial products must equal or surpass moxifloxacin's ability to penetrate safely into the deeper eye tissues for effective therapy of infections.

B. Prophylactic Usage

The prevention of infections before, during, and after surgery through the use

of prophylactic antibiotic products will undoubtedly continue in the future (Bratzler and Houck, 2004; Olson, 2004a,b; Tipperman, 2004). Since any microorganism can potentially become an opportunist and play havoc in the eye, the antibiotic with the widest antimicrobial spectrum, the lowest number of resistant strains, and the fewest side effects should be the agent of choice for prophylaxis. The broad, shotgun approach still has merit for preventing infections in the ophthalmic surgical suite (Dajcs *et al.*, 2004; Kowalski *et al.*, 2004; Thibodeaux *et al.*, 2004; Tipperman, 2004).

XI. ANTI-BACTERIAL AGENTS FOR OPHTHALMOLOGY

Antibacterial antibiotics have been the mainstay of therapy for infectious diseases since their origins in the 1940s. As microorganisms changed and resistance developed, more advanced antibiotics were ultimately needed to provide adequate coverage and spectrum. By selecting optimal antibiotics and dosing regimens, clinicians can avoid treatment failures and adverse events, and can help prevent the emergence of further antibiotic resistance. Current anti-infective products available to the ophthalmologist today contain fluoroquinolones, tobramycin, chloramphenicol, erythromycin, trimethoprim, polymyxin or sulfonamides. Natural products, synthetic, and semi-synthetic antimicrobials have been an important source for new anti-infective drugs. Researchers continue to identify new antimicrobial families for treating infections. In addition, they pursue novel approaches or delivery systems for older antimicrobials to treat and prevent ophthalmic infections (Yoneyama and Katsumata, 2006). This section reviews the potential of some of these older families for use in ophthalmology. Members of 6 major classes of antibacterial antibiotics (fluoroquinolones, aminoglycosides, macrolides, tetracyclines, beta-lactams, peptide antibiotics and chloramphenicol) have had roles in treating ocular infections (Kowalski and Dhaliwal, 2005; Zinner, 2005; Appelbaum and Jacobs, 2005).

A. Fluoroquinolone Antibiotics

Although quinolone antibiotics have been around since nalidixic acid, the addition of a fluorine group to the quinolone moiety revolutionized this family and created the fluoroquinolones (Dalhoff and Schmitz, 2003). There have been more than 10,000 fluoroquinolone agents synthesized and tested since the original discovery of nalidixic acid in 1962 (Mah, 2003). Currently, the fluoroquinolones (moxifloxacin, gatifloxacin, ofloxacin, ciprofloxacin) represent the leading antibiotic ophthalmic products. They block bacterial DNA synthesis by inhibiting one of the enzymes (DNA gyrase, topoisomerase) needed in this process. The fluoroquinolone family is still being researched and harvested. Fluoroquinolones are useful in the prevention and treatment of a variety of ocular infections; however, resistance to this class has been emerging (Alexandrakis *et al.*, 2000; Blondeau, 2004). Newer family members have better coverage. Beginning in 2003, the topical ocular fourth-generation fluoroquinolones, moxifloxacin and gatifloxacin, were approved for treating bacterial conjunctivitis. These antibiotics represent the most advanced group of compounds within the class, offer a unique dual-binding mechanism of action in gram-positive organisms, and have activity against otherwise resistant species (Blondeau, 2004). They are more active than either earlier fluoroquinolones or tobramycin, based on minimum inhibitory concentrations (MICs) and susceptibility results. *In vivo* studies using prophylactic models with rabbits have shown the potency of these antibiotics in preventing infections by common pathogens (Aliprandis *et al.*, 2005; Dajcs *et al.*, 2001; Kowalski *et al.*, 2004). Also, active ingredients that are innately

antimicrobial, such as antibiotics like the fluoroquinolones, have the opportunity to be formulated in multiple-dose containers without added antimicrobial preservative agents, such as benzalkonium chloride. This preservative has served the ophthalmic community well over the last 50 years, and is still required for preserving IOP-lowering and other ophthalmic products, but researchers generally avoid additional or unnecessary chemicals in any ophthalmic formulation. All fluoroquinolone ophthalmic products available in Japan are benzalkonium chloride-free. These are the "products to beat" in the future.

B. Aminoglycoside Antibiotics

This group of antibiotics interferes with bacterial protein synthesis and had their heyday in the 1970s–1980s with tobramycin and gentamicin products.

C. Macrolides

These antibiotics have been around for decades and include erythromycin; they inhibit translation by binding to ribosomes. Generally, they are active against gram-positive bacteria and weak against gram-negative bacteria, like *Pseudomonas aeruginosa*. Erythromycin and other macrolide antibiotics inhibit protein synthesis by binding to the 23S rRNA molecule (in the 50S subunit) of the bacterial ribosome blocking the exit of the growing peptide chain of sensitive microorganisms.

D. Tetracyclines

Tetracyclines have been available for some time; they target and inhibit protein synthesis by binding to the ribosomes of certain bacteria. This molecule of 4 fused cyclic 6-membered rings binds to the 30S subunit of the bacterial ribosome and effectively distorts the ribosome and stops the bacteria from growing. Therefore tetracyclines are bacteriostatic.

E. Beta-Lactam Antibiotics

These antibiotics contain a beta-lactam ring and include penicillins, cephalosporins, carbapenems and monobactams. Cephalosporins are similar to penicillins in their mode of action, but they treat a broader range of bacterial infections and many people are allergic to cephalosporins. This group of antibiotics has had a great impact on treating systemic infections, but because of their limited stability have had little application in treating ophthalmic infections.

F. Peptide Antibiotics

This group of antibiotics includes host defense proteins, such as the magainins, cecropins, and defensins. These are natural products found in all higher forms of life and provide the first lined defense against bacterial infections. Peptide antibiotics interfere with cell wall development by blocking the attachment of new cell wall subunits (muramyl pentapeptides). Vancomycin is a complex glycopeptide that binds to precursors of the peptidoglycan layer in bacterial cell walls. This effect prevents cell wall synthesis and produces a rapid bactericidal effect in dividing bacteria. Vancomycin is active against most gram-positive bacteria, but is not effective against gram-negative cells because of their large size and poor penetrability.

G. Chloramphenicol

Chloramphenicol inhibits microbial protein synthesis by binding to the 50S subunit of the 70S ribosome and impairing peptidyl transferase activity. The effect is usually bacteriostatic but, at high concentrations, chloramphenicol may be bactericidal for some species. Chloramphenicol inhibits protein synthesis in both prokaryotic and eukaryotic (mitochondrial) ribosomes.

XII. NOVEL APPROACHES

There are a number of non-traditional approaches being pursued beyond the traditional development for topical use in ophthalmology (Monaghan and Barrett, 2006).

A. Aganocide™ Compounds

Aganocide™ compounds are novel, non-antibiotic compounds that are synthetic analogs of compounds present in neutrophils during phagocytosis. Aganocide™ compounds kill pathogenic microbes, including normal bacteria, antibiotic-resistant bacteria, fungi, yeasts and spores. While the molecules formed in neutrophils are very unstable, Aganocide™ compounds are significantly more stable, have similar biological properties, have wide antimicrobial spectra and have excellent safety profiles. In contrast to their naturally occurring counterparts, Aganocide™ compounds are highly stable. The resulting long shelf-life makes them suitable as pharmaceutical products.

B. Biomimetics (e.g. acrylamides, phenylalkynes)

These antimicrobials are non-peptidic analogs that mimic structural properties of antimicrobial peptides (AMPs) that serve as a first line of defense against microbes on the ocular surface. These synthetic compounds have advantages over AMPs because of their small size, which increases stability and tissue distribution.

C. Cationic Peptides

Cationic peptides are natural products originally discovered in the skin of frogs, insects and human neutrophils. They act as potent antimicrobials by interacting with bacterial membranes (Wilcox, 2004). Some of these cationic peptides are being developed to treat infections of cystic fibrosis and catheterized patients.

D. Defensins

These are small cysteine-rich cationic proteins found in both vertebrates and invertebrates. They are active against bacteria, fungi and enveloped viruses.

E. Ceragenins (i.e. cationic steroid antibiotics or CSAs)

These compounds are small, synthetic molecules that have a sterol backbone with amino acids or other groups attached. They have a net positive charge that electrostatically attracts negatively charged cell membranes of certain viruses, fungi, and bacteria. CSAs have a great affinity for membranes and rapidly disrupt the target membranes leading to rapid cell death. CSA-13 is a small molecule aminosterol that mimics the activity of endogenous antimicrobial peptides and has bactericidal activity based on membrane disruption.

F. Monoclonal Antibodies

Antibody therapies can block bacterial toxin formation, bind the pathogen to host cells, or help clear or destroy pathogens by enhancing macrophage activity. It is doubtful that this approach would have much application to ophthalmology unless they can ameliorate the inflammation associated with infection.

G. Rifamycins

Several semisynthetic derivatives (rifamycin SV, rifampin (rifampicin), rifamide) of natural rifamycins have been used as extended-spectrum antibiotics. Rifamycins interfere with the synthesis of RNA in microorganisms by binding to subunits of sensitive DNA-dependent RNA polymerase. They are active against gram-positive organisms, some mycobacteria, a few strains of gram-negative bacteria (mostly cocci; bacilli are more resistant), some anaerobes, and chlamydiae.

H. Vaccines

Although vaccines have been extremely successful in controlling and eradicating diseases like polio, measles, mumps, and small pox, this approach has not had much success in ophthalmology in the past. Nevertheless, researchers at Brigham and Women's Hospital in Boston evaluated the protective and therapeutic efficacy of live-attenuated *Pseudomonas aeruginosa* vaccine in a murine corneal infection model. They noted that both active and passive immunization reduced intranasal vaccine protected mice against lethal pneumonia. The global market for prophylactic vaccines was estimated at $9 billion in 2004 and has grown by about 15% per year over the last decade. Vaccines have essentially eradicated smallpox, measles, polio, mumps, diphtheria, tetanus, rubella, and pertussis. Recent launches of vaccines against *Haemophilus influenzae, Streptococcus pneumoniae* (PREVNAR®) and human papilloma virus (HPV) indicate the importance of research in this area. The use of PREVNAR vaccine has reduced the incidence of *Streptococcus pneumoniae* conjunctivitis. Major pharmaceutical players in vaccine research include Glaxo Smith-Kline, Merck, Wyeth, and Chiron.

XIII. ANTI-FUNGAL AGENTS FOR OPHTHALMOLOGY

The primary fungal pathogens for ophthalmology include *Aspergillus, Candida,* and *Fusarium.* According to researchers at the University of Miami, *Fusarium* is becoming a common cause of keratitis in soft contact lens wearers.

A. Azoles

This group of antibiotics includes some classical antifungal agents, like natamycin and amphotericin. Pfizer Pharmaceuticals has launched a new antifungal, voriconazole, which might have some potential in *Fusarium* infections.

B. Imidazole/Triazole Antifungals

The mechanism of action and spectrum of agents belonging to these two chemical classes of anti-fungals are identical. The primary difference between the classes is that the newer triazole antifungals are metabolized at a slower rate than the older imidazoles.

XIV. ANTI-VIRAL AGENTS FOR OPHTHALMOLOGY

There are hundreds of viruses that infect humans and create a huge amount of morbidity and mortality. In the 1970s there were no FDA approved antiviral drugs. Today half of the 40 or so drugs on the market target HIV and herpes. Only one antiviral drug (rivavirin) is broad spectrum. In addition, untreatable virus infections are the most serious of the bioterrorism threats. HSV keratitis is the leading cause of corneal blindness in the US and affects up to 500,000 people. Ocular viral infections usually involve herpes (HSV), adenovirus (ADV) or cytomegalovirus (CMV). Despite significant knowledge of the molecular biology and genetics of ADV (Kinchington *et al.*, 2005), currently there is no clinically effective antiviral agent for the prevention or treatment of ADV infections (D'Cruz and Uckun, 2005). Topical trifluridine (1%) solution (VIROPTIC) remains the antiviral drug of choice for both dendritic and stromal HSV keratitis.

XV. SUMMARY

- Ocular infections are caused predominantly by gram-positive bacteria
- Opportunistic microorganisms gain access to ocular tissues either by foreign body injury, surgical misconduct, contact lens misuse, or contagion from others

- Successful anti-infectives target microbial protein synthesis, DNA or RNA synthesis, cell wall synthesis, membrane integrity, and fatty acid synthesis or bacterial efflux mechanisms
- Although the current pathogens plaguing the eye seem to be constant, they do change and become more resistant to current antibiotic agents
- Preventing ocular infections demands prophylactic medicines during surgery, or therapies that embolden the host or target the pathogen in a novel way
- Today's topical therapy for external infections of the eye includes classical antibiotics, like the fluoroquinolones, aminoglycosides, or macrolides
- Major antibiotic families still have a future in ophthalmology and companies continue to create new fluorquinolones or tetracyclines, as well as novel approaches for preventing and treating ocular infections
- Formulating specific anti-infective agents in acceptable ophthalmic preparations is the major challenge for ophthalmic companies.

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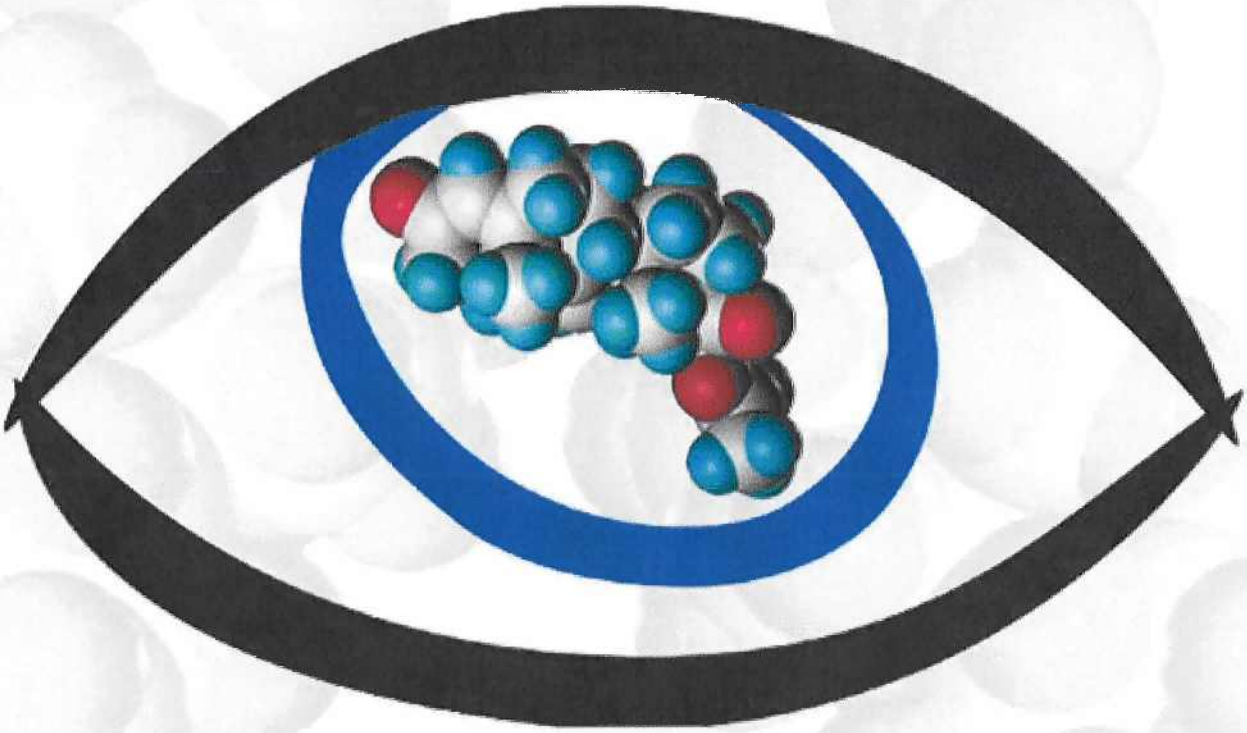
Eye on New Discoveries



Edited by
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AP

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