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EXPERT REVIEW

A European Perspective on Topical Ophthalmic Antibiotics: Current and Evolving Options

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Abstract
Background: Eye infections can be vision-threatening and must be treated effectively by appropriate and safe use of topical ophthalmic anti-infectives. This review will essentially consider the current and evolving treatment options for the various types of bacterial eye infections. Ocular surface bacterial infections affect subjects of all ages with a high frequency in newborns and children.
Methods: This article presents a review of the peer-reviewed published scientific literature in order to define the well-established uses of anti-infective eye drops in the field of ocular infections. A comprehensive search of the recent published literature including topical ophthalmic anti-infectives effective in bacterial ocular infections was performed. Clinical studies provide relevant data concerning the characteristics and clinical efficacy of antibacterial eye drops in ocular anterior segment infections or for perioperative prophylaxis. Publications were included to cover the current options of antibacterial eye drops available in Europe.
Results: Several recent publications identified effective topical ocular antibacterials requiring a reduced dose regimen and a short treatment course. Additional literature reviewed included data on novel perioperative prophylaxis, indications for topical fortified antibiotics and innovative research including the risk of resistance.
Conclusions: Safe and effective topical antibiotic eye drops for the treatment and prevention of ocular infections must be adapted to the type of bacteria suspected. Usual topical antimicrobials should be replaced by more recent and more effective treatments. The use of highly effective fluoroquinolones should be reserved for the most severe cases to avoid resistance. Short treatment courses, such as azithromycin, can be easily used in children, thereby improving quality of life.

Keywords: children, newborn, azithromycin eye drops, bacterial conjunctivitis, endophthalmitis prophylaxis, short treatment course

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Introduction

All parts of the eye may be infected by bacteria, fungi, parasites, or viruses. Anti-infectives such as antibiotics (ATB), antiseptics, antifungals, anti-helminths or anti-virals can be used depending on the type of infection. As this review focuses on bacterial infections, only antibiotics will be discussed.

Although ocular infection may be considered to be a minor infection, it can be "vision-threatening".

The external ocular surface acquires a microbial flora at birth and some of the commensal flora may become resident in the conjunctiva and eyelids with a potential to become pathogenic. Moreover, all microorganisms derived from the environment can also transiently colonize the eye and, when given the opportunity, can invade the ocular tissues. The modes of transmission of anterior and posterior segment infections comprise direct contact at the ocular surface or invasion of the blood-eye barrier.

Current Use of Topical Antibacterial Eye Drops
Ocular surface infection

- *Bacterial conjunctivitis*: Bacterial conjunctivitis is a microbial infection involving the mucous membrane of the surface of the eye. This condition is usually a self-limiting disease. Purulent bacterial conjunctivitis, characterized by mucopurulent discharge and hyperemia, affects all subjects of ages, but is particularly frequent in children. It represents one of the most common ocular diseases in childhood, occurring in approximately 1 in 8 children each year. Bacterial infection is a common cause of conjunctivitis and accounts for up to 50% of all cases of conjunctivitis in adults and 70% to 80% of all cases in children.[1–3] Globally, purulent bacterial conjunctivitis is mainly caused by Gram-positive organisms. The most common causative agents are *Staphylococcus epidermidis* (39% of cases), *Staphylococcus aureus* (22% of cases), and *Streptococcus pneumoniae* (6% of cases).[4] The most common Gram-negative microorganism found in acute conjunctivitis is *Haemophilus influenzae* (9% of cases).[4] In contact lens wearers, the trend is reversed and more Gram-negative strains are found. However, other bacterial strains can less frequently cause bacterial purulent conjunctivitis.

Although bacterial conjunctivitis can occur at any age, it frequently occurs in preschool- and school-age children. In these age groups, pathogens are frequently associated with epidemic occurrences of bacterial conjunctivitis. In infants, children and teenagers, the most common ocular pathogens are *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and also *Moraxella* species.[5–7]

Most cases of acute bacterial conjunctivitis resolve spontaneously within 7–10 days, but a broad-spectrum antibiotic can decrease disease severity, transmission and also minimize the complication and reinfection rates.[8] Practice patterns for prescribing topical antibiotics vary. Most practitioners prescribe a broad-spectrum agent on an empirical basis without culture for a routine, mild-to-moderate case of bacterial conjunctivitis and instruct patients to seek follow-up care if the expected improvement does not occur or if vision becomes affected.

- Sodium sulfacetamide, chloramphenicol, gentamicin, tobramycin, azithromycin, neomycin, trimethoprim and polymyxin B combination, ciprofloxacin, ofloxacin, gatifloxacin, and erythromycin are representatives of commonly used first-line agents.
  The respective advantages of eye drops and ointments include preserved visual acuity and prolonged contact, and a soothing effect.
- *Blepharitis:* Blepharitis is a chronic disorder producing inflammation of the eyelid margin. Blepharitis can be classified according to anatomic location: anterior blepharitis affects the base of the eyelashes and the eyelash follicles, and posterior blepharitis affects the Meibomian glands and gland orifices. Blepharitis has traditionally been clinically subcategorized as staphylococcal, seborrheic, Meibomian gland dysfunction (MGD), or a combination thereof.[9,10] Staphylococcal and seborrheic blepharitis mainly involve the anterior eyelid and both can be described as anterior blepharitis.[10] Meibomian gland dysfunction involves the posterior eyelid margin.

The organisms most commonly isolated in chronic blepharitis include: *Staphylococcus aureus*, coagulase-negative *Staphylococcus* spp., *Corynebacterium* spp. and *Propionibacterium acnes*.[11–14] The cause of inflammation appears to be bacterial by-products (proinflammatory cytokines, lipases) rather than the

bacteria themselves,[15] as, although pathogenic bacteria are rare in blepharitis, commensal organisms such as *S. epidermidis* and *S. aureus* can produce lipolytic exoenzymes and endotoxins.[12,16] Lipolytic enzymes hydrolyze wax and sterol esters in Meibomian gland secretions with the release of highly irritating fatty acids and other products resulting in disruption of tear film integrity.[17,18] These endotoxins can induce the production of proinflammatory cytokines, thus initiating inflammatory series.[19] Reducing the bacterial load is therefore part of the treatment of blepharitis.

Furthermore, in addition to their antibacterial activities, macrolides such as azithromycin exhibit potent anti-inflammatory activities.[20] They decrease the production of proinflammatory cytokines by macrophages and epithelial cells, and inhibit the activation and migration of neutrophils in vitro and in vivo.[21–23] At a gene expression level, macrolides have been reported to reduce induction of mucin 5 AC (MUC5 AC) synthesis after inflammatory stimuli[24–26] and decrease the expression of matrix metallopeptidase (MMP) 1, 9, 10 and 13.[25,27,28] Topical erythromycin ointments have been used up until now for the treatment of blepharitis. They provide prolonged contact time with the lid margin but limited penetration into eyelid tissue. However, azithromycin eye drops provide an advantage over other macrolides because this drug achieves sustained high concentrations in various ocular tissues including the lid margin.[29] Azithromycin 1% ophthalmic solution was recently tested in the treatment of blepharitis. Irrespective of the route of administration, drops into the eye or on an applicator applied directly to the eyelids, azithromycin eye drops was shown to be effective in treating signs and symptoms of blepharitis.[30–33]

- *Keratitis*: Bacterial keratitis is a vision-threatening process and a major cause of corneal opacity and loss of vision worldwide. A particular feature of bacterial keratitis is its rapid progression; corneal destruction may be complete in 24–48 hours with some of the more virulent bacteria. Corneal ulceration, stromal abscess formation, surrounding corneal edema, and anterior segment inflammation are characteristic of this disease. Bacterial keratitis is a potentially devastating ocular infection that may occur when the corneal epithelial barrier is compromised due to injury or trauma, leading to ulceration

and infiltration of inflammatory cells. Infection is largely due to Gram-positive *S. aureus*, *S. epidermidis*, and several *Streptococcus* and *Bacillus* spp., but also Gram-negative bacteria such as *P. aeruginosa*, *S. marcescens*, *Moraxella lacunata*, *Microbacterium liquefaciens,* and *H. influenzae*. Contact lenses are increasingly involved in keratitis: contact lens wear now accounts for more than one half of all cases of bacterial keratitis and has become the most important risk factor.[34] Although Gram-negative organisms such as *Pseudomonas aeruginosa* are known to be associated with contact lens-related corneal ulcers, Gram-positive organisms such as *Staphylococcus* species and *Streptococcus* species have also been shown to be frequently responsible for a significant proportion of these ulcers, even when Gram-negative organisms are recovered from the lens and lens-case. Indeed, a higher incidence of Gram-positive organisms than Gram-negative organisms recovered from infections associated with contact lens wear is reported.[35]

Immediate diagnosis and treatment are important to avoid vision-threatening outcomes, including corneal scarring or perforation. The choice of treatment is based on the use of a single antimicrobial, or a combination of antimicrobials, that provides a broad range of activity against both Gram-positive and Gram-negative bacteria. Once the pathogen has been isolated, treatment can be modified according to the in vitro susceptibility pattern of the isolate.[36] Specially prepared fortified combined antibiotics have been used to provide broad-spectrum coverage. The limited availability, cost, adverse effects, and inconvenience of these fortified preparations have led to the use of commercially topical fluoroquinolones. Consequently, emerging resistance of *Staphylococcus aureus* to ciprofloxacin and ofloxacin has raised concern over the use of monotherapy with these agents for suspected cases of bacterial keratitis. This is especially true given the high rates of microbial keratitis caused by Gram-positive organisms.[35] Nevertheless, fortified topical antibiotics and fluoroquinolones are still the mainstay of bacterial keratitis therapy.[37]

Perioperative prophylaxis

Cataract surgery has become one of the most prevalent surgical procedures due to changes in population structure and increasing life expectancy.[38] As a

result of technical progress, it is now a very safe and predictable procedure, but endophthalmitis is still one of the most serious complications of cataract surgery. The risk of endophthalmitis reported in 3 prospective studies is: 0.21%[39] and 0.32%[40] in France and 0.38% in Europe.[38] The microorganism responsible for endophthalmitis may be derived from conjunctival flora, contaminated instruments, irrigating solutions, the implant, or airborne contamination. The best means of prevention of endophthalmitis is therefore compliance with strict surgical hygiene. The organisms most commonly isolated from endophthalmitis occurring after cataract surgery are Gram-positive bacteria (86.7% of cases), including *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Streptococcus pneumoniae*, while Gram-negative bacteria represent 13.3% of cases.[41–43]

A variety of practices and procedures have been proposed for a long time in order to minimize the incidence of postoperative infection. Two approaches to prophylaxis have been proposed. One consists of reducing the number of organisms on the surface of the eye by using topically applied antisepsis and/or antibiotics. The other involves diffusion of antibiotics into the ocular tissues during the perioperative period via the topical, subconjunctival, systemic, or intracameral routes.[44]

The positive culture rate of normal eyes reported in the literature is about 70%.[45–47] Several clinical trials show that preoperative topical antibiotic prophylaxis reduces the number of bacteria in the conjunctival sac versus placebo. The use of postoperative topical antibiotics for up to two weeks is recommended to minimize the risk of infection, but their usefulness has never been formally demonstrated.[41,48,49] Moreover, the long treatment period and the excessive use of antibiotics play a role in the development of resistant bacterial strains.[44,50]

Only two of the various prophylactic methods proposed have been shown to be effective in endophthalmitis prevention[38]:

- Antisepsis and
- Intracameral injection of 1 mg cefuroxime at the end of the surgical procedure,

However, no commercially available antibiotic has been approved for prophylactic intraocular injection. Nevertheless, numerous studies have recently demonstrated the efficacy of intracameral injection of 1 mg cefuroxime in 0.1 ml normal saline at the end of cataract surgery (Table 1).[51–58] An European study conducted by the European Society of Cataract & Refractive Surgeons (ESCRS),[38,41,48] including 16,211 Intent-to-Treat (ITT) patients, also showed that the

Table 1. Incidence of postoperative endophthalmitis after intracameral cefuroxime prophylaxis—retrospective studies in various countries.

Country authors	Study period	Number of patients	Number of cases	POE incidence rate	Previous POE incidence rate reported*
Sweden Montan, 2002	Jan 1996 to Dec 2000	32,180	20	0.06%	0.26%
Sweden Wejde, 2005	Jan 1999 to Dec 2001	188,151	112	0.0595%	0.26%
Sweden Lundstrom, 2007	Jan 2002 to Dec 2004	225,471	109	0.048%	0.26%
Spain Diez, 2009	Oct 2003 to Sept 2008	4,281	5	0.11%	0.5%
Spain Garcia-Saenz, 2010	Jan 1999 to Sept 2005	6,595	39		0.590%
	Oct 2005 to Dec 2008	7,057	3	0.043%	
France Gualino, 2010	Jan 2007 to Dec 2008	3,316	2	0.06%	0.2% to 0.3%
UK Yu WaiMan, 2008	Jan 2000 to Nov 2003	19,425	27		0.139%
	Nov 2003 to Dec 2006	17,318	8	0.046%	

Note: *Previous POE incidence rate reported prior to routine use of intracameral cefuroxime prophylaxis.

use of intracameral cefuroxime at the end of surgery significantly reduced the incidence of postoperative endophthalmitis with a fivefold decreased risk of developing endophthalmitis.

Furthermore, over the last decade, Swedish cataract surgeons have routinely performed intracameral injection of 1 mg cefuroxime in 0.1 ml 0.9% saline at the end of phacoemulsification surgery before closing the wound,[55,56] usually without preoperative or postoperative topical antibiotics. This technique has been developed in Sweden and retrospective and prospective data from more than 400,000 Swedish patients have demonstrated the efficacy of intracameral cefuroxime.[54] The Swedish experience was presented in two retrospective studies, resulting in the lowest frequency of postoperative endophthalmitis in Europe,[54,57] after implementing this procedure in cataract surgery.

Miscellaneous
Intravitreal injection
Although intravitreal injection (IVT) of corticosteroids is still used, intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents is the current standard of care in the treatment of neovascular age-related macular degeneration (AMD). Intravitreal anti-VEGF therapy is also increasingly used for retinal venous occlusive disease, proliferative diabetic retinopathy and non-AMD-related choroidal neovascularization, such as pathologic myopia, glaucoma.[59] However, patients treated with anti-VEGF agents often receive intravitreal injections at regular 4- to 8-week intervals, resulting in repeated exposure to the risk of endophthalmitis. Furthermore, many patients ultimately require bilateral treatment.[60]

Among all of the various approaches proposed, only one prophylactic method has been shown to be effective in IVT endophthalmitis prevention: antisepsis.[61] In addition, although perioperative administration of topical antibiotics has not been shown to decrease the risk of endophthalmitis in humans, a recent study in rabbits demonstrated the efficacy of antibiotic prophylaxis to prevent endophthalmitis after intravitreal injection.[62]

Antibiotics have nevertheless been used for many years by ophthalmic surgeons before and/or during and/or after intravitreal injection for endophthalmitis prophylaxis, as they reduce the number of bacteria present in the eye. According to large-scale clinical trials based on almost 75,000 patients, the risk of post-injection endophthalmitis was decreased and ranged between 0.01% and 0.07%.[59,60,63–68]

The Summary of Product Characteristics (SPC) of some anti-VEGF recommend the use of antibiotics:

- for ranibizumab, before treatment, the patient should be instructed to self-administer antimicrobial drops (four times daily for 3 days before and following each injection)
- for pegaptanib, a broad-spectrum topical microbicide should be administered prior to the injection.

However, the efficacy of antibiotics to prevent endophthalmitis has not been formally demonstrated.

Various antibiotics have been used. The current trend is to use fluoroquinolones after the injection.[59,60,64,66,67] This approach raises two issues:

- the number of daily administrations (usually 4 drops per day),
- the emergence of resistant isolates (high risk with fluoroquinolone) resulting from mutations in genes encoding topoisomerases II and IV or acquired efflux systems.

Eye drops in newborns
Prophylaxis of ophthalmia neonatorum is a major element in the worldwide effort to prevent blindness. Neonatal conjunctivitis has decreased considerably in developed countries as a result of prophylaxis. However, it remains a major concern in developing countries. The bacteria commonly responsible for ophthalmia neonatorum are *Neisseria gonorrhoea* and *Chlamydia trachomatis* transmitted by the mother's genital tract and which require aggressive treatment.

Gonococcal infection affects 0.4 infants per 1,000 births.[69]

The range of available eye drop preparations has recently changed in many countries. In the past, silver nitrate was routinely used to prevent infection, but this agent can cause burns of the newborn's eyes. Erythromycin is now more commonly used, but is not available in all countries.

In France, the survey conducted by 17 Regional Pharmacovigilance Centres (CRPV)[70] revealed that:

- 1/3 of the 68 maternity units surveyed did not perform routine antibiotic prophylaxis;

- For the remaining 2/3 of maternity units, antibiotic prophylaxis usually comprised rifamycin, while the other products reported were: ciprofloxacin, gentamicin, tobramycin and picloxydine.

A survey conducted in 28 European countries[70] revealed that:

- 1/3 of the 22 responding countries did not perform routine antibiotic prophylaxis;
- For 4 countries, antibiotic prophylaxis was performed in several maternity units or in the presence of risk factors;
- For other countries, in which antibiotic prophylaxis was performed, silver nitrate was the agent most frequently used. Other products were: ampicillin, ciprofloxacin, erythromycin, povidone-iodine, tetracycline and tobramycin.

A distinct North-South gradient is observed, with the absence of antibiotic prophylaxis in Nordic countries. A resurgence of sexually transmissible infections including gonococcal infections is observed in industrialized countries, including France and the United Kingdom where ophthalmia neonatorum is under-reported.[71] However, no specific data are available concerning the epidemiology of gonorrhea and *Chlamydia trachomatis* in pregnant women or the incidence of specific infections in the newborn. Although no dosing regimen has been demonstrated to be effective by well designed studies, the majority of maternity units use a dosage of 1 drop in each eye of the newborn at birth. Given the pharmacokinetic-pharmacodynamic parameters of rifamycin, and taking into account the volume administered per drop of eye drops, it is recommended, in France, to instill one drop of rifamycin in each eye of the newborn at birth.[70] Nevertheless, *N. gonorrhoeae* and Chlamydial infection of the newborn require systemic treatment of the neonate, the mother, and at-risk contacts.

Trauma

Minor ocular trauma can occur at work or at home. These injuries usually consist of trivial superficial corneal epithelial abrasions. A period of several hours to several days may be required before onset of infection and development of true corneal ulcers. Upadhyay considered that this interval could constitute a "window of opportunity" to prevent the development of corneal ulcer.[72] He demonstrated that application of antibiotic in an eye within 18 hours after a traumatic corneal abrasion[72] prevents the subsequent development of suppurative ulceration in the treated cornea.

Current Options

Broad-spectrum antibiotic are commonly used to effectively treat ocular infection. Ophthalmic antibiotics available in Europe are presented in Table 2. However, pre-existing in vitro resistant bacteria may cause bacterial conjunctivitis. The frequency of resistant bacteria appears to be considerable on the basis of in vitro breakpoints applicable to systemic use.

This phenomenon does not alter:

- the clinical efficacy of topical antibiotics,
- the ability of these products to eliminate bacteria from the ocular surface.

Topical antibiotics are able to eradicate in vitro resistant strains in patients and provide the same cure rate for both susceptible and resistant strains.

According to Benitez del Castillo,[73] microorganisms known to be resistant to a systemic antibiotic, are often effectively treated by topical treatment due to the higher local concentrations induced by this route of administration.

This supports the notion that the breakpoints applicable to systemic antibiotics are not applicable to the treatment of bacterial conjunctivitis, as they are based on in vitro tests performed with systemic antibiotic concentrations. The European Medicines Agency (EMA) has elaborated a note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections: CPMP/EWP/558/95: "For topical preparations of antibacterial agents, … these breakpoints (ie, those applicable to systemic use) may not be applicable to topical application of the drug due to the local concentrations that are reached and the local physicochemical conditions that may influence the overall activity of the agent at the site of application".

Aminoglycosides

Aminoglycosides inhibit protein synthesis by binding to both the 16S (in the 30S subunit) and 23S (in the 50S subunit) rRNA molecules of the bacterial ribosome. They display a bactericidal effect against a broad

Table 2. Most common topical ophthalmic antibiotics available in Europe.

Class	Molecule	Regimen	Pediatric indication
Aminoglycosides	Tobramycin	For 5 to 15 days: up to 1 drop every hour until improvement occurs, followed by a decreasing frequency of administration	≥1 year old
	Gentamicin	Instill 1–2 drops into the affected eye every four hours as required.	
Quinolones	Norfloxacin	One or two drops in the affected eye(s) four times a day. In severe infections, the dosage for the first day may be one or two drops every two hours during the day.	
	Ofloxacin	One to two drops in the affected eye(s) every two to four hours for the first two days and then four times daily. The duration of treatment should not exceed ten days.	
	Lomefloxacin	At the beginning of therapy on Day 1, instill 5 drops into the conjunctival sac within 20 minutes. Thereafter, until Day 7–9 instill 1 drop 3 times daily into the conjunctival sac.	≥1 year old
	Ciprofloxacin	One or two drops four times a day. In severe infections, the dosage for the first two days may be one or two drops every two hours. A maximum duration of therapy of 21 days is recommended.	All age groups. However, the safety and efficacy of this product in children under the age of 1 year has not been established.
	Levofloxacin	For all patients, instill one to two drops in the affected eye(s) every two hours up to 8 times per day while awake for the first two days and then four times daily on days 3 through 5.	≥1 year old
	Moxifloxacin	Three times a day for 7 days	Particularly in new-born infants or children, the nasolacrimal ducts should be held closed with the fingers for 2 to 3 minutes after administering the drops.
Macrolides	Erythromycin	Ointment, available in a few European countries	≥2 years old for bacterial conjunctivitis ≥1 year old for trachoma
	Azithromycin	Instill 1–2 drops into the affected eye twice a day during 3 days.	
Others	Chloramphenicol	Two drops to be applied to the affected eye every three hours or more frequently if required. Treatment should be continued for at least 48 hours after eye appears normal.	All age groups
		One drop every two hours for the first 48 hours and 4 hourly thereafter for a total of 5 days.	≥2 years old
	Fusidic acid	One drop twice daily. Treatment should be continued for at least 48 hours after the eye returns to normal.	All age groups
	Rifamycin	1 to 2 drops, 4 to 6 times a day for 7 days.	
Tetracyclines (ointments)	Chlortetracycline	1 or 2 times a day for 7 days	≥8 years old
	Tetracycline	2 to 4 times a day. Treatment should be continued for at least 48 hours after symptoms have disappeared.	

spectrum of Gram-positive or Gram-negative aerobic bacteria such as *Staphylococcus spp., Haemophilus influenzae or Pseudomonas aeruginosa.*

Tobramycin, the most popular topical antimicrobial of this family, binds to the bacterial 30S and 50S ribosomes, preventing formation of the 70S complex. As a result, mRNA cannot be translated into protein and cell death ensues.

Fluoroquinolones

Fluoroquinolones belong to the family of synthetic antibiotics called quinolones. The newer fluoroquinolones are broad-spectrum bactericidal drugs with high conjunctival concentrations. They prevent bacterial DNA from unwinding and duplicating. Quinolones, in comparison to other antibiotic classes, are associated with the highest risk of causing colonization with Methicillin-resistant *Staphylococcus aureus* (MRSA).[74] For this reason, it is generally recommended to avoid fluoroquinolones based on available evidence and clinical guidelines.

Quinolones are grouped into "generations", the most recent being the 4th generation which, in the field of European ophthalmology, includes topical moxifloxacin, which is not yet available in France. However, several publications have already reported resistance to this molecule in the United States.[75]

Chloramphenicol

Chloramphenicol is bacteriostatic. It is a protein synthesis inhibitor, inhibiting the peptidyl transferase activity of the bacterial ribosome. Because it functions by inhibiting bacterial protein synthesis, chloramphenicol has a very broad spectrum of activity; it is effective against a wide variety of Gram-positive and Gram-negative bacteria, including most anaerobic organisms.

Due to resistance and safety concerns (adverse effects such as aplastic anemia), it is now less frequently prescribed as first-line agent in industrialized countries, except for the United Kingdom.

β-lactam antibiotics (penicillins and cephalosporins)

Penicillins and cephalosporins interfere with synthesis of the bacterial cell wall and are therefore bactericidal.

First-generation β-lactam antibiotics are predominantly active against Gram-positive bacteria, and successive generations have enhanced activity against Gram-negative bacteria. Cephalosporins are one of the most diverse classes of antibiotics, and are grouped into "generations" according to their antimicrobial properties. Each generation has a broader spectrum of activity than the previous one. A second-generation cephalosporin is now commonly used in ophthalmology: cefuroxime. In addition to the Gram-positive spectrum of first-generation cephalosporins, this agent has an expanded Gram-negative spectrum and is now one of the standard agents used for antibiotic prophylaxis in cataract surgery.

Macrolides

Macrolides are bacteriostatic, broad-spectrum antibiotics, binding with bacterial ribosomes to inhibit protein synthesis. Erythromycin is the prototype of this class. The frequency of mutation to macrolides in pathogens is very low (much lower for instance than that for rifampicin, for aminoglycosides or for fluoroquinolones that are also used as topic antimicrobials).

Azithromycin is one of the most recently approved ophthalmic antibiotics. Its broad spectrum is particularly suited to ocular infections and it has been demonstrated to be effective in several indications (trachoma, blepharitis, bacterial conjunctivitis).[5,30–33,76–78]

Azithromycin has a unique pharmacokinetic profile allowing rapid tissue distribution, sustained high tissue levels, good acid stability, good oral bioavailability, low protein binding, and enhanced absorption compared with erythromycin and it is taken up and transported by phagocytic cells.[79–81] Azithromycin achieves high intracellular concentrations that are beneficial for eradication of *Chlamydia trachomatis*, an obligate intracellular pathogen. More importantly, azithromycin has high tissue bioavailability and a tissue half-life of 2 to 4 days. These pharmacokinetic properties imply that the dosing period for azithromycin can be considerably reduced while still achieving high antimicrobial activity at sites of infection.[82] In addition to its antibacterial activities, azithromycin also exhibits potent anti-inflammatory activities.[20]

Other antibiotics

Fusidic acid
Fusidic acid is a bacteriostatic antibiotic, acting as a bacterial protein synthesis inhibitor selective for Gram-positive bacteria but with documented acquired resistance.[83]

Vancomycin
Vancomycin is a glycopeptide antibiotic used in the prophylaxis and treatment of Gram-positive bacterial infections. Vancomycin acts by inhibiting cell wall synthesis in Gram-positive bacteria, but is not active against Gram-negative bacteria (except for certain non-gonococcal species of *Neisseria*).

It has been traditionally reserved as a drug of "last resort", used only after failure of treatment with other antibiotics, ie, treatment of serious infections caused by vancomycin-susceptible penicillin- resistant organisms such as MRSA. Some surgeons now also use intracameral vancomycin for surgical prophylaxis during cataract surgery,[84] but it is not recommended by several national guidelines.[85,86]

Rifamycins
The biological activity of rifamycins is based on inhibition of DNA-dependent RNA synthesis. In ophthalmology, its spectrum is particularly adapted to Gram-negative bacteria.

Tetracyclines
Tetracycline is a broad-spectrum antimicrobial, whose clinical value has been reduced with the onset of bacterial resistance and safety issues. Tetracycline antibiotics are protein synthesis inhibitors, binding to the 30S subunit of microbial ribosomes. Tetracycline ointment remains one of the treatments of choice for chlamydial infections (trachoma) because it was the only available topical treatment for many years.

Evolving Options

Resistance
Growing resistance has been observed among ocular bacteria as with other systemic pathogens. The factors contributing to the development of drug resistance include overuse of antibiotics for systemic infection as well as overuse of topical antibiotics in the eye.[87] Reserving certain antibiotics for hospital use to avoid resistance to all antibiotics therefore appears to be a major issue to maintain the efficacy of certain "emergency" antibiotics.

An increasing number of guidelines recommend avoiding the use of fluoroquinolones and combinations except for the most severe infections or following treatment failure.[88–90] This strategy is designed to preserve the efficacy of these antibiotics by limiting their potential selective pressure due to their high frequency of mutation. Only a few of the registered antimicrobials are therefore recommended as first-line therapy.[90] Several of them (ie, rifampicin, aminoglycosides, fusidic acid) have a much higher frequency of mutation in pathogens than azithromycin.

Pharmaceutical forms adapted to modern life for a better quality of life
Most of the currently available antimicrobials require at least 5 to 10 days of treatment and are packaged in multidose vials with a risk of contamination and spread of infection during repeated use. Improved compliance is a key issue for antibiotic therapy, as it would ensure improved efficacy and, above all, less resistance.

Fewer instillations
These issues are crucial in ophthalmology, since repeated instillations of eye drops constitute a real challenge for patients and caretakers. Repeated instillation of antibiotic is particularly constraining in eyes with purulent secretions, combining the usual difficulties of instilling eye drops and special precautions for bacterial infections. Winfield[91] found that over one third of patients do not administer their own drops regularly.

These precautions are crucial in order to rapidly relieve the patient and break the contamination chain in the community.

Instillation is therefore a major issue for bacterial conjunctivitis, as registered ocular antimicrobials require more frequent administration than systemic antimicrobials (2 to 8 times a day for 5–15 days) and as they are packaged in multi-use containers, with a risk of self-recontamination and spread of infection when touching purulent secretions or eyelid margins

or eyelashes. These difficult dosing regimens do not facilitate compliance with treatment as:

- daily instillation is fairly challenging for outpatients, who usually do not stop work (except to avoid spread of infection).
- frequent instillations are constraining for children, the elderly or hospitalised patients, and for parents, caretakers or health professionals.

A *bis in die* (BID) dosing regimen has been demonstrated to improve compliance with treatment.[92,93] This improved compliance to BID dosing regimen is related to the strong correlation between living conditions and the rate of failure to use eye drops as prescribed. Missing instillations are consecutive to the following factors: away from home (26%), time/frequency (9%), inconvenient timing for instillations (9%).[94]

Instillations are particularly challenging for caretakers as children frequently cry when upset or during instillation of topical agents.

A twice daily regimen of antimicrobials is therefore more compatible with good quality of life and is expected to limit poor compliance (a major factor of resistance selection) by allowing a low-frequency dosing regimen. Treatment duration should also be limited to the period during which the patient is aware of the infection (ie, the first 3 days when clinical signs are present). Short-duration treatment for infections appears to be a more pressing need than in the past.[88]

Ointments (another alternative for low-frequency regimen) are poorly tolerated in children older than 9 months, because they blur vision, and applying a layer of ointment with a metal-tipped tube to a generally uncooperative, squirming youngster can be hazardous and is difficult for most parents.[1]

Rapid control of bacterial conjunctivitis is a public health issue in order to avoid outbreaks in preschool and school-aged patients. A good ATB should improve the quality of life for both children and parents, decrease the workload of families and services in charge of children, avoid long-term eviction of children from nurseries or schools and facilitate their rapid return.

Furthermore, to limit spread of bacteria, a packaging adapted to the context of infectious diseases (single-use units to be discarded after use) should be preferred. Preference should be given to single-use containers and preservative-free antibiotics to treat ocular infections.[89]

New forms

- *Insert*: Inserts ensuring sustained delivery of antibiotic could avoid compliance issues and therefore the emergence of resistance, as selection of mutants is very unlikely on the ocular surface due to the very few bacteria responsible for ocular infection that are confined to the very small volume of the palpebral fissure. The volume available for bacterial proliferation is very small (the volume of the palpebral fissure is usually slightly less than 10 µl) and the number of bacteria isolated from the ocular surface is very small[95] and often below the cut-off to obtain one mutant in vitro.

  Moreover, most types of mutants are unlikely to survive and to be selected by the high antibiotic concentrations reached in situ[96–98] when the concentration is maintained throughout treatment until eradication of pathogens. An insert would therefore improve compliance and antimicrobial concentrations during the treatment.

- *Soaked intraocular lens (IOL)*: Very recently, a new method was tested in vitro for postoperative endophthalmitis prophylaxis.[99] Hydrophobic and hydrophilic intraocular lens were soaked in 1 mL of commercially available moxifloxacin 0.5% for 1 min or 10 min and then placed in vials of 10 mL balanced saline solution for 30 min. The moxifloxacin levels achieved after soaking the hydrophobic lens were 0.238 and 0.342 µg/ml for 1- and 10-min soaks, respectively. The moxifloxacin levels achieved after soaking the hydrophilic lens were 0.283 and 0.717 µg/ml for 1- and 10-min soaks, respectively. Both lenses were therefore able to deliver clinically significant antibiotic levels after a 1-min soak. Moxifloxacin concentrations reached after 1- and 10-min soak times both exceeded the MIC90 of the pathogens most commonly responsible for postoperative endophthalmitis. The antibiotic-soaked IOL has the potential to become a clinically significant technique in the prevention of postoperative endophthalmitis.

New antibiotics

Some antibiotics are only available for systemic use and are not yet available in ophthalmology.

Marketed fortified antibiotics

Specially prepared fortified single or combined antibiotics (cefazolin, vancomycin, amikacin and ceftazidime) are used for immediate vision-threatening conditions (endophthalmitis, keratitis, etc.). These highly concentrated eye drops achieve high corneal antibiotic concentrations. However, local toxicity has been reported, which could be linked to the pH or osmolarity and very often leads to irritation.[100] Fortified eye drops also induce stinging and burning sensations.

Fortified antibiotics used to be prepared by hospital staff. To resolve the problem of continuous availability of these types of eye drops, some teams have tried to prepare fortified antibiotics under aseptic conditions from parenteral antibiotic solutions and to freeze these solutions for up to 75 days.[100]

Manufacture of fortified antibiotics by drug companies would avoid these problems of pH, osmolarity, preparation and storage.

Furthermore, one team studied a fixed combination of fortified antibiotics (vancomycin and amikacin) compared to separate therapy in the treatment of bacterial corneal ulcer. A similar efficacy was observed with the two treatments, but the fixed combination provided greater convenience and tolerability and therefore facilitated patient compliance, while also avoiding the washout effect, and reducing nursing time.[101]

Ophthalmological cefuroxime

Data based on more than 10 years of use of intracameral cefuroxime in more than 400,000 Swedish patients reveal a very low overall incidence of POE of about 0.05% of cataract operations.[54–57] A large comparative placebo-controlled and active-controlled study was carried out by ESCRS to evaluate antibiotic prophylaxis for endophthalmitis following cataract surgery. The results of this study, carried out in more than 16,000 patients, showed that the use of intracameral cefuroxime at the end of surgery significantly reduced the postoperative endophthalmitis rate with a 5-fold decreased risk of developing endophthalmitis.[38,41,48] The use of intracameral antibiotics for prophylaxis of postoperative endophthalmitis is now defined by numerous guidelines and recommendations. Clearly, the major barrier to the intracameral use of cefuroxime to prevent postoperative endophthalmitis in everyday practice is the lack of a commercially available preformulated preparation.

Intracameral injections of antibiotics, including cefuroxime, have not yet been approved by regulatory authorities and can only be prescribed at the surgeon's discretion. However, numerous good quality studies have been published showing the value of this route of administration and the efficacy of intracameral cefuroxime injection. This prophylactic approach is therefore now used by an increasing number of ophthalmologists in Europe and the US. Cefuroxime solutions are now prepared by hospitals/clinics and the protocol used could largely influence the quantity of cefuroxime actually injected.[102] Several authors have indicated their concerns about dosage variability associated with dilution of antibiotics for intracameral use.[102–104] Most studies in support of intracameral antibiotic prophylaxis used cefuroxime 1.0 mg in 0.1 ml, but did not specifically describe how this dose was determined or the accuracy of this determination.

A very recent report of misunderstanding of the dilution protocol was published by Delyfer et al.[105] Six patients received by mistake an intracameral injection of 40 to 50 mg of cefuroxime instead of the recommended dose of 1 mg. Fortunately final visual outcome was relatively satisfactory in all patients. This experience highlights the need to propose a "ready-to-use" formulation of cefuroxime for ocular intracameral use.

In the US, although 77% of respondents did not inject intracameral antibiotic agents, 82% said they would use a commercially available preparation.[103] Similar concerns were voiced in United Kingdom.[104] In the United Kingdom (UK), Murjaneh[106] reported that three years following the ESCRS recommendations, only 37.1% of National Health Service (NHS) ophthalmology units used intracameral cefuroxime as a standard protocol after cataract surgery partly due to the lack of a commercially available preparation. Similarly, French teams have highlighted the major barrier to further routine use of intracameral cefuroxime constituted by the lack of a commercially available preparation.[53,107]

On the other hand, a recent cost-effectiveness analysis on the use of ocular intracameral cefuroxime demonstrated that administration of ocular intracameral cefuroxime is cost-effective in preventing

endophthalmitis after cataract surgery. Due to their high costs, many commonly used topical antibiotics are not cost-effective compared with ocular intracameral cefuroxime, even under optimistic assumptions concerning their efficacy.[108]

Conclusion

Only a few non-combined antibiotics are available for ocular infections in the context of resistance, in which fluoroquinolones/combinations must be reserved for the most severe cases:

- "Old" topical antimicrobials from the sulfonamide,[109] aminoglycoside (neomycin,[110] kanamycin[110]) and tetracycline[111] classes have a fairly low activity.[109,110] Chloramphenicol has been shown to be less effective than other reference therapies[112] and is not used in some countries due to its systemic adverse effects. Polymyxin B and colistin have a narrow activity spectrum, particularly against *Pseudomonas aeruginosa* and other Gramnegative strains.[89] Bacitracin is usually combined with another antibiotic, except when formulated in an ointment.[89,113]

- Rifamycin remains an effective treatment,[114] but in vitro resistance may be rapidly induced by selection pressure.[115] Fusidic acid has a narrow spectrum against *Staphylococci*[89] and may rapidly develop resistance.[116]

- The more recent aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin) are widely used. Gentamicin and tobramycin are active against most *Staphylococci*, *Proteus* and *Enterobacteriaceae*, but resistant strains are now reported. In addition, aminoglycosides have a limited efficacy against *Streptococcus pneumoniae*, group A *Streptococcus* and *Haemophilus*.[89,110]

- The recently developed topical antimicrobial, azithromycin, seems suited to modern life and can be used as first-line therapy with a reduced dosage regimen and its broad spectrum of action.

Guidelines concerning ocular topical anti-infectives differ widely from those concerning systemic anti-infectives and more antimicrobial studies should be developed to provide a better understanding of the mechanisms of action of ocular antibiotics in order to ensure a better quality of life for the patient. As shown in the table, antibiotic eye drops can be used in children, although few clinical data are available in most cases and they must be used according to the adult dosage regimen, as no specific clinical development has been conducted and no pediatric forms are available. It would be useful to perform pediatric clinical trials on topical ophthalmologic antibiotics in order to comply with EMA or United States Food and Drug Administration requirements, as these authorities are increasingly encouraging drug companies to develop medicines adapted to and specifically studied in children.

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