Anti-infective ophthalmic preparations in general practice

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Introduction

Ocular infections may be bacterial, viral, fungal or parasitic in aetiology. Pharmacological preparations are available to treat infections that are caused by these groups of organisms. The majority of these preparations are intended for topical administration, although some systemically administered agents may be needed to treat or prevent specific ocular infections. This article discusses the different anti-infective options that are available to general practitioners to treat infections caused by each aetiological group. It also discusses the role that is played by povidone-iodine and antibiotic-steroid combinations to manage eye infections. A summary of all these drugs is provided in table form for easy reference.

Keywords: anti-infective ophthalmic preparations, general practice

Classification of anti-infective ophthalmic preparations

Preparations are available to treat eye infections that are caused by organisms in all four above-mentioned groups. Table I provides an outline of the different drug classes, as well as the specific available drugs in each class. A fifth class is also included. This contains preparations that are effective against more than one class of infectious organisms.

Antibacterial ophthalmic preparations

An asterix (*) denotes drugs not currently available in South Africa

Sulphacetamide

Available preparation: 10% ointment.

Sulphacetamide is a bacteriostatic sulphonamide with limited ophthalmic use. Sulphonamides are broad-spectrum antibiotics with good corneal penetration, but resistance is common. It has a synergistic effect when combined with trimethoprim and is effective in methicillin-resistant Staphylococcus aureus (MRSA) infection, Nocardia keratitis and Bartonella henselae conjunctivitis. It may also be combined with oral erythromycin, azithromycin or clarithromycin for the treatment of chlamydial conjunctivitis, and should then be used two or three times a day for 3–6 weeks. It should not be used by patients with a known hypersensitivity to sulphonamide drugs.

Fucidic acid

Available preparation: 10 mg/g viscous drops.

Fucidic acid is not a first-line agent due to the increased risk of resistance. Generally, fucidic acid is considered to have a narrow spectrum of activity which predominantly covers staphylococcal infections such as blepharitis or conjunctivitis. However, in a Canadian study that compared the topical use of 1% fusidic acid to 0.3% tobramycin to treat acute bacterial conjunctivitis, no difference in efficacy was demonstrated between the two drugs. It should not be used with fluoroquinolones as these drugs are antagonistic. The twice daily dosage regimen was also found to be more convenient than the frequent installations required for tobramycin drops.

Silver nitrate

The story of Dr Carl Credé and the prevention of ophthalmia neonatorum with silver nitrate drops is well worth reading, and may be accessed free of charge at the following web address: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1721147/pdf/v083p0f158.pdf.

Very few interventions have had such a profound impact on a medical condition worldwide. Credé originally advocated the use of a 2% silver nitrate solution, but this concentration was later halved. Today, silver nitrate is no longer widely used, although it should still be considered in cases in which Neisseria gonorrhoeae infection is prevalent. It does not provide adequate protection against Chlamydia trachomatis infection. This, combined with the occurrence of a mild chemical conjunctivitis in neonates, is the main reason why its use has been discontinued.
<table>
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<th>CLASS</th>
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<th>EXAMPLES</th>
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<tr>
<td>Antibacterial</td>
<td>Sulphacetamide (sulphonamide)</td>
<td>Lennon-Sulphacetamide® ointment</td>
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<td>Chlamydial conjunctivitis</td>
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<td>Ganciclovir</td>
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<td>150 µg/kg every 6 months</td>
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<td>Perioperative period. Not if diagnosis is uncertain</td>
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<td>0.2% solution</td>
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CMV = Cytomegalovirus; IM = intramuscularly; IV = intravenously; * Not available in South Africa.
Chloramphenicol

Available preparations: 0.5% preserved drops, 1% ointment and 0.5% preservative-free, single-dose units.

Chloramphenicol is the most frequently used broad-spectrum topical antibiotic in South Africa and is effective in more than 99% of superficial bacterial eye infections. It is clinically effective against the majority of Gram-positive and Gram-negative organisms. Therefore, it still plays an integral role in the first-line treatment of bacterial conjunctivitis and blepharitis. To limit adverse effects and resistance from developing, chloramphenicol should not be used for longer than five days.

The ocular toxicity of topical chloramphenicol is low, although it may serve as a trigger for delayed allergic contact dermatitis or conjunctivitis. Aplastic anaemia and other blood dyscrasias have been linked to the ocular use of chloramphenicol, although it has been shown that the risk is less than one per million treatment courses. Therefore, use of this drug to treat superficial eye infections should not be precluded. In South Africa, it is also recommended for the prevention of neonatal conjunctivitis.

Interestingly enough, the only drug that has been approved by the United States Food and Drug Administration for the prevention of neonatal conjunctivitis is erythromycin 0.5% ophthalmic ointment. This is not available in South Africa.

Tobramycin

Available preparations: 3 mg/ml drops and 3 mg/g ointment.

Since gentamycin eye drops were discontinued, tobramycin is now the only commercially available topical aminoglycoside preparation in South Africa. (In South Africa only fortified gentamycin eye drops can be prepared.)

Tobramycin is active against most Gram-negative bacteria, as well as a few aerobic Gram-positive microbes, especially staphylococci. It has been a reliable treatment option for superficial eye infections for many years, and was previously often used as the gold standard in clinical trials in which newer preparations needed to be compared to a well-established drug.

It may cause transient stinging after installation and hypersensitivity reactions have been reported, but these are rare.

Ciprofloxacin

Available preparations: 3 mg/ml drops and 3 mg/g ointment.

Ciprofloxacin, a class II second-generation fluoroquinolone, has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, although it is often not effective against Strepdlococcus pneumoniae. It is effective in most cases of bacterial conjunctivitis and will also successfully treat the majority of small peripheral corneal ulcers. Although newer fluoroquinolones are more efficacious against Gram-positive organisms, rising resistance of 80% for MRSA and 40% for Pseudomonas aeruginosa has been noted in recent ocular isolates. Oral administration of ciprofloxacin results in high intraocular levels of the drug. Therefore, it is recommended as prophylaxis for traumatic endophthalmitis in all open-eye injuries. This includes paediatric cases since the benefit is considered to outweigh the risk of damage to cartilage in weight-bearing joints. The recommended dose in adults is 750 mg twice daily, and in children, 5–10 mg/kg/dose twice daily, and up to a maximum of 500 mg per dose.

Ofloxacin

Available preparations: 3 mg/ml drops and 3 mg/g ointment.

Ofloxacin is another class II second-generation fluoroquinolone. Therefore, it has a similar spectrum of activity and application to ciprofloxacin, although it is not as effective against Pseudomonas aeruginosa.

Gatifloxacin

Available preparation: 3 mg/ml drops.

Gatifloxacin is a third-generation fluoroquinolone with a Gram-negative spectrum that is similar to that of the second-generation drugs, but with improved Gram-positive coverage. It is two to four times more active against S. pneumoniae than levofloxacin, another third-generation fluoroquinolone. Preferably, gatifloxacin should not be used as a first-line drug. It should rather be reserved to treat cases that are unresponsive to more conventional drugs. It is registered for the treatment of bacterial conjunctivitis that is caused by staphylococci, streptococci, Haemophilus influenzae and Corynebacterium propinquum. It is also very effective in treating more severe cases of bacterial keratitis.

Moxifloxacin

Available preparation: 5 mg/ml drops.

Moxifloxacin is another fourth-generation fluoroquinolone that covers the same spectrum as gatifloxacin, but demonstrates superior activity to S. pneumoniae. It is also effective against Acinetobacter spp., E. coli, Serratia marcescens and Chlamydia trachomatis. Despite only being licensed to treat bacterial conjunctivitis, moxifloxacin is often highly effective in treating moderate to severe bacterial keratitis. It should be reserved for more complicated cases to minimise the emergence of antibiotic resistance.

Levofloxacin

Available preparation: 5 mg/ml drops.

Levofloxacin has broad-spectrum antibacterial activity against Gram-positive and Gram-negative aerobes, as well as so-called ‘atypical’ bacteria such as Chlamydia trachomatis, but has limited activity against anaerobic bacteria. The main indications for treatment are bacterial blepharitis, conjunctivitis and keratitis (especially when associated with contact lenses).

Levofloxacin is the L-isomer of ofloxacin. The antibacterial activity of ofloxacin resides almost entirely in the L-isomer. Therefore, levofloxacin is, by its nature, twice as active as ofloxacin per unit of mass.
Besifloxacin

Available preparation: 0.6% drops.*

Besifloxacin is a new-generation broad-spectrum fluoroquinolone. It has been established as an effective and safe treatment for bacterial conjunctivitis, while further investigations are needed to assess its safety and efficacy in bacterial keratitis, antimicrobial prophylaxis in ocular surgery and for the treatment of bacterial lid disorders. Compared with other topical fluoroquinolones, besifloxacin ophthalmic suspension offers several potential therapeutic advantages, including higher ocular surface drug concentrations, longer ocular surface exposure times, and greater efficacy against FQ-resistant ocular pathogens, including MRSA and MRSE.12

Lomefloxacin

Available preparation: 0.3% drops.*

Lomefloxacin is a defluorinated-quinolone. The efficacy of lomefloxacin and tobramycin was tested in the treatment of acute bacterial conjunctivitis: both were well tolerated and showed a high degree of clinical and microbiological efficacy. Lomefloxacin caused less resistance than tobramycin.13

Doxycycline

Tetracyclines are broad-spectrum antibiotics that concentrate in oil glands, thus useful in Meibomian gland disease, but will take several weeks to exert its effect and will require maintenance dosing.1

Tetracycline eye ointment is indicated for the treatment of chlamydial inclusion conjunctivitis. Unfortunately, it is not available in South Africa.14 An alternative treatment option for this condition is an oral tetracycline, such as doxycycline 100 mg twice daily for three weeks. Trachoma, another chlamydial infection, may also be treated with the same oral dose of doxycycline, but requires a longer treatment period of 3–6 weeks. Furthermore, oral doxycycline is used in the treatment of other eye conditions, such as posterior blepharitis and ocular rosacea, although the mechanism of action is not antibacterial in these conditions but anti-inflammatory. For ocular rosacea and blepharitis one often requires long-term treatment of up to six months at a lower dose of 50 mg twice daily or daily for the anti-inflammatory benefit.

Azithromycin

Azithromycin is a macrolide antibiotic, active against Gram-positive and a few Gram-negative organisms such as Neisseria, but resistance is rising due to esterases in Enterobacteriaceae. Corneal penetration and penetration of the ocular-blood barrier is generally poor because of poor solubility, thus is given in an oral form.1

It provides a further treatment option for chlamydial inclusion conjunctivitis. In adults, a single dose of 1 g is given orally, while a single dose of 20 mg/kg,2 or alternatively three daily doses of 10 mg/kg, may be administered to neonates.3 Chlamydia conjunctivitis is a sexually transmitted infection in adults. Therefore, appropriate steps need to be taken to trace and treat all sexual partners.

Ceftriaxone

Ceftriaxone is a third-generation cephalosporin with excellent action against organisms such as H. influenzae, S. pneumoniae and N. gonorrhoeae.3 It is used to treat gonococcal conjunctivitis in both adults and neonates. A single dose of 1 g should be given intramuscularly to adults, while a single dose of 125 mg should be given to neonates. If corneal involvement is present, a topical fluoroquinolone or tobramycin for use every hour should also be commenced before the patient is referred to an ophthalmologist.2 Once again, the sexual partners of infected adults should be traced and treated.

Amoxicillin/Clavulanic acid

Amoxicillin/Clavulanic acid is often used to treat soft tissue infections around the eye, since it not only provides good Gram-positive and Gram-negative cover, but also exhibits good efficacy against anaerobic organisms. Mild cases of dacyrocystitis and preseptal cellulitis in patients who are otherwise well may safely be treated with Amoxicillin/Clavulanic acid in a family practice setting. Patients who are acutely ill, or those who may require surgical incision and drainage, should preferably be hospitalised and referred for an ophthalmology opinion.

Erythromycin

Erythromycin is a macrolide antibiotic that is effective against neonatal chlamydial conjunctivitis. The recommended oral dosage is 50 mg/kg/day in four divided doses for 2–3 weeks. This should be combined with topical sulphacetamide to be applied two to three times a day for 3–6 weeks, since neither erythromycin nor tetracycline are available in a topical preparation in South Africa.

Antiviral ophthalmic preparations

Aciclovir

Aciclovir is a guanosine analogue that is effective against a variety of herpesviridae, including herpes simplex 1 and 2, varicella-zoster virus and Epstein Barr virus. Aciclovir shows a high degree of selectivity for herpes-virus-infected cells, as a result of its unique mechanism of action. In short, phosphorylation of aciclovir to aciclovir monophosphate occurs more efficiently in virus-infected cells, because of the presence of viral thymidine kinase. The aciclovir monophosphate is then converted to a triphosphate form which inhibits viral DNA polymerase to a much greater extent than host cell DNA polymerase. Therefore, aciclovir has little effect on DNA synthesis in normal cells, but is a potent inhibitor of herpes-virus replication.15

If topical aciclovir* is not available, oral aciclovir 400 mg five times per day may be used as an alternative since orally administered aciclovir reaches therapeutic levels in the precorneal tear film. Oral aciclovir is more effective than a topical application in treating vesicular eruptions of the periorcular skin in primary herpetic blepharoconjunctivitis. In a general practice setting,
oral aciclovir is the most important drug in the treatment of herpes zoster ophthalmicus. The recommended dosage in adults is 800 mg five times a day for 7–10 days, but this dosage should be reduced in patients with renal impairment.

**Ganciclovir**

Ganciclovir is another guanosine analogue that is effective against all the herpesviridae, but is 10–25 times more active against cytomegalovirus (CMV) due to its specific chemical structure. Recently, a topical 0.15% preparation was launched in the USA to treat herpes keratitis. It was shown to be as effective as topical aciclovir for this indication, but is still not available in South Africa. Ganciclovir is also used by ophthalmologists to treat CMV retinitis in immunocompromised patients. It may be administered intravenously or by injection into the vitreous humour.

**Valaciclovir**

Valaciclovir is a prodrug of aciclovir which may also be used to treat herpes zoster ophthalmicus. The recommended oral dose is 1 g three times a day for seven days.

**Triflurorothymidine (TFT)**

Trifluorothymidine (TFT) is a thymidine analogue that inhibits the enzyme thymidine synthetase. As a result, it has a different mechanism of action to aciclovir. This implies that TFT should be effective in cases of aciclovir-resistant herpetic keratitis. Viroptic® is not available in South Africa, but TFT Ophthiole® is available.

**Idoxuridine**

In ocular HSV infections, topical idoxuridine is more effective in epithelial infections, especially initial episodes, than in stromal infections. In a systematic review of antiviral drugs and other treatments for herpes simplex virus epithelial keratitis, it was concluded that trifluridine and aciclovir are more effective than idoxuridine or vidarabine.

**Antifungal ophthalmic preparations**

Fungal keratitis is a sight-threatening condition that requires specialist management. A fungal aetiology should always be considered in any keratitis that results from an injury involving organic matter, especially if the injury leads to indolent ulceration. Natamycin is the drug of choice for a keratitis caused by Aspergillus and Fusarium. However, infections that are deeper and more severe may require treatment with antifungal medication such as amphotericin B, fluconazole, or voriconazole. These medications can be given orally, intravenously, or intravitreally.

Natamycin is derived from the bacterium, Streptomyces natalensis, which was first discovered in the former Natal province of South Africa and is now used worldwide as a first-choice agent in many cases of fungal keratitis. All other ophthalmic topical antifungal agents need to be specially prepared by a pharmacist and should be reserved for specialist use.

**Antiparasitic ophthalmic preparations**

Many parasites, both microscopic and macroscopic, may infect different parts of the eye. Examples include *Acanthamoeba* keratitis, *Microsporidium* keratitis, *Pneumocystis jiroveci* chorioiditis and *Toxoplasma gondii* retinitis. Infestation by *Onchocerca volvulus*, a helminth, causes onchocerciasis or river blindness, which commonly occurs in neighbouring countries such as Zimbabwe. It is also sporadically seen in South Africa. Treatment comprises a single 150 µg/kg dose of oral ivermectin. The dose may be repeated after six months if the patient is still symptomatic. Topical ivermectin cream (Soolantra and Cevamide) is also available for conditions such as Demodex and Rosacea causing blepharitis. Soolantra is not available in South Africa. All of these infections require specialist management, although fairly simple drugs sometimes play an important role in their treatment. Propamidine isethionate is sometimes used to treat superficial bacterial ocular infections, but also plays an important role in the treatment of *Acanthamoeba* keratitis, in combination with other agents such as 0.02% chlorhexidine gluconate solution.

**Miscellaneous ophthalmic preparations**

**Povidone iodine**

Povidone iodine 5%, an organic iodine antiseptic agent, is widely used in the preoperative cleansing of the periocular skin and ocular surface. It has brought about a dramatic reduction in the incidence of postoperative endophthalmitis. It has been shown that a 2.5% solution used on the conjunctivae of newborns was more effective than both silver nitrate and erythromycin in preventing ophthalmia neonatorum, but not quite as effective as 1% tetracycline ointment. However, the latter is not available in South Africa. Povidone iodine 2% possesses antiviral properties and has proved to be effective in relieving the symptoms of 77% of patients who were treated for epidemic keratoconjunctivitis (“pink eye”) within a week. Therefore, povidone iodine is an important anti-infective ophthalmic preparation. It plays both a prophylactic and a therapeutic role.

**Propamidine isethionate**

Available preparation: 1 mg/ml drops.

Propamidine isethionate may be used for treating mild bacterial conjunctivitis caused by staphylococci and streptococci, but is not effective against *Pseudomonas* spp. or *Escherichia coli*. If a superficial eye infection does not improve within one week of treatment, a change in therapy to a drug with a broader spectrum should be considered. Propamidine isethionate also plays an
important role in the treatment of Acanthamoeba keratitis, which needs to be excluded in contact lens wearers who present with a corneal infection that initially mimics herpetic keratitis, but does not respond to the usual treatment for that condition.

**Antibiotic-steroid combinations**

Many of the topical antibacterial agents are also available in combination with a topical corticosteroid. Examples include Tobradex® (tobramycin plus dexamethasone), Spersadex Comp® (chloramphenicol plus dexamethasone), Maxitrol (neomycin + polymyxin B plus dexamethasone), Betnesol N® (betamethasone plus neomycin) and Zypred (gatifloxacin plus prednisolone acetate). This combination is not yet available in South Africa. These drugs are predominantly used before and after eye operations to decrease inflammation and prevent infection in the operated eye. Their use is not recommended in the treatment of blepharitis, conjunctivitis or keratitis of unknown origin since the corticosteroid component will exacerbate any undiagnosed herpetic infection. Therefore, the use of combination therapy is not encouraged in general practice.

**Bacitracin/polymyxin B**

Bacitracin has a narrow antibacterial spectrum, covering Gram-positive organisms. It is used in combination with Polymyxin B and Neomycin to treat superficial infections of the conjunctiva, eyelids and cornea. A polymyxin B and trimethoprim preparation is available in an ointment and solution to treat Gram-negative infections.

**Polyhexamethylene biguanide**

PHMB and Chiorhexidine (CHG) are affective in the treatment of Acanthamoeba keratitis. Although a study done showed that neither PHMB nor CHG readily penetrated through the cornea to the anterior chamber, which may explain why treatment of Acanthamoeba keratitis requires many months of sustained topical drug administration.

**What should you consider when prescribing an antibiotic?**

- **Staphylococcus aureus** is the most common cause of bacterial conjunctivitis and blepharitis in the Western world.
- In South Africa, the most virulent organisms causing infective keratitis is Staphylococcus aureus, Pseudomonas aeruginosa and Streptococcus pneumoniae. Approximately 75% of infective keratitis cases in SA are Gram-positive infections and 25% Gram-negative.
- Accurate diagnosis and selection of the appropriate drug is essential.
- If there is inflammation associated with the infection, consider an antibiotic-steroid combination. However, evidence shows that steroids make no difference in the treatment of most cases of infective keratitis.
- Maintaining minimum inhibitory concentration is important, especially in moderate to severe infections. Treat q1h or q2h for the first two to three days, and then taper to q.i.d for five or six more days until the condition is resolved. Never taper below q.i.d.
- Prolonged use of antibiotics can allow overgrowth of non-susceptible organisms, including fungi. The vast majority of primary eye care conditions, when appropriately treated, respond in less than a week. It is therefore uncommon for therapy to continue beyond seven to ten days.
- If there is no improvement in two to three days, suspect non-compliance, microbial resistance, sub-therapeutic dosing frequency, inappropriate choice of drug, or most likely incorrect diagnosis. The number of topical anti-infective ophthalmic preparations that are available commercially is relatively small. The majority of these agents are intended for use against bacterial infections which are relatively easy to diagnose and treat. First-line drugs, such as tobramycin, chloramphenicol, ciprofloxacin and ofloxacin, are currently still very effective in curing most superficial bacterial ocular infections. Fluoroquinolones, gatifloxacin and moxifloxacin, should preferably be reserved for cases that do not respond to first-line agents to minimise the development of resistance to these drugs. Oral antibacterial drugs may also be required to prevent and treat certain ophthalmic conditions.

**Conclusion**

“If you are going to treat bacterial conjunctivitis, you had better treat it quickly before it gets better on its own” – Dr Louis Catania: Lecturer 1994 Pennsylvania College of Optometry, Philadelphia, USA.

It is important to remember that not all red eyes are bacterial conjunctivitis. Think of other ocular emergencies like uveitis, scleritis, keratitis and acute angle closure glaucoma.

Far fewer commercial options exist for the treatment of viral, fungal and parasitic infections. Both topical and oral aciclovir play an important role in the treatment of ocular herpetic infections. To prevent iatrogenic exacerbation, these infections need to be actively excluded before considering the use of a topical preparation that contains a corticosteroid. Fungal and parasitic infections often mimic bacterial infections and are then only diagnosed when they do not respond to antibiotic therapy. These conditions are notoriously difficult to treat and should rather be referred for specialist management.

Consider vaccinating all patients 50 years and older, at risk of Herpes Zoster infection (shingles) and post herpetic neuralgia. In the USA studies show that more than 99% of Americans aged 40 and older had chickenpox and are therefore at risk of shingles. This vaccine reduces the risk of developing shingles by 51% and PHN by 67%.

**References**