Chapter 11
Antimicrobial Agents for Ocular Use: Bacterial, Fungal, Viral, and Protozoal Infections

Namrata Sharma, Neelima Aron, Tushar Agarwal, and Charu Sharma

Abstract Ocular microbial infections are one of the leading causes of avoidable visual impairment in the world with higher prevalence in developing countries. The incidence and organism responsible for ocular infections are attributed to indiscriminate use of antibiotics, corticosteroids, poor sanitary conditions, rising trend of the use of contact lens etc. A wide variety of microorganisms; bacterial, fungal, viral and protozoal in origin are reported to be involved in ocular infections. These ocular infections include conjunctivitis, blepharitis, endophthalmitis and corneal ulcers which are vision threatening if not treated in time. This chapter dwells with the type of antibiotics/antimicrobial agents used for bacterial, fungal, viral and protozoal ocular infections and provides the insight for the judicious use of antibiotics/antimicrobial agents in treating these infections.

11.1 Antifungal Agents for Ocular Use

Infectious keratitis is one of the leading causes of corneal blindness in the world with a higher prevalence in developing countries. Infections caused by fungal organisms have been on a rise especially in developing countries where 50 % of

N. Sharma, MD • N. Aron • T. Agarwal
Cornea Services, Dr. Rajendra Prasad Center for Ophthalmic Sciences,
All India Institute of Medical Sciences, New Delhi, India
e-mail: namrata103@hotmail.com

C. Sharma, PhD (✉)
Department of Internal Medicine, College of Medicine and Health Sciences,
UAE University, Al-Ain, UAE
e-mail: shree.charu@gmail.com

T. Velpandian (ed.), *Pharmacology of Ocular Therapeutics*,
DOI 10.1007/978-3-319-25498-2_11

the cases are due to fungal organisms. The implicated factors in its causation are indiscriminate use of antibiotics and corticosteroids leading to ocular compromise. Despite the emergence of newer drugs, the cure still remains difficult in view of poor ocular penetration of the drugs.

The common antifungals used for fungal keratitis are classified as follows:

1. Polyenes
   (i) Large polyenes: Nystatin and amphotericin B
   (ii) Small polyenes: Natamycin
2. Azoles
   (i) Imidazoles: Miconazole, ketoconazole, and clotrimazole
   (ii) Triazoles: Fluconazole, itraconazole, voriconazole, and posaconazole
3. Pyrimidines

   Flucytosine
4. Echinocandins

   Caspofungin and micafungin

11.1.1 Polyenes

This class of drugs includes amphotericin B (AMB), natamycin, and nystatin. Nystatin is not used routinely to treat ocular infection due to its low intraocular penetration, toxicity, and resistance to the drug. However, natamycin and amphotericin B are the most commonly used drugs in cases of fungal keratitis.

11.1.1.1 Amphotericin B

AMB was the first broad-spectrum antifungal agent to be discovered. It is produced by the actinomycete *Streptomyces nodosus*. It was approved by the FDA in the 1960s due to its great efficiency in controlling disseminated fungal infections.

Mechanism of Action AMB works by creating pores in the cell wall by binding to ergosterol, allowing small ions such as potassium to leak out causing imbalances in the osmotic gradient and eventually cell lysis. Its action is primarily fungistatic, with fungicidal action depending on the concentration reached in the target tissue (Khoo et al. 1994).

AMB acts on both yeast and filamentous fungi. It has an excellent spectrum, being effective against *Candida* species, *Aspergillus* species, *Penicillium marneffei*, *Cryptococcus* species, and the causative agents of mucormycosis. It is also effective, to a lesser extent, against *Fusarium*.

Systemic administration of AMB produces little penetration into the ocular tissues and does not reach therapeutic levels in the cornea and aqueous or vitreous humor (Kaur et al. 2008 and O'Day et al. 1985). Also, the multiple side effects

preclude its systemic administration. Ocular administration therefore is the commonly used form of treatment. It is one of the few drugs which can be used through the subconjunctival, topical, intrastromal, intracameral, and intravitreal routes.

Dosage AMB is prepared from the intravenous formulation diluted in distilled water. It is used at a concentration of 1.5–5 mg/ml and administered at one-hour intervals at the beginning of treatment and then every 4 h once the therapeutic response is observed. Periodic debridement of the corneal epithelium is recommended since the drug has a poor penetration in an intact epithelium (O'Day et al. 1984).

Subconjunctival administration is used in patients not compliant to topical therapy; however, it is not preferred in view of reports of conjunctival necrosis, scleral thinning, and scleral melt (O'Day 1987). Intrastromal administration of AMB at a concentration of 5–10 μg is administered for deep infections affecting the stroma that do not respond well to topical and systemic treatment. The interval between two doses should be at least 72 h. Intracameral administration of the drug is suggested for infection penetrating the Descemet's membrane affecting the anterior chamber. Yoon et al. compared 14 eyes who were administered intracameral AMB versus 17 eyes who were on conventional antifungal therapy. It was noted that eyes that received intracameral AMB had an early disappearance of hypopyon and final improvement in comparison to eyes on conventional therapy (Yoon et al. 2007).

In keratitis associated with fungal endophthalmitis, intravitreal administration of AMB is recommended in a dose of 5–10 μg and may be repeated within 48–72 h.

Side Effects The main reason for the side effects of AMB is its binding to cholesterol which is present in the cell wall of the host cells. Systemic administration via infusion can lead to fever, chills, hyperventilation, hypotension, nausea and vomiting, and tubular injury. Intrastromal and intracameral administration of the drug may lead to pain, endothelial cell loss, iritis, and persistent corneal edema in doses greater than 15–20 μg. Intravitreal injections in higher doses can lead to retinal necrosis and toxicity.

11.1.1.2 Natamycin

Similar to amphotericin B, natamycin is a polyene antifungal and is the drug of choice for the treatment of keratitis caused by filamentous fungi.

Mechanism of Action Natamycin binds to ergosterol in the cell wall of the fungi, forming blisters and causing lysis of the cells. This action is not concentration dependent unlike AMB.

It is used in a concentration of 5 % (50 mg/ml) and is well tolerated when used topically. Epithelial debridement is recommended as an adjuvant therapy so that higher concentrations can be achieved in the corneal stroma. For deeper infections, natamycin should be combined with other antifungals for the treatment.

Natamycin is a broad-spectrum antifungal. Although it also works against *Candida* infection, AMB remains the drug of choice for yeast infections. The dosing interval is similar to AMB. The drug is administered at 1-h interval until the signs of resolution are visible. Once the therapeutic response is seen, the dosing interval

can be increased to one drop administered every 4 h. Natamycin is effective against *Fusarium,* and it has been observed that it has a lower minimum inhibitory concentration than AMB against both *Aspergillus* and *Fusarium* (Lalitha et al. 2007).

Subconjunctival injections can be given but are not recommended in view of risk of scleritis and melt. There are no reports of administration of NTM through other routes (intracameral, intravitreal, intrastromal, or systemic).

The Mycotic Ulcer Treatment Trial (MUTT) has been conducted to compare topical natamycin versus voriconazole in the treatment of filamentous fungal keratitis. It was a multicenter trial which randomized 368 patients of fungal keratitis to natamycin 5 % or voriconazole 1 %. It was found that the natamycin treatment was associated with significantly better clinical and microbiological outcomes than voriconazole treatment for smear-positive filamentous fungal keratitis, with much of the difference attributable to improved results in Fusarium cases (Prajna et al. 2013).

Another study was conducted comparing natamycin versus VZ in 120 patients with fungal keratitis in which there was no significant difference in visual acuity, scar size, and perforations between voriconazole- and natamycin-treated patients (Prajna et al. 2010).

11.1.2 Azoles

This class of drugs has a broader spectrum of activity as compared to AMB and fewer side effects. They are divided into two classes: imidazoles which were first to be introduced in the market, and followed by triazoles. The imidazoles used more often include miconazole (MCZ), econazole (ECZ), and ketoconazole (KCZ). Among the first-generation triazoles, the most often used are itraconazole (ICZ) and fluconazole. Second-generation triazoles were introduced into clinical practice in the past decade and include voriconazole and posaconazole (PCZ). Azoles act on cytochrome P450 enzymes and block the synthesis of ergosterol in the plasma membrane, thus inhibiting fungal growth.

11.1.2.1 Imidazoles

The imidazoles have various mechanisms of action for their antifungal activity. At low concentrations, they affect the formation of ergosterol present in the cell membranes. At higher concentrations, they can disrupt lysosomes, causing direct damage. Also, most imidazoles inhibit catalase and cytochrome C peroxidase intracellularly, causing accumulation of hydrogen peroxide leading to cell death.

11.1.2.2 Miconazole

It is a broad-spectrum antifungal with activity against *Cryptococcus*, *Fusarium*, *Aspergillus*, *Curvularia*, *Candida,* and *Trichophyton*. It not only acts on the synthesis of ergosterol but also leads to inhibition of peroxidases, resulting in the accumulation

of free radicals in the fungal cytoplasm which leads to cell death (Kobayashi et al. 2002). Topical use at a dose of 10 mg/ml or a 1 % solution is effective especially if associated with epithelial scraping. Compared to polyenes, MCZ is less effective but provides better penetration into ocular tissues (Foster and Stefanyszyn 1979).

11.1.2.3 Econazole

Econazole is primarily used in the treatment of superficial mycosis and not used routinely for the treatment of ocular infections. In a clinical trial, 116 eyes with fungal keratitis were randomized to either econazole 2 % or natamycin 5 %, and it was found that econazole is as efficacious as natamycin for the treatment of fungal keratitis (Prajna et al. 2010). However, the drug is not commercially available for ocular administration which prevents its ophthalmic use.

11.1.2.4 Ketoconazole

KCZ was the first systemic imidazole to be used successfully for the treatment of fungal infections. It is available in 200 mg tablets with a recommended dose of 200–400 mg daily. Its oral absorption depends on the gastric pH (pH < 3); therefore, it should be taken on empty stomach and without gastric acid suppressives. KCZ is available in a topical formulation of 1–5 % concentration, but other drugs have been shown to be superior in comparative studies (Torres et al. 1985).

Currently, systemic KCZ is indicated only for the adjuvant treatment of deep fungal keratitis. The indications of oral ketoconazole are fungal corneal ulcers >6 mm in size, >2/3rd in depth, perforated ulcer, impending perforation, and limbal and scleral involvement. Recently, a randomized controlled trial was carried out to assess the role of additive oral antifungal therapy in deep keratitis caused by filamentous fungi. All patients with corneal ulcer size measuring 2–6 mm and involving >50 % depth were randomized to topical natamycin 5 % alone or topical natamycin plus oral ketoconazole 200 mg twice a day. It was found that there was no statistically significant difference in the ulcer healing rates between the two groups. Hence, the study showed that oral KCZ did not add significant benefit to topical natamycin therapy in treating deep fungal keratitis (Torres et al. 1985).

The systemic side effects include pruritus, nausea, vomiting, diarrhea, cramps, reversible gynecomastia, and elevation in liver enzymes.

11.1.2.5 Triazoles

Itraconazole

ICZ is used in a dose of 400 mg/day in the treatment of infections by *Candida* spp. (Klotz et al. 1996). However, when administered orally, it exhibits lower bioavailability, solubility, and penetration into ocular tissues than other azoles (Rajaraman et al. 1987). However, ICZ has not been found to be very effective against *Fusarium*.

In a randomized controlled trial involving 100 patients, topical itraconazole 1 % was found to be inferior when compared to natamycin 5 % (Kalavathy et al. 2005). The study concluded that when natamycin is unavailable, topical itraconazole therapy could be used, particularly if the infections are due to *Aspergillus* or *Curvularia* spp. The MIC of ICZ is higher than both AMB and KCZ; hence, systemic use should be limited only to the adjuvant treatment of eye infections by yeasts.

Fluconazole

Oral use at 200–400 mg per day is effective in the treatment of eye infections, with or without topical NTM (Urbak and Degn 1994). Unlike KCZ and ICZ, FCZ shows excellent absorption from the gastrointestinal tract unaffected by gastric acidity. Its penetration into the ocular tissue is effective and reaches aqueous concentration similar to that of plasma (O'Day et al. 1990). FCZ achieves good intracorneal levels at a dose of 2 mg/ml with penetration being better after epithelial scraping. However, it is less effective in the treatment of fungal endophthalmitis.

The ocular penetration of FCZ has been shown to be superior to KCZ. However, the antifungal spectrum of FCZ is narrow. In many studies, it has shown to be effective against yeasts like *Candida,* whereas filamentous fungi like *Aspergillus* and *Fusarium* have shown to exhibit marked resistance to it (Li et al. 2008).

Topical FCZ 2 % was found to be effective in six eyes with microbiologically proven *Candida* keratitis with abscess formation. The average duration of healing was found to be 22.6 ± 2.3 days (Panda et al. 1996).

Voriconazole

VCZ is the next generation of triazoles with a similar mechanism of action but is more effective in blocking the synthesis of ergosterol. It has a lower MIC as compared to first triazoles which increases its efficacy against the filamentous fungi (Martinez 2006). VCZ is commercially available for oral and parenteral administration. It is given orally at a dose of 200 mg at 12-hour intervals reaching peak plasma concentrations after 2–3 h.

It is metabolized by the liver; therefore, liver enzymes should be monitored during the therapy. The side effects include visual disorders (blurred vision, change in color perception, and photophobia), which are present in about 30 % of patients using the drug and are usually reversible.

Topical VCZ has been used extensively in a concentration of 1 mg/ml for the treatment of fungal keratitis, both caused by *Candida* and filamentous fungi. Its advantages compared to polyenes include its greater stability to light and temperature, remaining effective for up to 30 days (Dupuis et al. 2009).

Intrastromal and intracameral VCZ has been used in cases with deep stromal involvement and anterior chamber penetration unresponsive to topical therapy. The

dose of VCZ used is 50–100 μg/0.1 ml which can be repeated every 72 h (Prakash et al. 2008). Intravitreal VCZ has been shown to be safe in animal models with no changes in electroretinogram (Gao et al. 2003).

Three eyes of three patients with deep stromal recalcitrant fungal keratitis not responding to topical antifungal medications were subjected to intrastromal injection of voriconazole 50 μg/0.1 ml as an adjunct to topical therapy. A faster reduction in the size of corneal infiltration was documented, and a complete resolution of the ulcers was seen within 3 weeks in all cases after the injection (Prakash et al. 2008).

Another study was conducted in 40 eyes comparing topical versus intrastromal voriconazole as an adjunct to natamycin in recalcitrant fungal keratitis. It was found that topical voriconazole was a useful adjunct to natamycin in fungal keratitis not responding to topical natamycin. Intrastromal injections did not offer any beneficial effect over topical therapy (Sharma et al. 2013a, b).

In another prospective randomized controlled trial, 118 patients with fungal keratitis were treated with either voriconazole 1 % or natamycin 5 %. Again, natamycin was found to be more effective than voriconazole in the treatment of fungal keratitis, especially *Fusarium* (Sharma et al. 2013a, b).

Posaconazole

Similar to VCZ, PCZ is a second-generation triazole introduced recently in medical practice. It is primarily indicated for the treatment of invasive fungal infections in onco-hematological patients. It is available in an oral preparation which is administered 200 mg four times a day or 400 mg twice a day. Only adverse effects reported until date include gastrointestinal side effects.

PCZ has been shown to have a broad spectrum of activity against both yeasts and filamentous fungi including Fusarium. It was shown to be effective in the treatment of recalcitrant fungal keratitis unresponsive to conventional therapy (fluconazole, amphotericin, natamycin, and voriconazole) (Altun et al. 2014).

11.1.3 Pyrimidines

They are represented by 5-fluorocytosine which is the only antifungal drug with intracellular action. After being absorbed by the fungus, it gets converted to 5-fluorouracil which acts as an antimetabolite and inhibits fungal DNA synthesis (Vermes et al. 2000).

It is not routinely used in the treatment of fungal keratitis in view of narrow antifungal spectrum and poor ocular penetration which makes it ineffective in comparison to the new triazoles and polyenes (Morris and Villmann 2006). It is effective against *Candida* and has varied action against *Aspergillus* species, whereas it is ineffective against *Fusarium*. It should be administered along with AMB due to its potentiating effect and to prevent the development of resistance to 5-FC.

11.1.4 Echinocandins

They are semisynthetic lipopeptides that inhibit the synthesis of glucan in the fungal cell wall through noncompetitive inhibition of 1,3-α-glucan synthase, causing osmotic imbalance and cell lysis. This class of drugs includes caspofungin and micafungin. They have fungicidal action against *Candida* species but not against other yeast cells. It has fungistatic action against *Aspergillus* but is ineffective against *Fusarium*.

Topical CFG is used in a concentration of 1.5–5 mg/ml and was found to be as effective as AMB in an animal model against *Candida* (Goldblum et al. 2005). Also, few case reports suggest successful topical application of caspofungin in the treatment of candida keratitis refractory to voriconazole (Hurtado-Sarrió et al. 2010).

11.1.5 Combination Therapy

In order to broaden the antifungal spectrum and increase the efficacy of treatment, two or more drugs are often combined in the treatment of fungal keratitis. Azoles are often combined with NTM or AMB. However, several studies showed an antagonistic effect between these drugs. The introduction of an azole decreases the synthesis of ergosterol in the cell membrane, a binding site for polyenes, whose action is therefore decreased. However, polyenes such as natamycin and triazoles such as voriconazole are often combined in the treatment of filamentous fungi and have shown a synergistic effect. The combination of two drugs of the same class is often discouraged such as NTM and AMB since it increases local and systemic toxicity and fails to increase therapeutic efficacy (Lin et al. 2005).

Table 11.1 depicts the dosing and indication of use of the various antifungal drugs available in the market.

11.1.6 Conclusion

To conclude, a variety of antifungal drugs are available in the market for topical and systemic use, the choice of which depends upon the causative organism, the location, and the extent of infection. Standard therapy with polyenes remains the first choice of treatment for fungal keratitis. New-generation triazoles act as an add-on therapy in cases of poor responsiveness to the former. Studies until date lack the demonstration of superiority of the newer-generation triazoles over the conventional therapy with polyenes.

Table 11.1 Antifungal agents and their indications

Drug	Route	Dosing	Indication
Amphotericin B	Topical	1.5–5 mg/ml	First choice in keratitis by yeasts
	Intrastromal	5–10 μg/0.1 ml	Deep keratitis with partial response to topical treatment
	Intracameral	5–10 μg/0.1 ml	Keratitis affecting anterior chamber/lens
	Intravitreal	1–10 μg/0.1 ml	First choice in fungal endophthalmitis (yeast/ filamentous fungi)
Natamycin	Topical	50 mg/ml	First choice in filamentous fungi
Miconazole	Subconjunctival	1.2–10 mg/1 ml	Associated with topical therapy in low adherence to treatment
Econazole	Topical	20 mg/ml	Alternative to NTM for filamentous fungi
Ketoconazole	Oral	100–400 mg every 12 h	Deep keratitis along with topical therapy
Itraconazole	Oral	400 mg/day	Deep keratitis by yeasts
Fluconazole	Topical	2 mg/ml	Alternative to polyenes in Candida keratitis
	Subconjunctival	2 mg/1 ml	Associated with topical therapy in low adherence to treatment
	Oral	200–400 mg/day	Deep keratitis
Voriconazole	Topical	1 mg/ml	Fungal keratitis resistant to polyenes and first-line triazoles
	Intrastromal	50 μg/0.1 ml	Deep keratitis with partial response to topical therapy
	Intracameral	50 μg/0.1 ml	Deep keratitis affecting anterior chamber/lens
	Intravitreal	50 μg/0.1 ml	Alternative to AMB in fungal endophthalmitis
	Oral	200 mg every 12 h	Deep keratitis
Posaconazole	Topical	100 mg/ml	Fungal keratitis resistant to polyenes or first-line triazoles
	Oral	200 mg every 6 h or 400 mg every 12 h	Deep keratitis or endophthalmitis
Flucytosine	Topical	10 mg/ml	Association with topical AMB in Candida keratitis
Caspofungin	Topical	1.5–5 mg/ml	Fungal keratitis by yeasts resistant to polyenes or first-line triazoles
Micafungin	Topical	1 mg/ml	Fungal keratitis by yeasts resistant to polyenes or first-line triazoles

11.2 Antiviral Drugs for Ocular Use

Neelima Aron, Tushar Agarwal, Neelima Sharma,

Viruses are intracellular microorganisms which replicate inside the host cell. The development of antiviral therapy involves the identification of drugs which only attack the virus without affecting the host cells. The recognition of viral enzymes and proteins that can serve as molecular targets for drugs has revolutionized the treatment of viral infections.

Topical antiviral therapy has been available since the past 50 years, but it is only with the advent of acyclovir that a safe and effective therapy has been established for the treatment of herpetic keratitis.

Table 11.1 enumerates the various topical antiviral drugs that are available in the market as of today.

Drug	Preparation	Dosage
Trifluridine	1 % solution	Initially, 1 drop every 2 h. On healing, treatment should be continued for 7 days at a dose of 1 drop every 4 h during day time
Vidarabine	3 % ointment	Applied daily at 4-h intervals. On healing, treatment should be continued for 7 days at a twice daily dose
Idoxuridine	0.1 % solution	One drop every 2 h during the day and every 4 h at night. Treatment should be continued for 3–5 days after healing is complete
	0.5 % ointment	Applied every 4 h during daytime. Treatment should be continued for 3–5 days on healing
Acyclovir	3 % ointment	Applied five times daily at 3–4-h intervals and continued for at least 3 days after complete healing
Ganciclovir	0.15 % ointment	Applied five times a day at 3–4-h intervals and continued for at least 3 days after epithelial healing

11.2.1 Idoxuridine

It was the first topical antiviral to be used for the treatment of herpetic epithelial keratitis (Kaufman et al. 1962a, b). However, it was later replaced by its thymidine analogue, trifluridine.

Mechanism of Action IDU owes its antiviral activity to the conversion into a triphosphate form, which mimics thymidine triphosphate and becomes incorporated into viral DNA which results in faulty transcription of viral proteins and inhibition of viral replication.

Indication IDU has been used in the treatment of herpetic epithelial keratitis. Owing to its lower intraocular penetration, it is ineffective in the treatment of herpetic stromal keratitis or uveitis. It is formulated as a 0.1 % solution and a 0.5 % ointment. The recommended regimen is one hourly during the day and 2 hourly at night and tapered once healing starts to take place (Kaufman et al. 1962a, b).

IDU has been replaced by trifluridine, and it is no longer commercially available for the treatment of viral keratitis.

Toxicity IDU gets incorporated into the mammalian DNA along with viral DNA and hence is toxic to replication of normal host cells. This results in a low therapeutic ratio and accounts for systemic toxicity (Boston Inter-Hospital Viral Study Group 1975). Its use has been associated with chronic follicular conjunctivitis, conjunctival scarring, punctate keratopathy, pseudodendrites, corneal edema and opacities, indolent ulceration, punctal and canalicular stenosis, narrowing of meibomian gland orifices, and contact dermatitis of the lids (Wilson 1979).

11.2.2 Trifluridine

Trifluridine, like IDU, is a thymidine analogue which is far more potent and has less ocular and systemic toxicity.

Mechanism of Action Trifluridine, like IDU, gets converted into a triphosphate form and gets incorporated into the viral DNA leading to inhibition of transcription and viral protein synthesis. Though it also gets incorporated into the host DNA, however, viral DNA polymerase utilizes trifluridine triphosphate more efficiently than does host cell DNA polymerase. Hence, it has a more selective antiviral activity with lower ocular toxicity as compared to IDU (Prusoff et al. 1985).

Indication Trifluridine is active in vitro and in vivo against HSV-1, HSV-2 (Kaufman and Heidelberger 1964), and vaccinia and in vitro against CMV and some strains of adenovirus. It is more potent than IDU against HSV. It is available as a 1 % solution. Though its penetration is better than IDU, however, it is not very efficient in iridocyclitis or stromal keratitis. The recommended dosage is one drop every 2 h until healing is complete. This is followed by one drop every 4 h for 7 days to prevent reactivation of disease (Coster et al. 1976).

In a study, it was found that trifluridine was at least as effective as topical vidarabine ointment in the treatment of superficial herpetic dendritic keratitis with insignificant difference in the efficacy of the two drugs (Travers and Patterson 1978).

Toxicity Toxic side effects in the eye are similar to those of IDU and include punctate keratopathy, filamentary keratopathy, epithelial and stromal edema, punctal narrowing, and contact blepharodermatitis. It is too toxic for systemic use (Wilson 1979).

11.2.3 Vidarabine

Vidarabine was the second agent approved for the topical treatment of herpetic epithelial keratitis. It was also the first antiviral agent approved for systemic use; however, recently it has been replaced with acyclovir.

Mechanism of Action Vidarabine is obtained from fermentation cultures of *Streptomyces antibioticus* (Lee et al. 1960). It is a purine nucleoside analogue that resembles deoxyadenosine. It gets converted into its triphosphate form which gets incorporated into the viral DNA. Unlike IDU, trifluridine, or acyclovir, vidarabine does not require viral thymidine kinase for its phosphorylation. Therefore, it might be expected to have high activity against thymidine kinase-deficient mutants of HSV (Larder and Darby 1986).

Indication It is highly effective in the treatment of herpetic epithelial keratitis. In a study comparing trifluridine and vidarabine in 66 patients with herpetic dendritic keratitis, no difference was noted in the antiviral activity of the two drugs (Van Bijsterveld and Post 1980). A meta-analysis concluded that vidarabine was superior to IDU and equivalent to topical acyclovir and trifluridine in relative efficacy for dendritic epithelial keratitis (Wilhelmus 2000). Similar to IDU and trifluridine, it is not effective in herpetic stromal keratitis and uveitis. It is available as a 3 % ophthalmic ointment to be applied 5 times daily. Therapy should not be continued for more than 21 days.

Toxicity It is less toxic than IDU to the regenerating corneal epithelium. Clinically, the ocular toxicity is similar to IDU. The major systemic side effects include gastrointestinal upset, elevation in liver enzymes (Nicholson 1984), and neurotoxicity (Sacks et al. 1982) when administered in patients with renal dysfunction.

11.2.4 Acyclovir

The development of acyclovir revolutionized the treatment of herpetic keratitis with its better efficacy and safety profile.

Mechanism of Action It is an acyclic analogue of guanosine which is activated by viral thymidine kinase and becomes a potent inhibitor of viral DNA polymerase. It gets converted into the triphosphate form and is found in HSV-infected cells in a concentration which is 40–100 times higher than uninfected cells (Elion 1982). It has a greater affinity of viral DNA polymerase as compared to cellular DNA polymerase.

Indications The drug inhibits HSV-1 and HSV-2, VZV, Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), and CMV (Wagstaff et al. 1994). It can be administered topically, orally, and intravenously. Topical acyclovir 3 % ophthalmic ointment has the best corneal penetration of any topical antiviral drug. It penetrates intact corneal epithelium to achieve aqueous levels well within the therapeutic range for HSV-1 and HSV-2. Hence, it is effective in the treatment of herpetic stromal keratitis and iridocyclitis.

Significant intraocular levels of the drug are also present after oral and intravenous administration. The oral dose is 400 mg five times a day (5 mg/kg body weight) for HSV and 800 mg five times a day (10 mg/kg body weight) for VZV (Biron and Elion 1980).

Prophylactic antiviral therapy is indicated in patients post-keratoplasty to prevent reactivation of the virus while patients are on topical corticosteroids. The drug is given in a dose of 400 mg twice a day for 1 year.

The Herpetic Eye Disease Studies were carried out in order to determine the role of acyclovir in the treatment of herpetic keratitis. HEDS I and HEDS II consisted of three randomized, placebo-controlled trials. It was found that compared with placebo, corticosteroid therapy reduced the risk of persistent or progressive stromal keratouveitis by 68 % with faster resolution of the ulcer. It determined that there is no clinical benefit of adjunctive oral acyclovir for treating HSV stromal keratitis in patients receiving concomitant topical corticosteroids and trifluridine (Barron et al. 1994). For the treatment of HSV iridocyclitis, there was a strong suggestion of clinical benefit from the addition of oral acyclovir 400 mg 5 times daily as an adjunct to topical corticosteroids and trifluridine (50 % treatment failures with acyclovir vs. 68 % with placebo) (the Herpetic Eye Disease Study Group, 1996). The addition of a 3-week course of oral acyclovir to topical trifluridine treatment of acute HSV epithelial keratitis did not prevent the subsequent development of stromal keratitis or iritis over the following year (the Epithelial Keratitis Trial, 1997). There is, however, a clear-cut benefit from long-term suppressive oral acyclovir in preventing recurrent HSV epithelial keratitis and stromal keratitis. The cumulative recurrence rate of any ocular HSV was significantly reduced from 32 to 19 % by acyclovir (Herpetic Eye Disease Study Group, 1998).

Toxicity It has not been shown to have a detrimental effect on the regenerating corneal epithelium. Superficial punctate keratopathy has been noted; however, the frequency is less than that seen with IDU. Other less common side effects include burning or stinging, tearing, follicular conjunctivitis, palpebral allergy, and punctal stenosis.

Oral acyclovir causes gastrointestinal side effects such as nausea, vomiting, and diarrhea. Liver function tests should be monitored every 2 weeks. Intravenous infusion of acyclovir can cause renal shutdown especially in patients with preexisting renal dysfunction.

11.2.5 Resistance

There are three mechanisms by which the virus can become resistant to acyclovir therapy. The most common mutation is loss of synthesis of viral thymidine kinase so that acyclovir is not phosphorylated to its active form (Wagstaff et al. 1994). A second type of mutation induces thymidine kinase with altered substrate specificity that phosphorylates thymidine but not acyclovir. Finally, a mutation of the viral DNA polymerase gene induces altered DNA polymerase that is not sensitive to inhibition by acyclovir triphosphate.

11.2.6 Ganciclovir

Ganciclovir is another antiviral agent that has been developed recently for ophthalmic use. It was the first drug to be approved by the Food and Drug Administration (FDA) for use in the treatment of CMV retinitis in immunocompromised patients.

Mechanism of Action Ganciclovir is a nucleoside analogue that is selectively phosphorylated by virus-encoded thymidine kinase and is subsequently phosphorylated by cellular enzymes. Similar to acyclovir, it is converted into ganciclovir triphosphate which inhibits herpesvirus DNA polymerase and arrests HSV replication (Davies et al. 1987).

Indication Following topical application of ganciclovir, it has been shown that the drug can penetrate the corneal stroma and can reach the aqueous humor in therapeutic levels. Corneal penetration of ganciclovir was due to the small size of the ganciclovir molecule, its high lipophilicity, and its high cellular affinity. It is available as an ophthalmic gel in a concentration of 0.15 % five times daily. Compared to acyclovir 0.3 % ointment, ganciclovir 0.15 % gel has been shown to be better tolerated and no less effective in several phase II and III trials. Randomized multicenter clinical trials demonstrated that ganciclovir ophthalmic gel 0.15 % is as effective as acyclovir in the treatment of acute epithelial herpetic keratitis. Also, ganciclovir is available in a gel form which induces lower blurring following its ophthalmic administration as compared to acyclovir which is available in an ointment form.

Ganciclovir 0.15 % gel may also help in the prevention of recurrences of herpetic keratitis in patients undergoing corneal transplantation. It is given in a dose of four times a day along with topical corticosteroids.

Toxicity The most frequent adverse effects clinically have been hematological, primarily neutropenia (40 % of patients) and thrombocytopenia (20 %) after systemic administration of the drug. No ocular toxicity has been noted after ophthalmic use.

11.2.7 Other Drugs

11.2.7.1 Valacyclovir

Valacyclovir, the L-valyl ester of acyclovir, is a prodrug that is rapidly and nearly completely converted to acyclovir after oral administration. Its excellent bioavailability results in serum acyclovir levels comparable to intravenous acyclovir but requiring less frequent dosing than oral acyclovir. Therefore, it has much the same antiviral indications and safety as oral acyclovir with the advantage of simpler dosing. For herpetic epithelial keratitis or iritis, it is used in a dose of 1000 mg twice or thrice a day which has been shown to be as effective as acyclovir 400 mg 5 times a day. For prophylaxis, it is used in a dose of 1000 mg once daily. A large multicentered randomized double-blind trial of herpes zoster was carried out which compared valacyclovir 1000 mg 3 times daily with acyclovir 800 mg 5 times daily. There was no significant difference between the drugs in the resolution of HZO. Valacyclovir, therefore, is a reasonable alternative to oral acyclovir for the treatment of HZO in immunocompetent patients at a dosage of 1000 mg 3 times daily for 7 days.

11.2.7.2 Famciclovir/Penciclovir

Famciclovir is the diacetyl-6-deoxyester prodrug of the acyclic guanosine analogue penciclovir which is similar in efficacy to acyclovir. Similar to valacyclovir, it is as effective as oral acyclovir with a less frequent dosing requirement. It is used in a dose of 250 mg three times daily for HSV and 500 mg three times daily for VZV. Tyring and associates performed a multicenter randomized study comparing famciclovir 500 mg 3 times daily with oral acyclovir 800 mg 5 times daily for 7 days in 454 immunocompetent patients with HZO. The efficacy of the two drugs was similar, with no significant difference in the percentage of patients who experienced ocular manifestations.

11.2.7.3 Valganciclovir

Valganciclovir is a valyl ester prodrug of ganciclovir that is well absorbed orally and rapidly metabolized to ganciclovir. It provides blood levels similar to that seen after intravenous infusion of ganciclovir and has been FDA approved for the induction and maintenance treatment of CMV retinitis. It is used in a dose of 900 mg twice daily for 3 weeks for induction followed by 900 mg once daily for chronic maintenance.

11.2.7.4 Foscarnet

Foscarnet has also been used for the treatment of CMV retinitis in AIDS patients. It is used in patients who are unresponsive to or intolerant to ganciclovir and in the treatment of acyclovir-resistant herpetic infections. Oral absorption is very poor; hence, the drug is administered intravenously. It is also given intravitreally for the treatment of CMV retinitis.

11.2.7.5 Cidofovir

Cidofovir has been approved only for intravenous therapy of CMV retinitis in AIDS patients. It is given in a dosage of 5 mg/kg once a week for 2 weeks induction and then every 2 weeks for maintenance therapy. Intravitreal injections have also been given for the same.

11.2.7.6 Fomivirsen

It belongs to a new class of drugs of antisense nucleotides to be used clinically. It is administered only via intravitreal injections and is a second-line drug in the treatment of CMV retinitis.[33]

11.2.8 Conclusion

A variety of antiviral drugs have been identified for the treatment of herpetic and other eye infections. The advent of acyclovir and its prodrugs has revolutionized the treatment of herpetic eye infections. The search for newer drugs with better efficacy and an enhanced safety profile is still on.

11.3 Antibacterial Agents in Ocular Infections

Antibiotics are the substances produced by microorganisms which selectively inhibit the growth of microorganisms (bacteriostatic drugs) or kill the microorganisms (bactericidal drugs). When bacteriostatic drugs are used to treat ocular infection, the host defense mechanisms are ultimately responsible for clearing and eradicating the infective organism (Leeming 1999). In bacterial keratitis, the infection develops in the avascular cornea, and in endophthalmitis it develops in the fluid-filled aqueous or vitreous cavity (Ryan and Durand 2011). In either case, the immune system may be unable to control the microorganism fast enough to prevent the sight-threatening sequelae. Within the first 24 h, pathogens may multiply and release toxins and degradative enzymes that destroy the function and integrity of ocular tissues (Snyder and Glasser 1994).

Therefore, the bactericidal drugs are preferred for the treatment of severe ocular infections. Sometime, for severe systemic infections involve ocular components, systemic antibiotics are instituted with adjunctive topical therapy (Andreoli et al. 2004). Systemic antibiotics have poor penetration into the anterior chamber of the eye, and thus, both systemic and topical aminoglycoside antibiotics, and occasionally subconjunctival injections, are required for effective treatment.

11.3.1 General Classification of Antibacterial Agents

The antibiotics are classified on the basis of the following:

- Chemical structure (sulfonamides, diaminopyrimidines, quinolones, β-lactam antibiotics, tetracyclines, nitrobenzene derivatives, macrolides, lincosamides, glycopeptides, oxazolidinones, polypeptides, nitrofuran derivatives, nitroimidazoles, azoles, and nicotinic acid derivatives)
- Mechanism of action (inhibit cell wall synthesis, disrupt cell membrane, inhibit protein synthesis, inhibit DNA topoisomerase, interfere with DNA function or synthesis, and interfere with intermediary metabolism)
- Spectrum of activity (narrow spectrum and broad spectrum)
- Type of action (bacteriostatic and bactericidal), origin (from bacteria, actinomycetes, and fungi)

- Type of organism against which they are primarily active (antibacterial, antifungal, antiviral, antiprotozoal, and anthelmintic).
- Site of action (usually target against cell wall, cytoplasmic membrane, intermediate metabolites, and DNA synthesis in microorganisms)

11.3.2 Factors Affecting the Choice of Antibacterial Agent

The choice of an antibacterial is based on considerations of pharmacodynamic, pharmacokinetic, and bacteriological characteristics, risk of selecting resistant mutants, and cost. The bioavailability of an antibacterial agent depends on the target bacterial species, the site of infection, and the integrity of the hemato-aqueous barrier (Leeming 1999). The bactericidal agents like Penicillins, cephalosporins, aminoglycosides and fluoroquinolones are used to treat ocular infections. Whereas, bacteriostatic agents like tetracyclines, erythromycin, chloramphenicol and sulfonamides are often used for less severe infections or for specific benefit such as tetracycline in the treatment of ocular rosacea.

Some agents (fusidic acid, quinolones) penetrate the cornea, passing into the anterior chamber of normal eyes at therapeutic concentrations, whereas others (polymyxin B, bacitracin) have no penetrating powers and remain at the surface of the eye. Toxicity is mostly manifested by allergic reactions to excipients or active ingredients in topical antibacterial preparations. A few cases of hematological toxicity have brought suspicion on topical chloramphenicol, but the link has yet to be proven. Erythromycin and polymyxin B are good to use as topical applications in pregnant women and nursing mothers (Robert and Adenis 2001; Leeming 1999).

The ophthalmic antibacterial preparations are frequently used topically either as eye drop or eye ointment in the treatment of patients with superficial ocular infections, including conjunctivitis, blepharitis, and corneal ulcers. In addition, these are also used to augment treatment for intraocular infection administered systemically or by local instillation. Topically administered antibiotics are appropriate for external ocular infections, including the conjunctiva and cornea. The addition of subconjunctival antibiotic administration is indicated for serious corneal as well as anterior segment infections. Intravitreal antibiotic administration is potentially hazardous but indicated for bacterial endophthalmitis. Some cataract surgeons incorporate antibiotics into infusion fluid during phacoemulsification. The knowledge of the pharmacokinetics of topically applied agents is useful in guiding treatment regimens, particularly in serious corneal infections (Robert and Adenis 2001).

Systemic ceftazidime can be used for many Gram-negative bacteria, but intravitreal injection is recommended for better coverage, especially for more-potent organisms. Systemic moxifloxacin can be considered for most Gram-positive and Gram-negative infections due to its excellent intraocular penetration and broad coverage, but the patient's previous history of its topical use and increasing resistance patterns must be considered (Ahmed et al. 2014). Intracameral cefuroxime is significantly more effective than not using prophylaxis or the use of a topical antibiotic.

The economic evaluation comparing different prophylaxis regimens had also shown that intracameral cefuroxime has best cost-effectiveness ratio (Linertová et al. 2014).

Costs of treatment must be evaluated as a whole (regimen, drug associations) as the prices for a bottle of eye drops or the ointments may vary severalfolds. The cheapest drugs include chloramphenicol, polymyxin B, and gentamicin, the most expensive being fusidic acid and the quinolones (Robert and Adenis 2001). Intravitreal antibiotic penetration of systemic antibiotics with or without penetrating ocular injury varies depending on the antibiotic. For prevention or treatment of Gram-positive bacteria-causing endophthalmitis, intravitreal vancomycin is necessary and provides the most reliable coverage.

The widespread use of an antibacterial increases risks of selecting resistance to it. Acquired resistance is well documented for fusidic acid and several cephalosporins and newly described fluoroquinolones. The details of each antibiotics class divided based on mechanism of action used in ocular preparation or ophthalmic usages are described below.

11.3.2.1 Cell Wall Synthesis Inhibitors

Penicillins, cephalosporins, glycopeptide, and polypeptide are the class of antibiotics known to target cell wall synthesis machinery.

Penicillins

The penicillins structurally consist of a thiazolidine ring with a β-lactam ring connected to a side chain. Several of the penicillins are used in ophthalmic preparations. These are as follows: penicillin G, penicillin V (acid-resistant penicillin), methicillin, cloxacillin (penicillinase-resistant penicillins), carbenicillin, mezlocillin, piperacillin, and ticarcillin (extended-spectrum penicillins).

Spectrum of Activity Penicillins have higher susceptibility against Gram-positive bacteria. Extended-spectrum penicillins have significant activity against Pseudomonas aeruginosa and certain Proteus, Enterobacter, and Acinetobacter spp. that are not susceptible to most other penicillins.

Mechanism of Action Penicillins act by interfering with synthesis of bacterial cell wall. They inhibit the transpeptidases so that cross-linking (which maintains the close knit structures of the cell wall) does not occur.

Indications Topical use of penicillins for treatment of eye disease is limited by their narrow spectrum and high incidence of allergic reaction to these drugs. Penicillin G has a narrow spectrum of activity though used for the treatment of patients with keratitis caused by susceptible *Streptococcus pneumoniae*. A 14-day course of high-dose intravenous penicillin G is first-line therapy for all stages of

ocular syphilis and chorioretinitis (Benson et al. 2015). Oral penicillin is used in the treatment of poststreptococcal syndrome uveitis (PSU), a newly recognized immune-mediated response to group A β-hemolytic streptococcus infection (Tinley et al. 2012).

Ticarcillin and piperacillin are used with an aminoglycoside antibiotic topically and subconjunctivally for the treatment of bacterial corneal ulcers caused by Pseudomonas and other Gram-negative rods. Carbenicillin is useful in corneal ulcer caused by the opportunistic organism Achromobacter xylosoxidans which developed during chronic topical steroid treatment of an eye with neovascular glaucoma (Newman et al. 1984). Topical piperacillin/tazobactam is used as an option for the treatment of therapy-resistant P. aeruginosa keratitis (Chew et al. 2010). Also, methicillin is preferred in combination with aminoglycoside for the treatment of keratitis.

Cephalosporins

Cephalosporins are semisynthetic antibiotics derived from a fungus, cephalosporium. It shares its pharmacology with penicillins in structure and mechanism of action. The compounds are commonly classified from first to fifth generation based on their clinical uses and varying spectrum of activity. The cephalosporins that belong to each generation used in ophthalmic preparations are the following: first-generation cephalosporins (cefazolin, cephalexin, and cefadroxil), second-generation cephalosporins (cefamandole, cefaclor, cefprozil, cefoxitin, and cefuroxime), third-generation cephalosporins (ceftriaxone, cefixime, cefoperazone, ceftazidime, ceftibuten, cefdinir, and cefepime), and fourth-generation cephalosporins (cefepime and cefpirome) appear more active against Gram-negative organisms and appear more active against Gram-negative enteric bacteria. All are effective against Gram-positive bacteria, but their activity against Gram-negative bacteria is relatively modest. The activity of cephalosporins increased toward Gram-negative bacteria along with generations.

Spectrum of Activity Second-generation cephalosporins appear more active against Gram-negative enteric bacteria. Third-generation cephalosporins are more active against Gram-negative organisms.

Mechanism of Action All cephalosporins are bactericidal and inhibit bacterial cell wall synthesis, similar to the penicillins, but bind to other proteins than penicillin.

Indications Cefazolin is used to treat bacterial corneal ulcers as part of a broad-spectrum approach in combination with an aminoglycoside or fluoroquinolone such as ciprofloxacin. It is used due to its activity against Gram-positive cocci, including penicillin-resistant Staphylococci. The clinical response is variable in infections caused by the viridans group of Streptococci. Cefazolin is not available as an ophthalmic preparation so it is administered topically as a specially prepared solution or subconjunctivally. It is found to be highly active against Gram-positive bacteria,

a common cause of bacterial keratitis (Rautaraya et al. 2014). Cefazolin and cefuroxime are resistant to staphylococcal β-lactamases and used in combination with aminoglycosides in the empirical treatment of keratitis. Cefazolin and cefuroxime intracameral injection are used to decrease the risk of endophthalmitis at the end of cataract surgery (Vazirani and Basu 2013; Kessel et al. 2015).

Second-generation cephalosporins have limited use in ophthalmic practice. Ceftazidime shows excellent activity against Gram-negative bacteria including Pseudomonas aeruginosa and remains the most popular mode of antibiotic prophylaxis in cataract surgery patients for prophylaxis from endophthalmitis (Sridhar et al. 2015). Ceftazidime is also suggested as an alternative for intravitreal amikacin in the treatment of endophthalmitis (Mehta et al. 2011). It possesses high therapeutic index with a lower risk of retinal toxicity than amikacin.

Polypeptide Antibiotic

Bacitracin, gramicidin, and colistin are the polypeptide antibiotics used in ophthalmic topical formulations.

Bacitracin

Spectrum of Activity It is active against Gram-positive bacteria, including Streptococci and Staphylococci.

Mechanism of Action It inhibits cell wall synthesis of bacteria by a different mechanism than do the β-lactam antibiotics.

Indications Because of its systemic renal toxicity, it is used topically alone and in fixed combination products. It is unstable in solution, thus available only as an ointment in combination with neomycin, effective against Gram-negative bacteria and polymyxin B. The inclusion of bacitracin produces broad antibacterial spectra against most common ocular pathogens. Bacitracin appears useful to clear corneal wound infection caused by Gram-positive organisms after phacoemulsification is a serious complication of cataract surgery (Cosar et al. 2001). Bacitracin or trimethoprim-polymyxin B sulfate is found useful for perioperative antibiotic prophylaxis (Ritterband et al. 2003).

Vancomycin

It is a glycopeptide antibiotic first isolated in 1953 from a soil bacterium *Amycolatopsis orientalis* (formerly known as *Nocardia orientalis*).

Spectrum of Activity It possesses broad-spectrum activity against Gram-positive bacteria including methicillin- and cephalosporin-resistant Staphylococci. Also, it

shows activity against coagulase-negative Staphylococcus, Gram-positive cocci, including Streptococcus, Staphylococcus, Clostridium, and Corynebacterium (Suemori et al. 2010).

Mechanism of Action It acts by inhibiting cell wall synthesis by binding to the two D-ala residues on the end of the peptide chain bound to the peptide chains prevents them from interacting properly with the cell wall cross-linking enzyme and cross-links are not formed and the cell wall falls apart.

Indications It is reserved for serious infections for which less toxic antibiotics are not indicated, not effective, or not tolerated. It is an excellent empiric antibiotic for treating endophthalmitis and an alternative to penicillins or cephalosporins for serious infections (Gentile et al. 2014). It is used as the final choice in serious cases of methicillin-resistant Staphylococcus aureus (MRSA) or methicillin-resistant Staphylococcus epidermidis (MRSE) keratitis. It is recommended as intravitreal, topical, or subconjunctival for treatment of bacterial endophthalmitis (Mehta et al. 2011).

11.3.2.2 Cytoplasmic Membrane Inhibitors

Polymyxin B and gramicidin are the antibiotics known to impair the bacterial cytoplasmic membrane.

Polymyxin B

Spectrum of Activity It is active against Gram-negative bacteria except Proteus, Serratia, and Neisseria. It is also active against Pseudomonas, Salmonella, and Shigella.

Mechanism of Action It is surfactant in nature that disrupts the osmotic integrity of bacterial cell membranes.

Indications Currently, it used as a last resort antibiotic for the treatment of infections caused by Gram-negative bacteria. Topical neomycin/polymyxin B is found effective in reducing the conjunctival bacterial load given before cataract surgery (Li et al. 2015). The combination of topical trimethoprim/polymyxin B and topical moxifloxacin is found to effectively control the corneal ulcer in keratitis caused by Elizabethkingia meningosepticum (Erdem et al. 2013). Polymyxin B and trimethoprim are found useful in infectious keratitis after photorefractive keratectomy (Donnenfeld et al. 2003). Topical therapy with gentamicin 1.3 %, cefazolin 5 %, chlorhexidine 0.02 %, propamidine 0.1 %, polymyxin B 30,000 IU eye drops, and neosporin (neomycin, bacitracin, polymyxin) eye ointment is used for the treatment of coinfection with Acanthamoeba and Pseudomonas aeruginosa in patients with contact lens-associated keratitis (Sharma et al. 2013a, b). Polymyxin

B-trimethoprim continues to be an effective treatment for acute conjunctivitis and bacterial keratitis and may combine with chloramphenicol and gentamicin (Williams et al. 2013). Polymyxin B may be used for multidrug-resistant Pseudomonas spp. It is available in combination with various other agents such as bacitracin (ointment), trimethoprim (eye drops and ointment), and neomycin plus gramicidin (eye drops).

Colistin

Spectrum of Activity It is active against the multidrug-resistant (MDR) Gram-negative organisms except Proteus, Serratia, and Neisseria. It is also active against Pseudomonas, Salmonella, and Shigella.

Mechanism of Action Its rapidly acting bactericidal agent exhibits a surfactant-like action on the cell membrane and causes distortion or pseudopor formation.

Indications Topical colistin 0.19 % found a safe and effective alternative in the management of multidrug-resistant P. aeruginosa bacterial keratitis (Jain et al. 2014).

Gramicidin

Spectrum of Activity It is active against Gram-positive bacteria, except for the Gram-positive bacilli, and against select Gram-negative organisms, such as *Neisseria.*

Mechanism of Action It is bactericidal and causes cell membrane leakage and uncouples oxidative phosphorylation in the microorganisms.

Indications It replaces bacitracin in some fixed combination formulations used topically for eye infections. It is used in therapeutics in the name of tyrothricin which is a mixture of gramicidin (20 %) and tyrocidine (80 %). Its use is limited to topical application only, as it is very toxic on systemic use.

Fusidic Acid

Spectrum of Activity It is a narrow-spectrum antibiotic effective against Streptococci, Haemophilus, and methicillin-susceptible Staphylococcus aureus.

Mechanism of Action It inhibits protein synthesis in bacteria.

Indications It achieves high concentrations at the surface of the eye. It is available as 1 % viscous drops which liquefy in contact with the eye and results in a relatively

better half-life in the tear film, therefore reducing the frequency of application compared to other formulations (Mason et al. 2003).

11.3.2.3 Protein Synthesis Inhibitors

Aminoglycosides, tetracyclines, and macrolide antibiotics as well as the individual drugs clindamycin and chloramphenicol inhibit the protein synthesis in bacteria.

Aminoglycosides

Gentamicin, neomycin, netilmicin, tobramycin, and amikacin are the aminoglycoside antibiotics used in ocular preparations. Gentamicin was discovered in 1963 and was introduced into parenteral usage in 1971. Since then, it has been widely used in medicinal applications including eye diseases (Chen et al. 2014).

Spectrum of Activity These are effective against most Gram-negative bacteria and Staphylococci with lesser activity against Streptococci. Aminoglycosides showed differences in the type and doses associated with toxic reactions; thereby, the following order of toxicity can be described (from most toxic to least toxic): gentamicin > netilmicin = tobramycin > amikacin = kanamycin (Penha et al. 2010). Aminoglycosides display concentration-dependent bactericidal activity and are the cornerstone of therapy against serious Gram-negative bacterial infections.

Mechanism of Action These inhibit protein synthesis by binding to 30S bacterial ribosomes and cause inaccurate mRNA translation and so inhibit the biosynthesis of proteins preceded by inhibition of ribosomal translocation, i.e., movement of the peptidyl-tRNA from the A to the P site.

Indications Gentamicin and tobramycin are more active than neomycin and framycetin, particularly against P. aeruginosa. The rapid bactericidal action of gentamicin and tobramycin and their potential activity against P. aeruginosa make them useful in the treatment of bacterial keratitis. They do not penetrate the cornea well; therefore, they are generally used at fortified concentrations until the condition of the cornea improves. Marked irritation can be experienced its use (McDonald et al. 2014).

Gentamicin is used to treat many bacterial infections such as conjunctivitis, blepharitis, and dacryocystitis. It is also used for the initial treatment of bacterial corneal ulcers or prophylaxis of endophthalmitis after cataract surgery by intracameral antibiotics or subconjunctival injection (Katibeh et al. 2015), though it is considered inadequate for the initial treatment of serious bacterial keratitis. The solutions containing fortified concentrations are prepared from sterile products to be intended for parenteral use. The fortified gentamicin or tobramycin solution is combined with a penicillinase-resistant cephalosporin and considered a useful initial

empiric treatment for serious bacterial keratitis. The initial loading dose of fortified aminoglycosides is given to increase the antibiotic concentrations in the cornea, followed by regular applications.

Neomycin is most commonly administered topically in combination with other antibiotics or corticosteroids. Topical application frequently results in sensitization to the drug; therefore, long-term use should be avoided. Netilmicin appears the most effective antibiotic tested against both MRSA and MRSE and may curtail the emergence, spreading, and persistence of antibiotic-resistant bacteria (Blanco et al. 2013). Netilmicin appears a safe and broad-spectrum antibiotic comparable with that of ciprofloxacin, ofloxacin, norfloxacin, and gentamicin that can be used as first-line therapy for the treatment of acute bacterial conjunctivitis (Papa et al. 2002).

Tobramycin is used similar to gentamicin; however, Staphylococci are generally susceptible to tobramycin, whereas Streptococci are not susceptible to tobramycin (Donnenfeld et al. 2003). Cross-resistance between gentamicin and tobramycin is common. Amikacin is usually effective for most strains of Klebsiella, Enterobacter, E. coli, and Serratia. However, for bacterial keratitis, tobramycin is often preferred in combination with ticarcillin. Dual therapy with a β-lactam agent is recommended for empirical therapy to cover streptococcal infection and improve activity against Staphylococci. The aminoglycosides are slowly inactivated in the presence of some β-lactams; thus, they should be administered separately, preferably at least 5 min apart.

Tobramycin 1.4 % topical is found useful in mycobacterial keratitis after laser in situ keratomileusis (LASIK) (Freitas et al. 2003) and infectious keratitis after photorefractive keratectomy (Donnenfeld et al. 2003). Tobramycin also may be useful as prophylactic topical antibiotics for preventing secondary corneal infections or recurrent corneal erosion syndrome (Park et al. 2015).

Amikacin, the first semisynthetic aminoglycoside, has been chemically modified to be protected from aminoglycoside-inactivating enzymes. It is popular as a primary antibiotic for intravitreal injection along with vancomycin for the treatment of bacterial endophthalmitis due to its broad spectrum against resistant Gram-negative organisms and reduced toxicity.

Tetracyclines

Tetracyclines were first acknowledged in 1948 as the natural fermentation product of the soil bacterium *Streptomyces aureofaciens* and, 6 years later, were chemically purified for the first time. Tetracycline analogues are classified as short-, intermediate-, and long-acting based on duration of action. Analogues in each category have generally similar patterns of bacterial susceptibility and resistance.

Spectrum of Activity Tetracyclines are the broad-spectrum antibiotics, active against Gram-positive, Gram-negative, aerobic, and anaerobic bacteria as well as Spirochetes, Mycoplasma, Rickettsia, Chlamydophila, Brucella, Bartonella, and a few protozoa.

Mechanism of Action Primarily these are bacteriostatic in action, inhibit protein synthesis by binding to 30S ribosomes, and interfere with attachment of aminoacyl-tRNA to the mRNA-ribosome complex and inhibition of growth of peptide chain required for protein synthesis.

Indications Tetracyclines also interact with matrix metalloproteinases (MMP), tissue inhibitors of MMPs, growth factors, and cytokines; therefore, tetracyclines are capable of affecting inflammation, immunomodulation, cell proliferation, and angiogenesis. Slow-release doxycycline 40 mg given daily appears an effective and safe therapy of ocular rosacea (Sobolewska et al. 2014). Oral minocycline or doxycycline can provide clinical benefits in treating moderate and severe meibomian gland dysfunction by reducing inflammatory cytokine levels.

Oral doxycycline is also used with topical amikacin, oral ketoconazole in the treatment of keratitis caused by Nocardia organisms. (TRichet et al. 2011). Oral doxycycline and topical corticosteroid are used in the treatment of recurrent corneal erosion syndrome (Wang et al. 2008). Tetracycline and chlortetracycline both are available in the ophthalmic preparations and indicated for the treatment of chlamydial (TRIC) infections. Several ocular surface infections caused by susceptible organisms respond satisfactorily to topical tetracyclines.

Macrolides

These antibiotics have macrocyclic lactone ring attached with sugar. Erythromycin, clarithromycin, and azithromycin are the popular macrolide antibiotics used in ocular preparations.

Spectrum of Activity It is narrow spectrum and active mainly against Gram-positive cocci, Streptococcus, Staphylococcus, Gram-positive rods, and a few Gram-negative bacteria. It is also effective against Mycoplasma, Rickettsia, and Chlamydophila.

Mechanism of Action These are primarily bacteriostatic at low concentration but become bactericidal at high concentration. They act by inhibiting protein synthesis through binding to the bacterial 50S ribosomal subunit and interfering with translocation in protein synthesis.

Indications The first-generation macrolide, erythromycin, is a widely used macrolide antibiotic for human external ocular infections because of its lack of toxicity and good activity against microorganisms. Erythromycin decreases the risk of gonococcal ophthalmia neonatorum in newborns (Darling and McDonald 2010). The American Academy of Pediatrics recommends a 14-day course of systemic erythromycin (50 mg/kg/day, divided in 4 doses).

The second-generation macrolide, azithromycin, is available as a 1.5 % ophthalmic solution for use in the treatment of bacterial or trachomatous conjunctivitis (Garnock-Jones 2012). Azithromycin 1.5 % ophthalmic solution for 3 days (1 drop twice daily) is found non-inferior to tobramycin 0.3 % ophthalmic solution for 7 days (1 drop every 2 h) in pediatric and adult patients with purulent bacterial

conjunctivitis, with regard to clinical cure and bacteriological resolution. Azithromycin administered orally is rapidly absorbed and widely distributed. A single oral dose of azithromycin can eliminate trachoma infection, but cannot be used in infants under 6 months old, and needs to be given every few years in communities with a high prevalence of disease (Baneke 2012).

Azithromycin 1 % ophthalmic solution is also used in the treatment of blepharitis and blepharitis-associated ocular dryness (Veldman and Colby 2011). Azithromycin 1.5 % ophthalmic solution was found effective in bacterial or trachomatous conjunctivitis and appears well tolerated (Garnock-Jones 2012). Topical azithromycin is also used in meibomian gland dysfunction, a common problem associated with evaporative dry eye disease (Foulks et al. 2013).

Mass azithromycin treatments are highly effective for the ocular strains of chlamydia causing trachoma (Keenan et al. 2012). Several extra-label dosage regimens have been anecdotally recommended (e.g., 5 mg/kg once daily for 2 doses and then every third day for 5 doses, 5 mg/kg once daily for 5 doses followed by the same dose every 3 days for 5 doses). A short course of oral azithromycin (20 mg/kg once daily for 3 days) appears an effective treatment alternative for Chlamydia trachomatis.

Macrolides are considered bacteriostatic, but clarithromycin may provide a bactericidal effect against non-tuberculous mycobacteria keratitis if used at a high concentration. Clarithromycin 1 % topical is found useful in mycobacterial keratitis after laser in situ keratomileusis (LASIK) (Freitas et al. 2003).

Chloramphenicol

It was first obtained from *Streptomyces venezuelae* in 1947.

Spectrum of Activity It is a broad-spectrum antibiotic and active against most Gram-positive and Gram-negative bacteria, Rickettsia, Chlamydophila, Spirochetes, and Mycoplasma except P. aeruginosa or Chlamydia trachomatis. It is effective against Haemophilus influenzae and Haemophilus parainfluenzae, Legionella pneumophila, Moraxella catarrhalis, Neisseria meningitidis, Pasteurella multocida, and Streptococcus pneumonia (Cagini et al. 2013).

Mechanism of Action It binds to 30S bacterial ribosomes and hinders the access of aminoacyl-tRNA to the acceptor site for amino acid incorporation and inhibits protein synthesis. Primarily, it is bacteriostatic in action.

Indications It is one of the oldest and commonest antibiotics, available over the counter and considered least expensive. It is used for the treatment of methicillin-resistant Staphylococcus aureus ocular surface infections and bacterial conjunctivitis and available as 0.5 % drops and 1 % ointments (Fukuda et al. 2002). A high incidence of resistance was reported, and even topical use also may cause bone marrow toxicity and aplastic anemia.

11.3.2.4 Intermediary Metabolism Inhibitors

The sulfonamides are the first antimicrobial agents and considered derivative of sulfanilamide. Several sulfonamides were developed and used extensively, but the emergence of resistance and availability of safer and effective agents currently limited the clinical usage. Currently they are used mainly in combination with pyrimethamine and trimethoprim.

Spectrum of Activity Sulfonamides are broad-spectrum drugs found effective against Gram-positive and Gram-negative bacteria as well as Chlamydophila, Actinomyces, Plasmodia, and Toxoplasma. They generally exert bacteriostatic effect; therefore, cellular and humoral immune mechanisms are potentially more important for eradicating bacterial infections when they are used than for some other antibiotic agents.

Mechanism of Action Mechanistically, sulfonamides inhibit synthesis of folic acid which is required for synthesis of nucleic acid and protein in bacteria. This inhibition can be reversed by several antagonists, i.e., para-aminobenzoic acid (PABA). Antibacterial action of sulfonamides is also inhibited by tissue breakdown products, blood and pus. Thus, sulfonamide treatment is contraindicated for infections with marked suppuration. Pyrimethamine and trimethoprim are chemically 4-diaminapyrimidine derivatives which inhibit folic acid synthesis. They appear synergistic when used in combination with the sulfonamides. The sulfonamides inhibit an early step in the synthesis of folic acid, and pyrimethamine or trimethoprim inhibits a later step in the pathway.

Indications Sulfonamides have been used to treat chlamydial diseases, but other antibiotics are now the first choice and in wide use due to availability of more effective and less irritant agents. Topical ophthalmic preparations of sulfonamides include 10 % sulfacetamide and sulfasoxasole as well as the former in combination with prednisolone. Sulfacetamide administered topically achieves high concentration aqueous humor and anterior segment. Intravitreal injection of vancomycin combined with ceftazidime following intravenous penicillin G and topical sulfacetamide sodium is found to be effective in endogenous endophthalmitis caused by Actinomyces neuii (Graffi et al. 2012). Sulfacetamide sodium in combination with betamethasone is found useful in patients with meibomian gland dysfunction (Akyol-Salman et al. 2012).

Pyrimethamine in combination with sulfadiazine is an effective therapy for the treatment of toxoplasmic encephalitis, whereas trimethoprim + sulfamethoxazole and pyrimethamine + clindamycin are possible alternatives. Treatment with either oral or intravitreal antibiotics seems reasonable for ocular toxoplasmosis (Rajapakse et al. 2013).

Trimethoprim in combination with polymyxin B is available as a topical ophthalmic solution used against Gram-negative bacteria including Pseudomonas. The combination of trimethoprim-sulfamethoxazole is found to clear corneal wound

infection caused by Gram-positive organisms after phacoemulsification is a serious complication of cataract surgery (Cosar et al. 2001).

11.3.2.5 Bacterial DNA Synthesis Inhibitors

Fluoroquinolones antibiotics have quinolone moiety with one or more fluorine substitutions. These are divided into generations based on their antibacterial spectrum. Most of the quinolone including nalidixic acid belongs to first generation. Second-generation fluoroquinolones include ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, nadifloxacin, and pefloxacin. Third-generation fluoroquinolones include balofloxacin, levofloxacin, grepafloxacin, and sparfloxacin. Fourth-generation fluoroquinolones include gatifloxacin, moxifloxacin, gemifloxacin, and trovafloxacin.

Spectrum of Activity They are active against the majority of ocular pathogens, including Staphylococci, Haemophilus spp., Chlamydia trachomatis, Neisseria gonorrhoeae, Enterobacteriaceae, Listeria, Legionella, Brucella, Shigella, Proteus, Klebsiella, Bacillus anthracis, and Pseudomonas aeruginosa, but modest activity against Streptococci. These drugs have bactericidal action and relatively confer higher potency against Gram-positive bacteria. Most of the fluoroquinolone drugs penetrate corneal stroma and exhibit MICs against Gram-positive and Gram-negative bacteria. Fluoroquinolones have greater efficacy and a broader spectrum of activity than some other antibacterial drugs, including bacitracin, erythromycin, tobramycin, and gentamicin against ocular pathogens (Smith et al. 2001).

Mechanism of Action The fluoroquinolones inhibit the bacterial enzyme DNA gyrase, which required for nicking double-stranded DNA and introducing the negative supercoils.

Indications Quinolones, such as ciprofloxacin, ofloxacin, norfloxacin, levofloxacin, gatifloxacin, and moxifloxacin, are available as topical ophthalmic solution, and application remains the most popular mode of antibiotic prophylaxis in cataract surgery patients for prophylaxis from endophthalmitis (Vazirani and Basu 2013; Sridhar et al. 2015). They are also effective agents for non-tuberculous mycobacterial keratitis. They are well tolerated and effective in the treatment of patients with superficial eye infection.

Monotherapy of bacterial keratitis with ciprofloxacin or ofloxacin eye drops is found superior over conventional regimens of multiple fortified agents. Topical ciprofloxacin is effective for bacterial conjunctivitis and is also used to treat bacterial keratitis caused by a variety of pathogens. It is found effective in perioperative prophylaxis for endophthalmitis after cataract surgery (Katibeh et al. 2015). Ciprofloxacin is also available as an ointment too.

Ciprofloxacin may be useful as prophylactic topical antibiotics for preventing secondary corneal infections or recurrent corneal erosion syndrome (Park et al. 2015). Topical formulation with intravenous ofloxacin achieves aqueous and vitreous levels that inhibit many common pathogens and hold promise for treating intraocular infections. The empiric use of second-generation fluoroquinolones (ciprofloxacin and ofloxacin) seems to be contraindicated in the treatment of MRSA keratitis (Chang et al. 2015).

Norfloxacin is indicated for the treatment of bacterial conjunctivitis but is not useful for bacterial keratitis due to lesser penetration of the cornea thanofloxacin.

Levofloxacin recently became available as a 0.5 % ophthalmic solution. It exhibits high solubility in comparison with ciprofloxacin. It possesses greater activity against Streptococcus species than ciprofloxacin or ofloxacin.

Moxifloxacin has an impressive spectrum of coverage, and this pharmacokinetic study reinforces its potential as a prophylactic drug against intraocular infections, given the high aqueous level post topical administration (Sharma et al. 2015). Intravitreal moxifloxacin is found useful for the treatment of bacterial endophthalmitis (Mehta et al. 2011). Topical moxifloxacin with tobramycin is found effective in postoperative prophylaxis against infectious keratitis after laser in situ keratomileusis (LASIK) and surface ablation (Ortega-Usobiaga et al. 2015). Intracameral moxifloxacin appears most suitable for the prevention of endophthalmitis (Kessel et al. 2015).

Topical besifloxacin seems to be a useful adjunct agent in the treatment of nontuberculous mycobacterial keratitis by Mycobacterium chelonae and may be viable for use as a first-line agent in cases of nodular conjunctivitis by Mycobacterium chelonae (Nguyen et al. 2015). Besifloxacin 0.6 % produces similar antibacterial and clinical efficacy as that with moxifloxacin 0.5 % in the treatment of bacterial conjunctivitis (Garg et al. 2015).

Gatifloxacin is found effective against Gram-negative bacteria, a common cause of bacterial keratitis (Rautaraya et al. 2014). Gatifloxacin 0.5 % ophthalmic solution is found safe and effective for the treatment of acute bacterial conjunctivitis with twice-daily administration for 5 days in patients 1 year of age or older (Heller et al. 2014).

Sparfloxacin 0.3 % is a broad-spectrum fluoroquinolone antibiotic commonly used for various bacterial corneal infections (Agarwal et al. 2014). Topical fluoroquinolone therapy may be an adjunct to the innate immune response in eradicating less fulminant keratomycosis (Munir et al. 2007).

Topical use of fluoroquinolones is considered to be safe leading to their widespread use. Common indications include blepharitis, conjunctivitis, and corneal ulcers. However, unsupervised prolonged use is associated with deposition of crystalline material in the epithelial and anterior stromal layers of the cornea. Several fluoroquinolones which were not promoted for systemic use are currently under evaluation (including grepafloxacin and moxifloxacin) for their favorable activity against Gram-positive cocci.

11.3.3 Topical Drug Therapy for Resistant Microbial Infections

11.3.3.1 MRSA

With the early discovery of antibiotics, adaptation of bacteria to resist against the antibiotics has become a growing concern. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are the nosocomial infection, where the *S. aureus*

bacteria have developed immunity against the methicillin, penicillin, and beta lactam antibiotics including third- and fourth-generation fluoroquinolones. The important aspect of these bacteria is they often colonize in the nose and skin of the patients, and that might be a precipitating factor of hospital-based infections and contamination of postsurgical wounds (Mamalis 2014). MRSA infections have been observed in high prevalence rate in ophthalmic setup following routine ophthalmic surgery, like cataract, laser in situ keratomileusis, and photorefractive keratectomy, and MRSA wound infections have been reported with clear corneal phacoemulsification wounds, penetrating keratoplasty, lamellar keratoplasty, and following ex vivo epithelial transplantation associated with amniotic membrane grafts. MRSA infection is also prevalent in patients wearing therapeutic contact lenses following corneal corrective surgeries (Koh et al. 2012 and Khalil and Sonbol 2014).

Treatment Modalities

Cefazolin and other fourth-generation fluoroquinolones are used to treat MRSA infection. Vancomycin, which is sensitive to Gram-positive pathogen, has reported to be beneficial in treating MRSA ophthalmic infection (Nick Mamalis 2014). Beside vancomycin, chloramphenicol, ciprofloxacin, clindamycin, gentamicin, and sulfamethoxazole/trimethoprim have shown effectiveness in controlling MRSA infection (Donald et al. 2012) .

11.3.3.2 VRSA

MRSA is a resistant nosocomial infection, which is very difficult to treat and accounts for nosocomial infection-related death worldwide. Vancomycin is an effective bactericidal against MRSA; however, this species has developed resistance to vancomycin, and since 2002, a number of case have been reported for the vancomycin-resistant Staphylococcus aureus (VRSA) (Kos et al. 2012).

Treatment Modalities

Ceftobiprole, linezolid, and trimethoprim/sulfamethoxazole are common treatment options to treat VRSA infection.

11.4 Antimicrobial Agents for Ocular Use: Protozoal Infections

The Protozoans are considered to be a subkingdom of the kingdom Protista, although in the classical system, they were placed in the kingdom Animalia. They are free-living organisms found almost in every possible habitat. All humans have exposure

to protozoa in their life, as some are considered commensals, i.e., normally not harmful, whereas others are pathogenic and may produce disease. The diseases range from very mild to life-threatening specifically in immunosuppressed patients with acquired immune deficiency syndrome (AIDS).

The Protozoans known for their disease capabilities are Pneumocystis carinii (pneumonia), Toxoplasma gondii (fatal toxoplasmic encephalitis), Cryptosporidium and Microsporidiosis in AIDS patients, and Acanthamoeba species (keratitis), specifically in contact lens users through contaminated lens cleaning solutions. The lack of effective vaccines, the scarcity of reliable drugs, and other problems, including difficulties of vector control, prompted the World Health Organization to target these protozoal diseases.

The pharmacological agents used in the treatment of these protozoal diseases and their basis of pharmacological basis of inclusion in therapeutics are presented further in next paragraphs.

11.4.1 Acanthamoeba Keratitis

Acanthamoeba keratitis (AK) is a debilitating eye disease that requires effective topical alone or followed by oral drug therapy. Acanthamoeba spp. (Acanthamoeba polyphaga, A. castellanii, and A. hatchetti) are small, free-living Protozoans that cause AK.

Pharmacological agents in treatment: The susceptibility tests of isolates are needed to choose the most appropriate agent, and our results can be a guideline for choosing the most appropriate agent for immediate empirical treatment of AK (Sunada et al. 2014). *Acanthamoeba* cysts are most susceptible to topical natamycin (5.0 %), povidone-iodine (1.0 %), benzalkonium chloride (0.05 %), chlorhexidine gluconate (0.02 %), hexamidine diisethioonate (0.1 %), propamidine isethionate (0.1 %), polyhexamethylene biguanide (PHMB, 0.02 %), voriconazole (1.0 %), clotrimazole (1 %), and paromomycin (0.1 %) or propamidine isethionate (Kowalski et al. 2013; Lin et al. 2009).

Pharmacological basis of therapeutics and indications:

Natamycin and povidone-iodine had excellent cystic-static (or cysticidal) effects (Sunada et al. 2014). Intracameral voriconazole (1 %), an antifungal agent, is found beneficial in AKI followed by institution of oral as well as topical voriconazole drops. A novel combination treatment of chlorhexidine gluconate and natamycin (pimaricin) and debridement has been found successful for AK.

Voriconazole and chlorhexidine are also indicated for the treatment of Acanthamoeba infections (Cabello-Vílchez et al. 2014). Voriconazole oral monotherapy is also found successful in chronic stromal AK (Tu et al. 2010), whereas topical and intrastromal voriconazole is found successful in treating AK in cases of chlorhexidine- and hexamidine-resistant Acanthamoeba (Bang et al. 2010).

Moxifloxacin can be an adjuvant to consider as it is effectively prevents encystation of the amoeba which often complicates infection resolution. In addition,

moxifloxacin is effective in preventing secondary bacterial infections (Martín-Navarro et al. 2013).

In addition, cycloplegic agents, which include atropine, cyclopentolate, homatropine, scopolamine, and tropicamide, are indicated for the pain relief in addition to nonsteroidal anti-inflammatory drugs. PHMB, also known as polyhexanide and polyaminopropyl biguanide, is commonly used as antiseptic in contact lens cleaning solutions and perioperative cleansers. The germicidal effect of PHMB (0.02 %) as eye drops prior to cataract surgery is well tolerated with minimal patient discomfort.

11.4.2 Chagas' Disease

Chagas' disease (CD), also known as American or African trypanosomiasis or sleeping sickness, is the infection caused by Trypanosoma cruzi and results from bite by a kissing bug. It is a major public health issue in many Central and South American countries (Santamaria et al. 2014). A palpebral and periorbital edema, known as Romana's sign, is a hallmark of acute CD.

Pharmacological agents in treatment: The antitrypanosomal agents include nifurtimox, eflornithine, melarsoprol, and benznidazole and are most successful (Dias et al. 2014). These agents are not commercially available for topical use. Thus, only oral or parenteral form which is used for CD is believed to be useful in the treatment of trypanosomiasis and its ocular manifestations (Barrett and Croft 2012).

Pharmacological basis of therapeutics and indications:

Nifurtimox is a 5-nitrofuran derivative available for oral and parenteral use in CD (Le Loup et al. 2011). Due to appearance of relapses (reported in about 50 % patients) with monotherapy, the combination of nifurtimox with melarsoprol is preferred owing to superior efficacy (Wolf et al. 2011). There is only report available showing the microfilaricidal effect of nifurtimox in the treatment of onchocerciasis, though failed to improve corneal lesions in the study (Fuglsang and Anderson 1978).

Eflornithine (α-difluoromethylornithine or DFMO) is termed as a "suicide inhibitor," irreversibly binding to the enzyme ornithine decarboxylase and preventing the natural substrate ornithine from accessing the active site (Heby et al. 2007). It is used with melarsoprol or nifurtimox (Burri and Brun 2003; Jennings 1988). Periocular injections of DFMO, which decreases polyamine levels, are believed to inhibit choroidal neovascularization (Lima e Silva et al. 2005). The side effects are transient and reversible. Seizures, hearing loss, and hematological abnormalities may occur.

Melarsoprol is a prodrug, which is metabolized to melarsen oxide (Mel Ox) as its active form which irreversibly binds with trypanothione and forms an adduct that inhibits trypanothione reductase and kills the parasitic cell. Due to high toxicity,

oral melarsoprol is reserved only for the most dangerous of cases – stage 2 infections (Rodgers et al. 2011). It produces adverse effects similar to arsenic poisoning and may cause convulsions, fever, rashes, bloody stools, nausea, vomiting, and rarely encephalopathy.

Nifurtimox-eflornithine combination therapy which has superior efficacy is reserved for the treatment of second-stage CD or T. rhodesiense (Priotto et al. 2009).

Benznidazole acts by the production of free radicals and injurious to the sensitive T. cruzi as it possesses reduced detoxification capabilities (Medeiros 2009). In a clinical study, BENEFIT trial (BENznidazole Evaluation For Interrupting Trypanosomiasis) appears effective in chronic stages of CD (Coura and Borges-Pereira 2010). It is found successful in both adult and juvenile (Le Loup et al. 2011). The common side effects are ash and gastrointestinal disturbances and, rarely, peripheral neuropathy.

Posaconazole, a new drug, showed antitrypanosomal activity in patients with chronic CD in randomized clinical trials (Molina et al. 2014). Benznidazole is found to induce reduction, but not elimination, of circulating T. cruzi levels, whereas posaconazole led to a successful resolution of the infection, despite the maintenance of immunosuppressive therapy in CD (Pinazo et al. 2010).

11.4.3 Giardiasis

Giardiasis is caused by Giardia lamblia, transmitted from person-to-person through contaminated food and water (Lal et al. 2013). The ocular manifestations may include chorioretinitis, iridocyclitis, uveitis, and vitreal and retinal hemorrhage, described as "salt-and-pepper" changes (Turnbull et al. 2013; Corsi et al. 1998). No commercial formulations as eye drop/ointment are available for topical use in the eye.

Pharmacological agents in treatment: The recommended treatment includes metronidazole, albendazole, or paromomycin (Granados et al. 2012).

Pharmacological basis of therapeutics and indications:

Metronidazole is an antibiotic and an antiprotozoal drug used against amoebiasis, giardiasis, and trichomoniasis (Granados et al. 2012). It acts by inhibiting nucleic acid synthesis by disrupting the DNA of microbial cells. This function only occurs when metronidazole is partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic bacteria. The common side effects of metronidazole are nausea, abdominal pain, headache, dizziness, and metallic taste (Pasupuleti et al. 2014).

Albendazole, a benzimidazole broad-spectrum anthelmintic drug, is used in the treatment of worm infestations such as roundworms, tapeworms, giardiasis, trichuriasis, filariasis, neurocysticercosis, hydatid disease, enterobiasis, and

ascariasis (Granados et al. 2012). It causes degenerative changes and impairs the energetics of the worms. The common side effects are raised liver enzymes, abdominal pain, dizziness, headache, fever, nausea, and vomiting (Meltzer et al. 2014; Granados et al. 2012).

Paromomycin, also known as monomycin and aminosidine, is an aminoglycoside antibiotic. It inhibits protein synthesis by binding to 16S ribosomal RNA. It is an effective treatment for ulcerative cutaneous leishmaniasis apart from amoebiasis and leishmaniasis (Meltzer et al. 2014; Granados et al. 2012). It is found successful in the treatment of metronidazole-refractory giardiasis (Stover et al. 2012; Mørch et al. 2008). The common side effects are nephrotoxicity and ototoxicity with oral doses.

11.4.4 Leishmaniasis

Leishmaniasis is caused by obligate intracellular protozoans, hemoflagellates through the bite of a sandfly (Khadem and Uzonna 2014). It is a disease of the developing world, throughout Africa, Southern Europe, and Central Asia (Elmahallawy et al. 2014; Khyatti et al. 2014). Symptomatic ocular manifestations of visceral leishmaniasis are rare, but conjunctivitis, blepharitis, uveitis, keratitis, iritis, papillitis, and chorioretinitis occur with visceral leishmaniasis (Maude et al. 2014; Khalil et al. 2011; Yaghoobi et al. 2010; Sadeghian et al. 2005; Montero et al. 2003).

Pharmacological agents in treatment: Current strategies to control this disease are mainly based on chemotherapy. Due to high resistance and adverse effects, the antileishmanial drugs are used in combination treatment regimens (Sundar and Chakravarty 2015; Mahajan et al. 2015). Single dose of liposomal amphotericin B (LAmB), or multidrug therapy (L-AmB + miltefosine, L-AmB + paromomycin, or miltefosine + paromomycin), pentavalent antimonials, and paromomycin are usually used in the treatment of visceral leishmaniasis. The treatment is determined by where the disease is acquired, the species of Leishmania, severity of clinical lesions, type of infection, and its potential to develop into mucosal leishmaniasis (Khadem and Uzonna 2014). Bilateral, multifocal retinal hemorrhages get improved by specific antileishmanial therapy (Sundar and Chakravarty 2015; Montero et al. 2003).

11.4.4.1 Pharmacological Basis of Therapeutics and Indications

Amphotericin B is an effective antifungal and antiparasitic drug and is the first line of therapy for leishmaniasis (Sundar et al. 2011). Currently LAmB is the most effective anti-*Leishmania* drug and is administered by intravenous infusion (Sundar et al. 2010). However, LAmB limitations include efficacy, expensiveness, and nephrotoxicity. It is the first line of therapy for leishmaniasis and often used as a single dose with high success rate.

Like other polyene antifungals, it binds with the component of fungal cell membranes, forming a transmembrane channel, which causes leakage of monovalent ions

and resultant fungal cell death. Combining intravitreal amphotericin B and voriconazole found a novel treatment strategy in the management of endophthalmitis caused by filamentous fungus. The ocular complications of interstitial keratitis were found successfully treated by amphotericin (Roizenblatt 1979).

The pentavalent antimonials are a group of compounds used for the treatment of leishmaniasis. The agents, sodium stibogluconate and meglumine antimoniate, are available either as slow intravenous or intramuscular injection, but due to resistance, amphotericin or miltefosine is now preferred. Combined stibogluconate and allopurinol may be an effective therapy in ocular leishmaniasis (Abrishami et al. 2002). Systemic sodium stibogluconate is found successful in cutaneous and ocular leishmaniasis (Sadeghian et al. 2005). The side effects are anemia, rash, headache, abdominal pain, myalgia, and raised liver enzymes.

Miltefosine is a phospholipid compound that kills Leishmania parasites and is the first (and still the only prescribed) oral drug in the treatment of leishmaniasis. Recently, it is approved by USFDA for any form of leishmaniasis including cutaneous or mucosal leishmaniasis. It acts as a protein kinase B (Akt) inhibitor in the microbial cell. It is also approved for topical treatment of leishmaniasis and appears promising for the topical treatment of Acanthamoeba infections (Walochnik et al. 2009).

Miltefosine was originally formulated as a topical treatment for cutaneous cancers (Sindermann and Engel 2006). The combination of LAmB and oral miltefosine is found successful in multiple relapses of visceral leishmaniasis in patient with HIV (Patole et al. 2014).

11.4.5 Malaria

Malaria is caused by the different species of Plasmodium (Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium falciparum) and transmitted by the bite of female anopheles mosquito. Ocular manifestations occur during infection with the following signs: retinal whitening, papilledema, and cotton wool spots.

Pharmacological agents: The antimalarials are used in the treatment of malaria, though the antimalarials chloroquine and hydroxychloroquine on long-term use may cause retinal toxicity in offspring of women exposed to antimalarials during pregnancy (Osadchy et al. 2011).

11.4.6 Microsporidiosis

Microsporidia are the intracellular pathogens that cause superficial punctate keratitis and stromal keratitis in both immunocompromised and immunocompetent individuals (Khandelwal et al. 2011). Ocular findings are generally limited to the conjunctiva and cornea and occur either by direct inoculation into eye structures or by dissemination systemically.

Pharmacological agents: The agents used in the treatment include albendazole, an anthelmintic agent; fumagillin, itraconazole, and voriconazole, antifungal agents; and metronidazole, an antiamoebic agent. Topically, propamidine isethionate is also used in the treatment. Oral medications, such as albendazole and itraconazole, have shown efficacy, but the risk of systemic adverse effects and drug-drug interactions exists (Loh et al. 2009). Combinations of medications, both topical and oral, have been attempted with varying success.

Pharmacological basis of therapeutics and indications:

Fumagillin is currently an orphan drug used within the European Union to treat microsporidiosis in immunocompromised or immunocompetent individuals (Kulakova et al. 2014; Chan et al. 2003). Treatment regimen includes topical fluoroquinolones (ciprofloxacin 0.3 %, moxifloxacin 0.5 %, gatifloxacin 0.5 %, levofloxacin 0.5 %, or norfloxacin 0.3 %) as monotherapy or in combination with topical fumagillin and/or systemic albendazole (Loh et al. 2009). The topical fumagillin and oral albendazole are found useful in microsporidial stromal keratitis following deep anterior lamellar keratoplasty (Ang et al. 2009). Fumagillin acts similar to angiogenesis inhibitors by blocking new blood vessel formation by binding to an enzyme methionine aminopeptidase.

Itraconazole is a broad-spectrum triazole antifungal agent that, like other azole antifungals, inhibits the fungal-mediated synthesis of ergosterol. It also inhibits both the hedgehog signaling pathway and angiogenesis. Oral itraconazole is found successful in the treatment of microsporidial keratoconjunctivitis (Sridhar and Sharma 2003). It also recommended in ocular, nasal, and paranasal sinus infection caused by Encephalitozoon cuniculi parasites when treatment with albendazole fails (Rossi et al. 1999).

Itraconazole administered topically, orally, and intravenously also has a high success rate in fungal keratitis and endophthalmitis (Jin et al. 2014; Mochizuki et al. 2013). Topical voriconazole (1 %) is found to be an effective treatment for keratitis due to microsporidia (Khandelwal et al. 2011) and in fungal corneal ulcers too (Parchand et al. 2012).

11.4.7 Toxoplasmosis

Toxoplasmosis is caused by an opportunistic parasite Toxoplasma gondii which infects about one third of the human population worldwide and appears as latent infection (Delair et al. 2011). Ocular toxoplasmosis frequently presents as a focal necrotizing retinitis or gray-white punctate lesions in the outer retina and retinal pigment epithelium (Park and Nam 2013; Antoniazzi et al. 2008).

Majority of cases of ocular toxoplasmosis are congenital (Noble 2007). Among the clinical manifestations of congenital ocular toxoplasmosis reported in infants are microphthalmia, enophthalmos, ptosis, nystagmus, choroidal colobomas, and

strabismus (Pleyer et al. 2014; Maenz et al. 2014; Harrell and Carvounis 2014). Acute infection in newborns and patients infected with HIV may lead to an intense necrotizing chorioretinitis (Pleyer et al. 2014; Pfaff et al. 2014).

Pharmacological agents for treatment: Sulfonamides, pyrimethamine and/or sulfadiazine, folinic acid, trimethoprim/sulfamethoxazole (Opremcak et al. 1992), and macrolide antibiotics; azithromycin (Yazici et al. 2009); spiramycin (Cassaday et al. 1964); clindamycin (Tate and Martin 1977; Guldsten 1983); and antimalarial atovaquone, alone or in combination, are generally used in the treatment of toxoplasmosis and its ocular manifestations (de-la-Torre et al. 2011).

The first-line therapy of T. gondii-related chorioretinitis involves the use of pyrimethamine with sulfadiazine beyond the resolution of symptoms (Harrell and Carvounis 2014; Holland and Lewis 2002). The alternative regimens include the use of pyrimethamine with clindamycin, clarithromycin, or azithromycin.

The treatment regimens consisted of either pyrimethamine (100 mg for 1 day, then 25 mg bid), sulfadiazine (1 g qid), folinic acid (5 mg), and prednisone (60 mg then taper); clindamycin (300 mg qid), sulfadiazine (1 g qid), and prednisone (60 mg, then taper); or trimethoprim-sulfamethoxazole (160–800 mg bid for 2 weeks then 80–400 mg bid) (Harrell and Carvounis 2014). Randomized clinical trials showed that intravitreal clindamycin-dexamethasone is effective for *Toxoplasma* retinochoroiditis (Soheilian et al. 2011).

Trimethoprim-sulfamethoxazole is considered the best first-line treatment of *Toxoplasma* retinochoroiditis, with intravitreal clindamycin with dexamethasone an alternative for patients intolerant and unresponsive or with a contraindication (such as pregnancy) to trimethoprim-sulfamethoxazole. There is considerable evidence that administering trimethoprim-sulfamethoxazole combination can intermittently reduce the risk of recurrence. Corticosteroids are used as adjuvant, though a very recent Cochrane Review found no evidence from randomized controlled studies to support their use or indeed support concerns to anti-Toxoplasma treatment that may lead to worse outcomes (Vedula and Nguyen 2008).

A combination of pyrimethamine, sulfadiazine, and folinic acid is preferred as treatment for women in whom fetal infection has been confirmed or is highly suspected by a positive amniotic fluid polymerase chain reaction (Paquet 2013), whereas congenital toxoplasmosis appears suitably treated with combination of pyrimethamine, sulfadiazine, and leucovorin (Kaye 2011). As soon as the maternal infection is suspected, preventive treatment with spiramycin begins; the treatment is changed to a combination of pyrimethamine-sulfonamide if fetal infection is proven (Garcia-Méric et al. 2010).

Intravitreal clindamycin plus dexamethasone was found superior than conventional oral therapy including pyrimethamine, sulfadiazine, folinic acid, and prednisone in the treatment of active toxoplasmic retinochoroiditis (Baharivand et al. 2013). Adverse drug reaction appears as DRESS syndrome reported in pediatric patient following treatment with standard combination regimen includes oral sulfadiazine, pyrimethamine, folinic acid, and steroids for toxoplasma retinochoroiditis (Yusuf et al. 2013).

Pharmacological basis of therapeutics and indications:

Patients infected with HIV showing signs of previous infection receive primary prophylaxis with trimethoprim-sulfamethoxazole (Campos et al. 2014). In patients with AIDS showing toxoplasmic chorioretinitis, sulfadiazine, pyrimethamine, and folinic acid should be continued indefinitely following initial therapy. Folinic acid is added to prevent bone marrow toxicity, and spiramycin is considered relatively safe by USFDA for use in pregnancy. It is used popularly to prevent the toxoplasmosis and a popular choice in pregnancy (Asproudis et al. 2013; Garcia-Méric et al. 2010).

Pyrimethamine, an antimalarial drug, is used in the treatment of Toxoplasma gondii infections in immunocompromised patients such as HIV-positive individuals. It is typically given with a sulfadiazine and folinic acid (Butler et al. 2013). Sulfonamides inhibit dihydropteroate synthetase, an enzyme that participates in folic acid synthesis from para-aminobenzoic acid and works synergistically with pyrimethamine by blocking a different enzyme required for folic acid synthesis. Pyrimethamine may cause skin rash, gastrointestinal disturbances, headache, ataxia, and hematological side effects (Rajapakse et al. 2013).

Folinic acid is a folic acid derivative which is converted to tetrahydrofolate (the primary active form of folic acid) in vivo without relying on dihydrofolate reductase. Thus, folinic acid reduces side effects related to folate deficiency in the patient (Shea 2013).

Trimethoprim/sulfamethoxazole or co-trimoxazole, also known as SXT, TMP-SMX, TMP-SMZ, or TMP-sulfa, is a wide spectrum antimicrobial agent that consists of one part trimethoprim and five parts of sulfamethoxazole. It is used in the treatment of bacterial, fungal, and protozoal infections and shows greater effect when given together and behaves as bactericidal, though individually bacteriostatic (Manyando et al. 2013). The combination inhibits successive steps in the folate synthesis pathway. Trimethoprim causes a backlog of dihydrofolate (DHF), and this backlog works against the inhibitory effect the drug has on tetrahydrofolate biosynthesis; this is where the sulfamethoxazole comes in its role is in depleting the excess DHF by preventing it from being synthesized. It is antifolate in nature inhibiting both de novo folate biosynthesis and metabolism (Bentley 2009).

Atovaquone, a naphthoquinone compound, is an analog of ubiquinone with antipneumocystic activity. It is available in liquid form or oral suspension. Atovaquone (750 mg) orally given two to three times daily together with oral steroids is found effective in toxoplasmic retinochoroiditis (Winterhalter et al. 2010). Generally, co-trimoxazole is considered first-line agents, but atovaquone can be used in patients who cannot tolerate or are allergic to co-trimoxazole.

Macrolide antibiotics such as azithromycin and spiramycin and lincosamide antibiotic and clindamycin are also used to treat toxoplasmosis and various infections of the soft tissues (Hosseini et al. 2014; Yazici et al. 2009; Bonfioli and Orefice 2005). Azithromycin oral monotherapy is found effective and well tolerated for the treatment of active, non-vision-threatening toxoplasmic retinochoroiditis

(Balaskas et al. 2012). Azithromycin is an azalide, a subclass of macrolide antibiotic. The macrolides and lincosamides both act as a bacterial protein synthesis inhibitor by inhibiting ribosomal translocation through binding to the 50S rRNA of the large bacterial ribosome subunit. The common side effects of macrolides and lincosamides are nausea, vomiting, abdominal pain, nervousness, and dermatological reactions.

References

A controlled trial of oral acyclovir for iridocyclitis caused by herpes simplex virus. The Herpetic Eye Disease Study Group. Arch Ophthalmol. 1996;114(9):1065–72.

A controlled trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with herpes simplex virus epithelial keratitis. The Epithelial Keratitis Trial. The Herpetic Eye Disease Study Group. Arch Ophthalmol. 1997;115(6):703–12.

Acyclovir for the prevention of recurrent herpes simplex virus eye disease. Herpetic Eye Disease Study Group. N Engl J Med. 1998;339(5):300–6.

Altun A, Kurna SA, Sengor T, Altun G, Olcaysu OO, Aki SF, Simsek MH. Effectiveness of posaconazole in recalcitrant fungal keratitis resistant to conventional antifungal drugs. Case Rep Ophthalmol Med. 2014;2014:701653.

Barron BA, Gee L, Hauck WW, Kurinij N, et al. Herpetic Eye disease study. A controlled trial of oral acyclovir for herpes simplex stromal keratitis. Ophthalmology. 1994;101(12): 1871–82.

Biron KK, Elion GB. In vitro susceptibility of varicella-zoster virus to acyclovir. Antimicrob Agents Chemother. 1980;18(3):443–7.

Boston Interhospital Viral Study Group. Failure of high dose 5-iodo-2'-deoxyuridine in the therapy of herpes simplex virus encephalitis. Evidence of unacceptable toxicity. N Engl J Med. 1975;292(12):599–603.

Coster DJ, McKinnon JR, McGill JI, Jones BR, Fraunfelder FT. Clinical evaluation of adenine arabinoside and trifluorothymidine in the treatment of corneal ulcers caused by herpes simplex virus. J Infect Dis. 1976;133(Suppl):A173–7.

Davies ME, Bondi JV, Grabowski L, Schofield TL, Field AK. 2'-nor-2'deoxyguanosine is an effective therapeutic agent for treatment of experimental herpes keratitis. Antiviral Res. 1987;7(2): 119–25.

Dupuis A, Tournier N, Le Moal G, Venisse N. Preparation and stability of voriconazole eye drop solution. Antimicrob Agents Chemother. 2009;53(2):798–9.

Elion GB. Mechanism of action and selectivity of acyclovir. Am J Med. 1982;73(1A):7–13.

Foster CS, Stefanyszyn M. Intraocular penetration of miconazole in rabbits. Arch Ophthalmol. 1979;97(9):1703–6.

Gao H, Pennesi M, Shah K, Qiao X, Hariprasad SM, Mieler WF, et al. Safety of intravitreal voriconazole: electroretinographic and histopathologic studies. Trans Am Ophthalmol Soc. 2003; 101:183–9.

Goldblum D, Frueh BE, Sarra GM, Katsoulis K, Zimmerli S. Topical caspofungin for treatment of keratitis caused by Candida albicans in a rabbit model. Antimicrob Agents Chemother. 2005;49(4):1359–63.

Hurtado-Sarrió M, Duch-Samper A, Cisneros-Lanuza A, Díaz-Llopis M, Peman-Garcíia J, Vazquez-Polo A. Successful topical application of caspofungin in the treatment of fungal keratitis refractory to voriconazole. Arch Ophthalmol. 2010;128(7):941–2.

Kalavathy CM, Parmar P, Kaliamurthy J, Philip VR, Ramalingam MD, Jesudasan CA, Thomas PA. Comparison of topical itraconazole 1% with topical natamycin 5% for the treatment of filamentous fungal keratitis. Cornea. 2005;24(4):449–52.

Kaufman H, Martola E, Dohlman C. Use of 5-iodo-2'-deoxyuridine (IDU) in treatment of herpes simplex keratitis. Arch Ophthalmol. 1962a;68:235–9.
Kaufman HE, Heidelberger C. Therapeutic antiviral action of 5-trifluoromethyl-2'-deoxyuridine in herpes simplex keratitis. Science. 1964;145(3632):585–6.
Kaufman HE, Nesburn AB, Maloney ED. IDU therapy of herpes simplex. Arch Ophthalmol. 1962b;67:583–91.
Kaur IP, Rana C, Singh H. Development of effective ocular preparations of antifungal agents. J Ocul Pharmacol Ther. 2008;24(5):481–93. Review.
Khoo SH, Bond J, Denning DW. Administering amphotericin B—a practical approach. J Antimicrob Chemother. 1994;33(2):203–13.
Klotz SA, Zahid M, Bartholomew WR, Revera PM, Butrus S. Candida albicans keratitis treated successfully with itraconazole. Cornea. 1996;15(1):102–4.
Kobayashi D, Kondo K, Uehara N, Otokozawa S, Tsuji N, Yagihashi A, Watanabe N. Endogenous reactive oxygen species is an important mediator of miconazole antifungal effect. Antimicrob Agents Chemother. 2002;46(10):3113–7.
Lalitha P, Shapiro BL, Srinivasan M, Prajna NV, Acharya NR, Fothergill AW, et al. Antimicrobial susceptibility of Fusarium, Aspergillus, and other filamentous fungi isolated from keratitis. Arch Ophthalmol. 2007;125(6):789–93.
Larder BA, Darby G. Susceptibility to other antiherpes drugs of pathogenic variants of herpes simplex virus selected for resistance to acyclovir. Antimicrob Agents Chemother. 1986;29(5): 894–8.
Lee W, Benitez A, Goodman L, Baker BR. Potential Anticancer Agents. XL. Synthesis of the β-Anomer of 9-(D-Arabinofuranosyl)adenine. J Am Chem Soc. 1960;82:2648–9.
Li L, Wang Z, Li R, Luo S, Sun X. In vitro evaluation of combination antifungal activity against Fusarium species isolated from ocular tissues of keratomycosis patients. Am J Ophthalmol. 2008;146(5):724–8.
Lin HC, Chu PH, Kuo YH, Shen SC. Clinical experience in managing Fusarium solani keratitis. Int J Clin Pract. 2005;59(5):549–54.
Martinez R. Atualização no uso de agentes antifúngicos. J Bras Pneumol. 2006;32(5):449–60.
Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, part 1. Am J Health Syst Pharm. 2006;63(18):1693–703. Review.
Nicholson KG. Properties of antiviral agents. 1. Lancet. 1984;2(8401):503–6.
O'Day DM, Foulds G, Williams TE, Robinson RD, Allen RH, Head WS. Ocular uptake of fluconazole following oral administration. Arch Ophthalmol. 1990;108(7):1006–8.
O'Day DM, Ray WA, Head WS, Robinson RD. Influence of the corneal epithelium on the efficacy of topical antifungal agents. Invest Ophthalmol Vis Sci. 1984;25(7):855–9.
O'Day DM. Selection of appropriate antifungal therapy. Cornea. 1987;6(4):238–45. Review.
O'Day DM, Head WS, Robinson RD, Stern WH, Freeman JM. Intraocular penetration of systemically administered antifungal agents. Curr Eye Res. 1985;4(2):131–4.
Panda A, Sharma N, Angra SK. Topical fluconazole therapy of Candida keratitis. Cornea. 1996;15(4):373–5.
Prajna NV, Krishnan T, Mascarenhas J, Rajaraman R, Prajna L, Srinivasan M, Raghavan A, Oldenburg CE, Ray KJ, Zegans ME, McLeod SD, Porco TC, Acharya NR, Lietman TM, Mycotic Ulcer Treatment Trial Group. The mycotic ulcer treatment trial: a randomized trial comparing natamycin vs voriconazole. JAMA Ophthalmol. 2013;131(4):422–9.
Prajna NV, Mascarenhas J, Krishnan T, Reddy PR, Prajna L, Srinivasan M, et al. Comparison of natamycin and voriconazole for the treatment of fungal keratitis. Arch Ophthalmol. 2010; 128(6):672–8.
Prakash G, Sharma N, Goel M, Titiyal JS, Vajpayee RB. Evaluation of intrastromal injection of voriconazole as a therapeutic adjunctive for the management of deep recalcitrant fungal keratitis. Am J Ophthalmol. 2008;146(1):56–9.
Prusoff WH, Zucker M, Mancini WR, Otto MJ, Lin TS, Lee JJ. Basic biochemical and pharmacological aspects of antiviral agents. Antiviral Res. 1985;Suppl 1:1–10.

Rajaraman R, Bhat P, Vaidee V, Maskibail S, Raghavan A, Sivasubramaniam S, Rajasekaran J, Thomas PA, Kalavathy CM, Joseph PC, Abraham DJ. Itraconazole therapy for fungal keratitis. Indian J Ophthalmol. 1987;35(5–6):157–60.

Sacks SL, Scullard GH, Pollard RB, Gregory PB, Robinson WS, Merigan TC. Antiviral treatment of chronic hepatitis B virus infection: pharmacokinetics and side effects of interferon and adenine arabinoside alone and in combination. Antimicrob Agents Chemother. 1982;21(1):93–100.

Sharma N, Chacko J, Velpandian T, Titiyal JS, Sinha R, Satpathy G, Tandon R, Vajpayee RB. Comparative evaluation of topical versus intrastromal voriconazole as an adjunct to natamycin in recalcitrant fungal keratitis. Ophthalmology. 2013a;120(4):677–81.

Sharma S, Das S, Virdi A, Fernandes M, Sahu SK, Kumar Koday N, Ali MH, Garg P, Motukupally SR. Re-appraisal of topical 1% voriconazole and 5% natamycin in the treatment of fungal keratitis in a randomised trial. Br J Ophthalmol. 2015;99(9):1190–5.

Torres MA, Mohamed J, Cavazos-Adame H, Martinez LA. Topical ketoconazole for fungal keratitis. Am J Ophthalmol. 1985;100(2):293–8.

Travers JP, Patterson A. A controlled trial of adenine arabinoside and trifluorothymidine in herpetic keratitis. J Int Med Res. 1978;6(2):102–4.

Urbak SF, Degn T. Fluconazole in the management of fungal ocular infections. Ophthalmologica. 1994;208(3):147–56.

Van Bijsterveld OP, Post H. Trifluorothymidine versus adenine arabinoside in the treatment of herpes simplex keratitis. Br J Ophthalmol. 1980;64(1):33–6.

Vermes A, Guchelaar HJ, Dankert J. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. J Antimicrob Chemother. 2000;46(2):171–9.

Wagstaff AJ, Faulds D, Goa KL. Aciclovir. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs. 1994;47(1):153–205.

Wilhelmus KR. The treatment of herpes simplex virus epithelial keratitis. Trans Am Ophthalmol Soc. 2000;98:505–32.

Wilson 2nd FM. Adverse external ocular effects of topical ophthalmic medications. Surv Ophthalmol. 1979;24(2):57–88.

Yoon KC, Jeong IY, Im SK, Chae HJ, Yang SY. Therapeutic effect of intracameral amphotericin B injection in the treatment of fungal keratitis. Cornea. 2007;26(7):814–8.

Agarwal AK, Ram J, Singh R. Sparfloxacin-associated corneal epithelial toxicity. BMJ Case Rep. 2014;19:2014.

Ahmed S, Kuruvilla O, Yee DC, et al. Intraocular penetration of systemic antibiotics in eyes with penetrating ocular injury. J Ocul Pharmacol Ther. 2014;30(10):823–30.

Akyol-Salman I, Azizi S, Mumcu UY, et al. Comparison of the efficacy of topical N-acetylcysteine and a topical steroid-antibiotic combination therapy in the treatment of meibomian gland dysfunction. J Ocul Pharmacol Ther. 2012;28(1):49–52.

Andreoli CM, Wiley HE, Durand ML, et al. Primary meningococcal conjunctivitis in an adult. Cornea. 2004;23(7):738–9.

Baneke A. Review: targeting trachoma: strategies to reduce the leading infectious cause of blindness. Travel Med Infect Dis. 2012;10(2):92–6.

Benson CE, Soliman MK, Knezevic A, et al. Bilateral papillitis and unilateral focal chorioretinitis as the presenting features of syphilis. J Ophthalmic Inflamm Infect. 2015;5:16.

Blanco AR, SudanoRoccaro A, Spoto CG, et al. Susceptibility of methicillin-resistant Staphylococci clinical isolates to netilmicin and other antibiotics commonly used in ophthalmic therapy. Curr Eye Res. 2013;38(8):811–6.

Cagini C, Piccinelli F, Lupidi M, et al. Ocular penetration of topical antibiotics: study on the penetration of chloramphenicol, tobramycin and netilmicin into the anterior chamber after topical administration. Clin Experiment Ophthalmol. 2013;41(7):644–7.

Chang VS, Dhaliwal DK, Raju L, Kowalski RP. Antibiotic resistance in the treatment of staphylococcus aureus keratitis: a 20-year review. Cornea. 2015;34(6):698–703.

Chen C, Chen Y, Wu P, et al. Update on new medicinal applications of gentamicin: evidence-based review. J Formos Med Assoc. 2014;113(2):72–82.

Chew FL, Soong TK, Shin HC, et al. Topical piperacillin/tazobactam for recalcitrant pseudomonas aeruginosa keratitis. J Ocul Pharmacol Ther. 2010;26(2):219–22.
Cosar CB, Cohen EJ, Rapuano CJ, et al. Clear corneal wound infection after phacoemulsification. Arch Ophthalmol. 2001;119(12):1755–9.
Darling EK, McDonald H. A meta-analysis of the efficacy of ocular prophylactic agents used for the prevention of gonococcal and chlamydial ophthalmianeonatorum. J Midwifery Womens Health. 2010;55(4):319–27.
Donnenfeld ED, O'Brien TP, Solomon R, et al. Infectious keratitis after photorefractive keratectomy. Ophthalmology. 2003;110(4):743–7.
Erdem E, Abdurrahmanoglu S, Kibar F, et al. Posttraumatic keratitis caused by Elizabeth kingia-meningosepticum. Eye Contact Lens. 2013;39(5):361–3.
Foulks GN, Borchman D, Yappert M, et al. Topical azithromycin and oral doxycycline therapy of meibomian gland dysfunction: a comparative clinical and spectroscopic pilot study. Cornea. 2013;32(1):44–53.
Freitas D, Alvarenga L, Sampaio J, et al. An outbreak of Mycobacterium chelonae infection after LASIK. Ophthalmology. 2003;110(2):276–85.
Fukuda M, Ohashi H, Matsumoto C, et al. Methicillin-resistant Staphylococcus aureus and methicillin-resistant coagulase-negative Staphylococcus ocular surface infection efficacy of chloramphenicol eye drops. Cornea. 2002;21(7 Suppl):S86–9.
Garg P, Mathur U, Sony P, et al. Clinical and antibacterial efficacy and safety of besifloxacin ophthalmic suspension compared with moxifloxacin ophthalmic solution. Asia Pac J Ophthalmol (Phila). 2015;4(3):140–5.
Garnock-Jones KP. Azithromycin 1.5% ophthalmic solution: in purulent bacterial or trachomatous conjunctivitis. Drugs. 2012;72(3):361–73.
Gentile RC, Shukla S, Shah M, et al. Microbiological spectrum and antibiotic sensitivity in endophthalmitis: a 25-year review. Ophthalmology. 2014;121(8):1634–42.
Graffi S, Peretz A, Naftali M. Endogenous endophthalmitis with an unusual infective agent: Actinomyces neuii. Eur J Ophthalmol. 2012;22(5):834–5.
Heller W, Cruz M, Bhagat YR, et al. Gatifloxacin 0.5% administered twice daily for the treatment of acute bacterial conjunctivitis in patients one year of age or older. J Ocul Pharmacol Ther. 2014;30(10):815–22.
Hsiao CH, Chuang CC, Tan HY, Ma DH, Lin KK, Chang CJ, Huang YC. Methicillin-resistant Staphylococcus aureus ocular infection: a 10-year hospital-based study. Ophthalmology. 2012;119(3):522–7. doi: 10.1016/j.ophtha.2011.08.038. Epub 2011 Dec 15.
Jain R, Murthy SI, Motukupally SR, et al. Use of topical colistin in multiple drug-resistant Pseudomonas aeruginosa bacterial keratitis. Cornea. 2014;33(9):923–7.
Katibeh M, Ziaei H, Mirzaei M, et al. Perioperative prophylaxis for endophthalmitis after cataract surgery in iran. J Ophthalmic Vis Res. 2015;10(1):33–6.
Keenan JD, Moncada J, Gebre T, et al. Chlamydial infection during trachoma monitoring: are the most difficult-to-reach children more likely to be infected? Trop Med Int Health. 2012;17(3):392–6.
Kessel L, Flesner P, Andresen J, et al. Antibiotic prevention of postcataract endophthalmitis: a systematic review and meta-analysis. Acta Ophthalmol. 2015;93(4):303–17.
Koh S, Maeda N, Soma T, Hori Y, Tsujikawa M, Watanabe H, Nishida K. Development of methicillin-resistant staphylococcus aureus keratitis in a dry eye patient with a therapeutic contact lens. Eye Contact Lens. 2012;38(3):200–2.
Leeming JP. Treatment of ocular infections with topical antibacterials. Clin Pharmacokinet. 1999;37(5):351–60.
Li B, Miño de Kaspar H, Haritoglou C, et al. Comparison of 1-day versus 1-hour application of topical neomycin/polymyxin-B before cataract surgery. J Cataract Refract Surg. 2015;41(4):724–31.
Linertová R, Abreu-González R, García-Pérez L, et al. Intracameral cefuroxime and moxifloxacin used as endophthalmitis prophylaxis after cataract surgery: systematic review of effectiveness and cost-effectiveness. Clin Ophthalmol. 2014;8:1515–22.

Khalil MA, Sonbol FI. Investigation of biofilm formation on contact eye lenses caused by methicillin resistant Staphylococcus aureus. Niger J Clin Pract. 2014;17(6):776–84.
Mason BW, Howard AJ, Magee JT. Fusidic acid resistance in community isolates of methicillin-susceptible Staphylococcus aureus and fusidic acid prescribing. J Antimicrob Chemother. 2003;51(4):1033–6.
McDonald EM, Ram FS, Patel DV, et al. Topical antibiotics for the management of bacterial keratitis: an evidence-based review of high quality randomised controlled trials. Br J Ophthalmol. 2014;98(11):1470–7.
Mehta S, Armstrong BK, Kim SJ, et al. Long-term potency, sterility, and stability of vancomycin, ceftazidime, and moxifloxacin for treatment of bacterial endophthalmitis. Retina. 2011;31(7):1316–22.
Munir WM, Rosenfeld SI, Udell I, et al. Clinical response of contact lens-associated fungal keratitis to topical fluoroquinolone therapy. Cornea. 2007;26(5):621–4.
Newman PE, Hider P, Waring 3rd GO, Hill EO, Wilson LA, Harbin TS. Corneal ulcer due to Achromobacter xylosoxidans. Br J Ophthalmol. 1984;68(7):472–4.
Nguyen AT, Hong AR, Baqai J, Lubniewski AJ, Huang AJ. Use of topical besifloxacin in the treatment of Mycobacterium chelonae Ocular Surface Infections. Cornea. 2015;34(8):967–71.
Mamalis N. Ocular methicillin-resistant Staphylococcus aureus. J Cataract Refract Surg. 2014;40(11):1757–8. doi: 10.1016/j.jcrs.2014.09.016. Epub 2014 Oct 23.
Ortega-Usobiaga J, Llovet-Osuna F, Djodeyre MR, et al. Incidence of corneal infections after laser in situ keratomileusis and surface ablation when moxifloxacin and tobramycin are used as postoperative treatment. J Cataract Refract Surg. 2015;18.
Papa V, Aragona P, Scuderi AC, et al. Treatment of acute bacterial conjunctivitis with topical netilmicin. Cornea. 2002;21(1):43–7.
Park YM, Kwon HJ, Lee JS. Microbiological study of therapeutic soft contact lenses used in the treatment of recurrent corneal erosion syndrome. Eye Contact Lens. 2015;41(2):84–6.
Penha FM, Rodrigues EB, Maia M, et al. Retinal and ocular toxicity in ocular application of drugs and chemicals – part II: retinal toxicity of current and new drugs. Ophthalmic Res. 2010;44(4):205–24.
Rajapakse S, Chrishan SM, Samaranayake N, et al. Antibiotics for human toxoplasmosis: a systematic review of randomized trials. Pathog Glob Health. 2013;107(4):162–9.
Rautaraya B, Sharma S, Ali MH, et al. A 3½-year study of bacterial keratitis from Odisha, India. Asia Pac J Ophthalmol (Phila). 2014;3(3):146–50.
Ritterband DC, Shah M, Seedor J. Antibiotic prophylaxis in clear corneal cataract surgery. Arch Ophthalmol. 2003;121(2):296. author reply 296.
Robert PY, Adenis JP. Comparative review of topical ophthalmic antibacterial preparations. Drugs. 2001;61(2):175–85.
Ryan ET, Durand M. Ocular disease. In: Tropical infectious diseases: principles, pathogens and practice. Saunders Elsevier 2011. p. 991–1016.
Sharma R, Jhanji V, Satpathy G, et al. Coinfection with Acanthamoeba and Pseudomonas in contact lens-associated keratitis. Optom Vis Sci. 2013b;90(2):e53–5.
Sharma T, Kamath MM, Kamath MG, et al. Aqueous penetration of orally and topically administered moxifloxacin. Br J Ophthalmol. 2015;30.
Smith A, Pennefather PM, Kaye SB, Hart CA. Fluoroquinolones: place in ocular therapy. Drugs. 2001;61(6):747–61.
Snyder RW, Glasser DB. Antibiotic therapy for ocular infection. West J Med. 1994;161:579–84.
Sobolewska B, Doycheva D, Deuter C, et al. Treatment of ocular rosacea with once-daily low-dose doxycycline. Cornea. 2014;33(3):257–60.
Sridhar J, Kuriyan AE, Flynn Jr HW, et al. Endophthalmitis caused by Pseudomonas aeruginosa : clinical features, antibiotic susceptibilities, and treatment outcomes. Retina. 2015;35(6):1101–6.
Suemori S, Sawada A, Komori S, et al. Case of endogenous endophthalmitis caused by Streptococcus equisimilis. Clin Ophthalmol. 2010;4:917–8.
Tinley C, Van Zyl L, Grötte R. Poststreptococcal syndrome uveitis in South African children. Br J Ophthalmol. 2012;96(1):87–9.

Trichet E, Cohen-Bacrie S, Conrath J, et al. Nocardia transvalensis keratitis: an emerging pathology among travelers returning from Asia. BMC Infect Dis. 2011;11:296.
Vazirani J, Basu S. Role of topical, subconjunctival, intracameral, and irrigative antibiotics in cataract surgery. Curr Opin Ophthalmol. 2013;24(1):60–5.
Veldman P, Colby K. Current evidence for topical azithromycin 1% ophthalmic solution in the treatment of blepharitis and blepharitis-associated ocular dryness. Int Ophthalmol Clin. 2011;51(4):43–52.
Kos VN, Desjardins CA, Griggs A, Cerqueira G, Van Tonder A, et al. Comparative genomics of vancomycin-resistant staphylococcus aureus strains and their positions within the Clade Most Commonly Associated with Methicillin-Resistant S. aureus Hospital-Acquired Infection in the United States. mBio. 2012;3(3):e00112–12.
Wang L, Tsang H, Coroneo M. Treatment of recurrent corneal erosion syndrome using the combination of oral doxycycline and topical corticosteroid. Clin Experiment Ophthalmol. 2008;36(1): 8–12.
Williams L, Malhotra Y, Murante B, et al. A single-blinded randomized clinical trial comparing polymyxin B-trimethoprim and moxifloxacin for treatment of acute conjunctivitis in children. J Pediatr. 2013;162(4):857–61.
Abrishami M, Soheilian M, Farahi A, Dowlati Y. Successful treatment of ocular leishmaniasis. Eur J Dermatol. 2002;12(1):88–9.
Andersen SL, Oloo AJ, Gordon DM, Ragama OB, Aleman GM, Berman JD, Tang DB, Dunne MW, Shanks GD. Successful double-blinded, randomized, placebo-controlled field trial of azithromycin and doxycycline as prophylaxis for malaria in western Kenya. Clin Infect Dis. 1998;26(1): 146–50.
Ang M, Mehta JS, Mantoo S, Tan D. Deep anterior lamellar keratoplasty to treat microsporidial stromal keratitis. Cornea. 2009;28(7):832–5.
Antoniazzi E, Guagliano R, Meroni V, Pezzotta S, Bianchi PE. Ocular impairment of toxoplasmosis. Parassitologia. 2008;50(1–2):35–6.
Asproudis I, Koumpoulis I, Kalogeropoulos C, Sotiropoulos G, Papassava M, Aspiotis M. Case report of a neonate with ocular toxoplasmosis due to congenital infection: estimation of the percentage of ocular toxoplasmosis in Greece caused by congenital or acquired infection. Clin Ophthalmol. 2013;7:2249–52.
Baharivand N, Mahdavifard A, Fouladi RF. Intravitreal clindamycin plus dexamethasone versus classic oral therapy in toxoplasmic retinochoroiditis: a prospective randomized clinical trial. Int Ophthalmol. 2013;33(1):39–46.
Balaskas K, Vaudaux J, Boillat-Blanco N, Guex-Crosier Y. Azithromycin versus Sulfadiazine and Pyrimethamine for non-vision-threatening toxoplasmic retinochoroiditis: a pilot study. Med Sci Monit. 2012;18(5):CR296–302.
Bang S, Edell E, Eghrari AO, Gottsch JD. Treatment with voriconazole in 3 eyes with resistant Acanthamoeba keratitis. Am J Ophthalmol. 2010;149(1):66–9.
Barrett MP, Croft SL. Management of trypanosomiasis and leishmaniasis. Br Med Bull. 2012;104: 175–96.
Bentley R. Different roads to discovery; Prontosil (hence sulfa drugs) and penicillin (hence betalactams). J Ind Microbiol Biotechnol. 2009;36(6):775–86.
Bonfioli AA, Orefice F. Toxoplasmosis. Semin Ophthalmol. 2005;20(3):129–41.
Burri C, Brun R. Eflornithine for the treatment of human African trypanosomiasis. Parasitol Res. 2003;90(Supp 1):S49–52.
Butler NJ, Furtado JM, Winthrop KL, Smith JR. Ocular toxoplasmosis II: clinical features, pathology and management. Clin Experiment Ophthalmol. 2013;41(1):95–108.
Cabello-Vílchez AM, Martín-Navarro CM, López-Arencibia A, Reyes-Batlle M, Sifaoui I, Valladares B, Piñero JE, Lorenzo-Morales J. Voriconazole as a first-line treatment against potentially pathogenic Acanthamoeba strains from Peru. Parasitol Res. 2014;113:755–9.
Campos FA, Andrade GM, Lanna Ade P, Lage BF, Assumpção MV, Pinto JA. Incidence of congenital toxoplasmosis among infants born to HIV-coinfected mothers: case series and literature review. Braz J Infect Dis. 2014;18(6):609–17.

Cassaday JV, Bahler JW, Hinken MV. Spiramycin for toxoplasmosis. Am J Ophthalmol. 1964;57:227–35.
Chan CM, Theng JT, Li L, Tan DT. Microsporidial keratoconjunctivitis in healthy individuals: a case series. Ophthalmology. 2003;110(7):1420–5.
Corsi A, Nucci C, Knafelz D, Bulgarini D, Di Iorio L, Polito A, De Risi F, Ardenti Morini F, Paone FM. Ocular changes associated with Giardia lamblia infection in children. Br J Ophthalmol. 1998;82(1):59–62.
Coura JR, Borges-Pereira J. Chagas disease: 100 years after its discovery. A systemic review. Acta Trop. 2010;115(1–2):5–13.
Delair E, Latkany P, Noble AG, Rabiah P, McLeod R, Brézin A. Clinical manifestations of ocular toxoplasmosis. Ocul Immunol Inflamm. 2011;19(2):91–102.
de-la-Torre A, Stanford M, Curi A, Jaffe GJ, Gomez-Marin JE. Therapy for ocular toxoplasmosis. Ocul Immunol Inflamm. 2011;19(5):314–20.
Dias JCP, Coura JR, Yasuda MAS. The present situation, challenges, and perspectives regarding the production and utilization of effective drugs against human Chagas disease. Rev Soc Bras Med Trop. 2014;47(1):123–5.
Elmahallawy EK, Sampedro Martinez A, Rodriguez-Granger J, Hoyos-Mallecot Y, Agil A, Navarro Mari JM, Gutierrez FJ. Diagnosis of leishmaniasis. J Infect Dev Ctries. 2014;8(8):961–72.
Fuglsang H, Anderson J. A preliminary trial of nifurtimox in the treatment of onchocerciasis. Tropenmed Parasitol. 1978;29(3):335–8.
Garcia-Méric P, Franck J, Dumon H, Piarroux R. Management of congenital toxoplasmosis in France: current data. Presse Med. 2010;39(5):530–8.
Gaynor BD, Amza A, Kadri B, Nassirou B, Lawan O, Maman L, Stoller NE, Yu SN, Chin SA, West SK, Bailey RL, Rosenthal PJ, Keenan JD, Porco TC, Lietman TM. Impact of mass azithromycin distribution on malaria parasitemia during the low-transmission season in Niger: a cluster-randomized trial. Am J Trop Med Hyg. 2014;90(5):846–51.
Granados CE, Reveiz L, Uribe LG, Criollo CP. Drugs for treating giardiasis. Cochrane Database Syst Rev. 2012;12:CD007787. doi: 10.1002/14651858.CD007787.pub2.
Guldsten H. Clindamycin and sulphonamides in the treatment of ocular toxoplasmosis. Acta Ophthalmol (Copenh). 1983;61(1):51–7.
Harrell M, Carvounis PE. Current treatment of toxoplasma retinochoroiditis: an evidence-based review. J Ophthalmol. 2014;2014:273506.
Heby O, Persson L, Rentala M. Targeting the polyamine biosynthetic enzymes: a promising approach to therapy of African sleeping sickness, Chagas' disease, and leishmaniasis. Amino Acids. 2007;33(2):359–66.
Holland GN, Lewis KG. An update on current practices in the management of ocular toxoplasmosis. Am J Ophthalmol. 2002;134:102–14.
Hosseini SM, Abrishami M, Mehdi ZM. Intravitreal clindamycin in the treatment of unresponsive zone one toxoplasmic chorioretinitis: a case report. Iran Red Crescent Med J. 2014;16(11), e15428.
Jennings FW. Chemotherapy of trypanosomiasis: the potentiation of melarsoprol by concurrent difluoromethylornithine (DFMO) treatment. Trans R Soc Trop Med Hyg. 1988;82(4):572–3.
Jin KW, Jeon HS, Hyon JY, Wee WR, Suh W, Shin YJ. A case of fungal keratitis and onychomycosis simultaneously infected by Trichophyton species. BMC Ophthalmol. 2014;14:90.
Kaye A. Toxoplasmosis: diagnosis, treatment, and prevention in congenitally exposed infants. J Pediatr Health Care. 2011;25(6):355–64.
Khadem F, Uzonna JE. Immunity to visceral leishmaniasis: implications for immunotherapy. Future Microbiol. 2014;9(7):901–15.
Khalil EA, Musa AM, Younis BM, Elfaki ME, Zijlstra EE, Elhassan AM. Blindness following visceral leishmaniasis: a neglected post-kala-azar complication. Trop Doct. 2011;41(3):139–40.
Khandelwal SS, Woodward MA, Hall T, Grossniklaus HE, Stulting RD. Treatment of microsporidia keratitis with topical voriconazole monotherapy. Arch Ophthalmol. 2011;129(4):509–10.

Khyatti M, Trimbitas RD, Zouheir Y, Benani A, El Messaoudi MD, Hemminki K. Infectious diseases in North Africa and North African immigrants to Europe. Eur J Public Health. 2014;24 Suppl 1:47–56.

Kowalski RP, Abdel Aziz S, Romanowski EG, Shanks RM, Nau AC, Raju LV. Development of a practical complete-kill assay to evaluate anti-Acanthamoeba drugs. JAMA Ophthalmol. 2013;131(11):1459–62.

Kulakova L, Galkin A, Chen CZ, Southall N, Marugan JJ, Zheng W, Herzberg O. Discovery of novel antigiardiasis drug candidates. Antimicrob Agents Chemother. 2014;58(12):7303–11.

Lal A, Baker MG, Hales S, French NP. Potential effects of global environmental changes on cryptosporidiosis and giardiasis transmission. Trends Parasitol. 2013;29(2):83–90.

Le Loup G, Pialoux G, Lescure FX. Update in treatment of Chagas disease. Curr Opin Infect Dis. 2011;24(5):428–34.

Lima e Silva R, Saishin Y, Saishin Y, Akiyama H, Kachi S, Aslam S, Rogers B, Deering T, Gong YY, Hackett SF, Lai H, Frydman BJ, Valasinas A, Marton LJ, Campochiaro PA. Suppression and regression of choroidal neovascularization by polyamine analogues. Invest Ophthalmol Vis Sci. 2005;46(9):3323–30.

Lin HC, Hsiao CH, Ma DH, Yeh LK, Tan HY, Lin MY, Huang SC. Medical treatment for combined Fusarium and Acanthamoeba keratitis. Acta Ophthalmol. 2009;87(2):199–203.

Loh RS, Chan CM, Ti SE, Lim L, Chan KS, Tan DT. Emerging prevalence of microsporidial keratitis in Singapore: epidemiology, clinical features, and management. Ophthalmology. 2009; 116(12):2348–53.

Maenz M, Schlüter D, Liesenfeld O, Schares G, Gross U, Pleyer U. Ocular toxoplasmosis past, present and new aspects of an old disease. Prog Retin Eye Res. 2014;39:77–106.

Mahajan R, Das P, Isaakidis P, Sunyoto T, Sagili KD, Lima MA, Mitra G, Kumar D, Pandey K, Van Geertruyden JP, Boelaert M, Burza S. Combination Treatment for Visceral Leishmaniasis Patients Coinfected with Human Immunodeficiency Virus in India. Clin Infect Dis. 2015;61(8):1255–62. doi: 10.1093/cid/civ530. Epub 2015 Jun 30.

Manyando C, Njunju EM, D'Alessandro U, Van Geertruyden JP. Safety and efficacy of co-trimoxazole for treatment and prevention of Plasmodium falciparum malaria: a systematic review. PLoS One. 2013;8(2), e56916.

Martín-Navarro CM, López-Arencibia A, Arnalich-Montiel F, Valladares B, Piñero JE, Lorenzo-Morales J. Evaluation of the in vitro activity of commercially available moxifloxacin and voriconazole eye-drops against clinical strains of Acanthamoeba. Graefes Arch Clin Exp Ophthalmol. 2013;251(9):2111–7.

Maude RJ, Ahmed BU, Rahman AH, Rahman R, Majumder MI, Menezes DB, Abu Sayeed A, Hughes L, MacGillivray TJ, Borooah S, Dhillon B, Dondorp AM, Faiz MA. Retinal changes in visceral leishmaniasis by retinal photography. BMC Infect Dis. 2014;14:527.

Medeiros FPM. Current situation and new perspectives for the treatment of Chagas disease. Prospects for production and distribution of benznidazole. Rev Soc Bras Med Trop. 2009;42(Supl II):79.

Meltzer E, Lachish T, Schwartz E. Treatment of giardiasis after nonresponse to nitroimidazole. Emerg Infect Dis. 2014;20(10):1742–4.

Mochizuki K, Niwa Y, Ishida K, Kawakami H. Intraocular penetration of itraconazole in patient with fungal endophthalmitis. Int Ophthalmol. 2013;33(5):579–81.

Molina I, Gómez i Prat J, Salvador F, Treviño B, Sulleiro E, Serre N, Pou D, Roure S, Cabezos J, Valerio L, Blanco-Grau A, Sánchez-Montalvá A, Vidal X, Pahissa A. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. N Engl J Med. 2014;370(20): 1899–908.

Montero JA, Ruiz-Moreno JM, Sanchis E. Intraretinal hemorrhage associated with leishmaniasis. Ophthalmic Surg Lasers Imaging. 2003;34(3):212–4.

Mørch K, Hanevik K, Robertson LJ, Strand EA, Langeland N. Treatment-ladder and genetic characterisation of parasites in refractory giardiasis after an outbreak in Norway. J Infect. 2008;56(4):268–73.

Noble A. Cataracts in congenital toxoplasmosis. J AAPOS. 2007;11:551–4.
Opremcak EM, Scales DK, Sharpe MR. Trimethoprim-sulfamethoxazole therapy for ocular toxoplasmosis. Ophthalmology. 1992;99(6):920–5.
Osadchy A, Ratnapalan T, Koren G. Ocular toxicity in children exposed in utero to antimalarial drugs: review of the literature. J Rheumatol. 2011;38(12):2504–8.
Paquet C. Yudin MH; Toxoplasmosis in pregnancy: prevention, screening, and treatment. Society of Obstetricians and Gynaecologists of Canada. J Obstet Gynaecol Can. 2013;35(1):78–81.
Parchand S, Gupta A, Ram J, Gupta N, Chakrabarty A. Voriconazole for fungal corneal ulcers. Ophthalmology. 2012;119(5):1083.
Park YH, Nam HW. Clinical features and treatment of ocular toxoplasmosis. Korean J Parasitol. 2013;51(4):393–9.
Pasupuleti V, Escobedo AA, Deshpande A, Thota P, Roman Y, Hernandez AV. Efficacy of 5-nitroimidazoles for the treatment of giardiasis: a systematic review of randomized controlled trials. PLoS Negl Trop Dis. 2014;8(3), e2733.
Patole S, Burza S, Varghese GM. Multiple relapses of visceral leishmaniasis in a patient with HIV in India: a treatment challenge. Int J Infect Dis. 2014;25:204–6.
Pfaff AW, de-la-Torre A, Rochet E, Brunet J, Sabou M, Sauer A, Bourcier T, Gomez-Marin JE, Candolfi E. New clinical and experimental insights into Old World and neotropical ocular toxoplasmosis. Int J Parasitol. 2014;44(2):99–107.
Pinazo MJ, Espinosa G, Gállego M, et al. Successful treatment with posaconazole of a patient with chronic Chagas disease and systemic lupus erythematosus. Am J Trop Med Hyg. 2010;82:583–7.
Pleyer U, Schlüter D, Mänz M. Ocular toxoplasmosis: recent aspects of pathophysiology and clinical implications. Ophthalmic Res. 2014;52(3):116–23.
Priotto G, Kasparian S, Mutombo W, Ngouama D, Ghorashian S, Arnold U, Ghabri S, Baudin E, Buard V, Kazadi-Kyanza S, Ilunga M, Mutangala W, Pohlig G, Schmid C, Karunakara U, Torreele E, Kande V. Nifurtimox-eflornithine combination therapy for second-stage African Trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. Lancet. 2009;374(9683):56–64.
Rodgers J, Jones A, Gibaud S, Bradley B, McCabe C, Barrett MP, Gettinby G, Kennedy PG. Melarsoprol cyclodextrin inclusion complexes as promising oral candidates for the treatment of human African trypanosomiasis. PLoS Negl Trop Dis. 2011;5(9), e1308.
Roizenblatt J. Interstitial keratitis caused by American (mucocutaneous) leishmaniasis. Am J Ophthalmol. 1979;87(2):175–9.
Rossi P, Urbani C, Donelli G, Pozio E. Resolution of microsporidial sinusitis and keratoconjunctivitis by itraconazole treatment. Am J Ophthalmol. 1999;127(2):210–2.
Sadeghian G, Nilfroushzadeh MA, Moradi SH, Hanjani SH. Ocular leishmaniasis: a case report. Dermatol Online J. 2005;11(2):19.
Santamaria C, Chatelain E, Jackson Y, Miao Q, Ward BJ, Chappuis F, Ndao M. Serum biomarkers predictive of cure in Chagas disease patients after nifurtimox treatment. BMC Infect Dis. 2014;14:302.
Shea B. Folic acid or folinic acid for reducing side effects of methotrexate for people with rheumatoid arthritis. J Evid Based Med. 2013;6(3):202–3.
Sindermann H, Engel J. Development of miltefosine as an oral treatment for leishmaniasis. Trans R Soc Trop Med Hyg. 2006;100 Suppl 1:S17–20.
Soheilian M, Ramezani A, Azimzadeh A, et al. Randomized trial of intravitreal clindamycin and dexamethasone versus pyrimethamine, sulfadiazine, and prednisolone in treatment of ocular toxoplasmosis. Ophthalmology. 2011;118(1):134–41.
Sridhar MS, Sharma S. Microsporidial keratoconjunctivitis in a HIV-seronegative patient treated with debridement and oral itraconazole. Am J Ophthalmol. 2003;136(4):745–6.
Stover KR, Riche DM, Gandy CL, Henderson H. What would we do without metronidazole? Am J Med Sci. 2012;343(4):316–9.

Sunada A, Kimura K, Nishi I, Toyokawa M, Ueda A, Sakata T, Suzuki T, Inoue Y, Ohashi Y, Asari S, Iwatani Y. In vitro evaluations of topical agents to treat Acanthamoeba keratitis. Ophthalmology. 2014;121(10):2059–65.

Sundar S, Chakravarty J, Agarwal D, Rai M, Murray HW. Single-dose liposomal amphotericin B for visceral leishmaniasis in India. N Engl J Med. 2010;362(6):504–12.

Sundar S, Chakravarty J. An update on pharmacotherapy for leishmaniasis. Expert Opin Pharmacother. 2015;16(2):237–52.

Sundar S, Sinha PK, Rai M, Verma DK, Nawin K, Alam S, Chakravarty J, Vaillant M, Verma N, Pandey K, Kumari P, Lal CS, Arora R, Sharma B, Ellis S, Strub-Wourgaft N, Balasegaram M, Olliaro P, Das P, Modabber F. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. Lancet. 2011;377(9764):477–86.

Tate Jr GW, Martin RG. Clindamycin in the treatment of human ocular toxoplasmosis. Can J Ophthalmol. 1977;12(3):188–95.

Taylor WR, Richie TL, Fryauff DJ, Picarima H, Ohrt C, Tang D, Braitman D, Murphy GS, Widjaja H, Tjitra E, Ganjar A, Jones TR, Basri H, Berman J. Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia. Clin Infect Dis. 1999;28(1): 74–81.

Tu EY, Joslin CE, Shoff ME. Successful treatment of chronic stromal acanthamoeba keratitis with oral voriconazole monotherapy. Cornea. 2010;29(9):1066–8.

Turnbull AM, Lin Z, Matthews BN. Severe bilateral anterior uveitis secondary to giardiasis, initially misdiagnosed as a side effect of metronidazole. Eye (Lond). 2013;27(10):1225–6.

Vedula SS, Nguyen QD. Corticosteroids for ocular toxoplasmosis. Cochrane Database Syst Rev. 2008;4:CD007417.

Walochnik J, Obwaller A, Gruber F, Mildner M, Tschachler E, Suchomel M, Duchêne M, Auer H. Anti-acanthamoeba efficacy and toxicity of miltefosine in an organotypic skin equivalent. J Antimicrob Chemother. 2009;64(3):539–45.

Winterhalter S, Severing K, Stammen J, Maier AK, Godehardt E, Joussen AM. Does atovaquone prolong the disease-free interval of toxoplasmic retinochoroiditis? Graefes Arch Clin Exp Ophthalmol. 2010;248(8):1187–92.

Wolf A, Boulliat C, Coillot C, Rouault M, Gaillard K, Beranger C, Oliver M. Nifurtimox, a bright future for treatment of Chagas disease. Med Trop (Mars). 2011;71(2):131–3.

Yaghoobi R, Maraghi S, Bagherani N, Rafiei A. Cutaneous leishmaniasis of the lid: a report of nine cases. Korean J Ophthalmol. 2010;24(1):40–3.

Yazici A, Ozdal PC, Taskintuna I, Kavuncu S, Koklu G. Trimethoprim/Sulfamethoxazole and azithromycin combination therapy for ocular toxoplasmosis. Ocul Immunol Inflamm. 2009;17(4):289–91.

Yusuf IH, Sahare P, Hildebrand GD. DRESS syndrome in a child treated for toxoplasma retinochoroiditis. J AAPOS. 2013;17(5):521–3.