

# Ocular side effects of systemic drugs

## Part 5 – Antimicrobial agents

This series of articles on ocular side effects of drugs considers all the major classes of drugs sequentially, system by system. The first four articles concentrated on cardiovascular drugs. This article covers infections by various microbes, their treatment and the ocular complications of these treatments.

Several types of bacteria and viruses live on and in our bodies, particularly on the skin and mucous membranes (e.g. the respiratory passages and the lining of the gut) without causing any adverse effects. In fact, the commensal bacteria in the ileum are of benefit in helping prevent virulent organisms from flourishing and digest extrinsic matter.

Some of these microorganisms, including bacteria, viruses, fungi, chlamydiae and protozoa, may cause diseases in man (Figures 1 and 2). These infections have very diverse clinical features, and can be life-

threatening. Infections of the eyes are familiar to optometrists, particularly the very common acute infective conjunctivitis. The latter, although usually minor, can be caused by a variety of organisms, most commonly adenoviruses or streptococci (haemophilus in children).

Microorganisms which cause disease are usually parasites, but can occasionally live as saprophytes or commensals. There are several groups of microorganisms which can cause disease. Bacteria and viruses are the most widely known; bacteria can be sub-divided into gram positive and gram negative bacteria according to how they stain with the gram stain, a dye used to make them viewable with a light microscope.

The much smaller organisms called viruses are only visible under the electron microscope. They consist of a core of nucleic acid (either DNA or RNA) surrounded by protein; they are classified into DNA and RNA viruses, according to which nucleic acid they contain. Further subdivision depends on their morphology or

the diseases caused by them, e.g. rhinoviruses cause colds; picornaviruses are minute RNA viruses (PICO + RNA + VIRUS). Viruses cannot exist independently, but can only live and replicate within living cells of the host. Protozoa are unicellular organisms which are notorious for causing disease in the tropics. Plasmodium species (see later) cause malaria, which results in thousands of deaths and millions of lost man hours every year. Malaria is transmitted by the female Anopheles mosquito (the Culex mosquito is the insect vector for the transmission of yellow fever). Sleeping sickness is caused by another protozoan, Trypanosoma species, which is transmitted by the tsetse-fly.

Worms can also cause disease, e.g. Filariasis caused by Wuchereria bancrofti, and of relevance to the optometrist, Onchocerca volvulus, which leads to so-called 'river blindness' (onchocerciasis) in North Africa.

In 1941, penicillin was used to treat bacterial infections for the first time. An antibiotic is defined as a substance produced by one living organism, which is harmful or lethal to another (micro) organism. The term antimicrobial agent has a broader meaning and includes synthetic drugs, e.g. sulphonamides as well as anti-protozoal agents such as suramin.

There are several groups of 'antibiotics' and classification by their mechanisms of action is the most useful. This is presented below:

- Agents which attack the bacterial cell wall, e.g. **penicillins**, **cephalosporins**, **bacitracin** (CICATRIN), **miconazole** (DAKTARIN)
- Agents which affect cell membrane permeability, e.g. **polymyxin** (NEOSPORIN, OTOSPORIN), **nystatin** (NYSTAN, TRI-ADCORTYL)
- Antimetabolites which inactivate specific enzymes of metabolism, e.g. **trimethoprim** (MONOTRIM), **sulphonamides**. These two

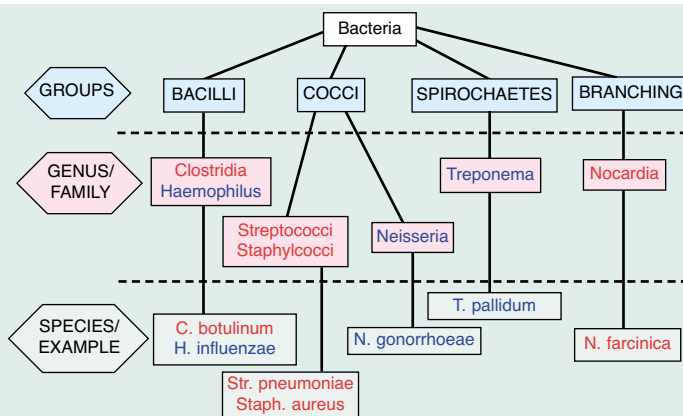


Figure 1  
Brief classification of bacteria showing just a few examples; the organisms named in red are gram-positive, and those in blue, gram-negative

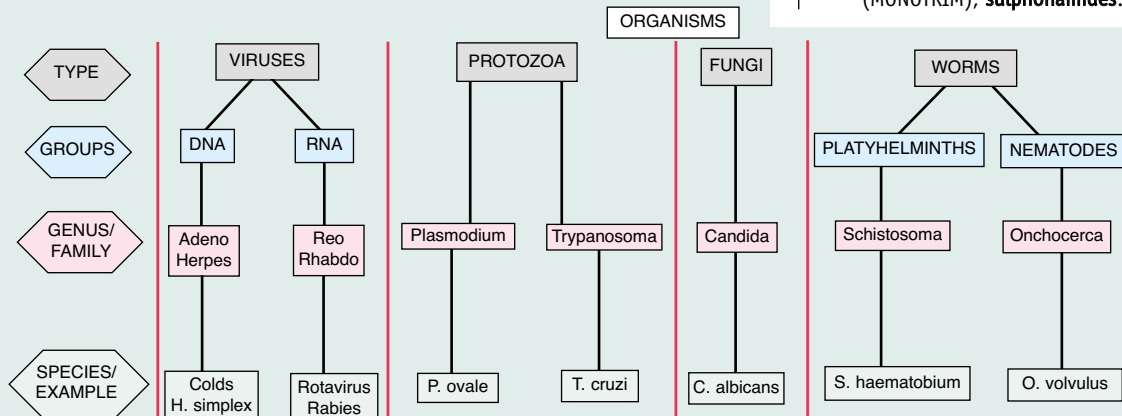


Figure 2  
Brief classification of pathogenic organisms other than bacteria; this diagram is not a comprehensive representation of parasitology, but rather attempts to illustrate the basic principles involved

types of antimicrobial drugs inhibit two sequential stages in the metabolism of folate in bacteria

- Nucleic acid analogues, e.g. **vidarabine**, **acyclovir** (ZOVIRAX)
- Inhibitors of protein synthesis, e.g. **chloramphenicol** (CHLOROMYCETIN), **tetracycline** (ACHROMYCIN)
- Agents which bind the 30 S ribosomal subunit and alter protein synthesis by causing a misreading of the genetic code, e.g. aminoglycosides
- Agents which affect nucleic acid metabolism, e.g. **rifampicin** (RIFADIN)
- Other enzyme inhibitors e.g. **ciprofloxacin** and **ofloxacin** inhibit gyrase

The number of different strains of microorganisms is immense and certain individual antibiotics are more effective against a particular organism than others, e.g. **chloramphenicol** (CHLOROMYCETIN) is the drug of first choice in *Haemophilus influenzae* meningitis, and the drug of second choice in meningitis caused by this organism is **amoxycillin** (AMOXIL). In identifying the best drug for a particular situation, efficacy against the particular pathogenic organism, penetration of the drug into the relevant tissue, lack of toxicity in effective dosages and other factors need to be taken into consideration.

Optimal selection of antimicrobial agents for the therapy of infectious diseases is a complex procedure which requires sound clinical judgement and detailed knowledge of pharmacological and microbiological factors (these are outlined later).

When a patient presents to a medical practitioner with an infection, a specimen of tissue (or biological media, e.g. sputum, urine, etc) is taken before commencing a broad spectrum antibiotic to cover a wide range of possible causative bacteria. This is called empirical antibiotic therapy. When the actual bacterium responsible has been identified by the laboratory, the best antibiotic against that organism is substituted. This later specific therapy is called definitive antimicrobial therapy.

Extensive use of antibiotics has resulted in the development of resistant strains of microorganisms. For instance, some decades ago, **penicillin G** (benzylpenicillin) was very effective against *Staphylococcus aureus*. But various biological processes, including translocation, conjugation and transduction, have led to development of strains of *S. aureus*, which can produce penicillinase, an enzyme which destroys penicillin G. Penicillins resistant to penicillinase-producing bacteria were developed following the above development, e.g. **flucloxacillin** (FLOXAPEN), **temocillin** (TEMOPEN). However, in this 'resistance race', bacteria are always one step ahead of available antibiotics, and the development of better antibiotics will continue into the foreseeable future.

**Clavulanic acid** is a 'suicide' inhibitor of beta-lactamase produced by a wide range of gram positive and gram negative organisms. It is an example of a molecule which can bind to beta-lactamases and inactivate them, thus preventing the destruction of beta-lactam antibiotics which are substrates for these enzymes. It is called a 'suicide' drug because it is inactivated during its action. Clavulanic acid has been combined with **amoxycillin** as an oral preparation (AUGMENTIN). Amoxycillin plus clavulanate is effective in vitro and in vivo for beta-lactamase-producing strains of *Staphylococci*, *H. influenzae*, *gonnococci*, and *E. coli*<sup>1</sup>.

### Choosing an optimal antimicrobial agent

Three factors need to be taken into consideration when choosing the optimal antimicrobial agent – action required, pharmacokinetic factors and host factors.

#### 1. Action required

Bactericidal drugs kill the organism, while bacteriostatic ones only inhibit their growth. It is not advisable to combine a bactericidal drug with a bacteriostatic one as this results in a greatly reduced efficacy.

#### 2. Pharmacokinetic factors

The Minimum Inhibitory Concentration (MIC) of an antibiotic is the smallest strength of drug which will prevent replication or cause death of organisms. The MIC, and preferably multiples of it, must be achieved at the site of infection for effective eradication of an infection. This is determined by the characteristics of absorption, distribution, metabolism and excretion of the drug. The route of administration, oral, parenteral, nasal, rectal or sublingual, is also important.

#### 3. Host Factors

- a) The state of the immune system of the patient can affect efficacy of an antimicrobial agent. Reduced immunity, as in Acquired Immune Deficiency Syndrome (AIDS) decreases the effectiveness of certain antibiotics. Pus, which consists of phagocytes, protein, debris and fibrin, has a tendency to bind aminoglycosides (e.g. **streptomycin**), resulting in reduced antimicrobial activity<sup>2</sup>.
- b) Age and general health: Hepatic metabolism and renal excretion of drugs is poorly developed in the newborn. A similar situation exists in elderly patients, and in patients with compromised hepatic or renal function. For the latter, a quick look at the blood urea levels will prevent inappropriate choice of drug. Tetracyclines should not be used in young children as they bind to developing teeth and bones, and can cause retardation of bone growth and staining of tooth enamel.
- c) Pregnancy: Administration of streptomycin to pregnant women has been associated

with hearing loss in the offspring. The lactating mother may pass antibiotics to her breast-fed child.

- d) Drug allergy: Allergic reactions to penicillin are well known. This drug should not be administered in susceptible patients, and any physician prescribing penicillin always asks if the patient has taken it before and if any allergic reaction occurred in the past.
- e) Genetic factors: Patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency develop haemolysis if certain drugs (including **chloramphenicol**) are administered. This is of relevance to the optometrist in that these patients may also have congenital cataract.

### Ocular side effects

The use of antibiotics is extremely widespread in terms of the actual numbers of prescriptions for these drugs being written (sometimes indiscriminately) by general practitioners. Considering this fact, the frequency of reports of ocular toxicity is relatively small. However, the actual number of side effects reported is still very large, and it is important to interpret reports or published letters in perspective.

#### Penicillins

Certain individuals have an intrinsic propensity to developing a severe allergic reaction to penicillin. This takes the form of swelling of the eyelids and conjunctiva occurring as part of a general reaction or more localised angioneurotic oedema<sup>3</sup>. This condition, also known as anaphylactic shock in its severe form, is life-threatening due to the possibility of cardiovascular collapse or laryngeal oedema (obstructing the airway). It is due to a Type I or immediate-type hypersensitivity reaction mediated by the release of chemical substances from mast cells activated by IgE. Parenteral hydrocortisone or adrenaline may be necessary to prevent severe shock or even death. Doctors always ask about past allergy to penicillin before prescribing a drug of this class.

Erythema multiforme or the more severe Stevens-Johnson syndrome is a severe Type III dermatological reaction to certain drugs, most commonly antibiotics<sup>4</sup>. In the eyes, an exudative conjunctivitis and keratitis may be followed by conjunctival shrinkage and the dry eye syndrome. Stevens-Johnson syndrome due to **amoxycillin** (AMOXIL) has been reported by Davidson and Windebank<sup>2</sup> among others.

Penicillins also occasionally cause a dose related neurotoxicity consisting of convulsions, respiratory embarrassment (due to suppression of the medullary respiratory centre), cranial nerve toxicity and neuromuscular blockade<sup>6</sup>. In the eyes, these effects may manifest themselves as optic neuritis, drug-induced myopia or strabismus due to blockade of terminals of oculomotor, trochlear or abducent nerves.

## Quinolones

This newer group includes **ciprofloxacin** (CIPROXIN), **ofloxacin** (EXOCIN) and **levofloxacin** (TAVANIC). The drugs are indicated in a variety of systemic infections including urinary tract infections (UTI), certain types of pneumonia and sinusitis.

Very recently, it was shown<sup>7</sup> that levofloxacin, when given orally, penetrates the vitreous posteriorly. The study was performed to elucidate the possible efficacy of the drug in intraocular infections, but it has implications on the possibility of ocular side effects when used systemically.

## Tetracyclines

This small group of antibiotics includes **tetracycline** (ACHROMYCIN), **minocycline** (MINOCIN) and **oxytetracycline** (OXYTET). They inhibit bacterial protein synthesis. They are particularly useful in the long-term treatment of rosacea and acne vulgaris, but are also used in other infectious conditions, notably urinary tract infections (UTI).

Pseudotumor cerebri, presenting with headaches and bilateral visual loss secondary to papilloedema was recently reported associated with combination therapy with **tetracycline** and **isotretinoin** (ROACCUTANE) for acne<sup>8</sup> and has also been reported with tetracyclines alone.

Lee's<sup>8</sup> report was regarding a 14-year old white male diagnosed with acne by a dermatologist. The patient was at one time treated with isotretinoin 40mg per day and tetracycline 500mg per day. Over three weeks, the patient noticed decreased visual function in both eyes. All other findings were negative at this stage. Later, visual field testing revealed an inferonasal defect in the right eye, and a superior paracentral defect in the left eye. Lumbar puncture showed increased intracranial pressure (ICP) and the patient underwent optic nerve sheath decompression of the left eye, followed one month later by optic nerve sheath decompression of the right eye. Patients on one of the tetracyclines who experience symptoms of blurred vision, headache, nausea and vomiting, diplopia or transient visual loss should be promptly referred.

It has already been mentioned that tetracycline can lead to discolouration of growing bones and teeth. Pigmentation of various body sites including skin, nails, bone, mouth and eyes secondary to minocycline therapy has been reviewed recently<sup>9</sup>. They found that pigmentation of the skin and oral mucosa is reversible on withdrawal of the drug; however, although eye pigmentation is less common, it is usually irreversible. Scleral pigmentation (specifically) consisting of a blue-grey 3-5mm band starting at the limbus due to this drug has also been reported<sup>10</sup>.

Staining of developing bones, teeth, nails and thyroid associated with tetracycline therapy is well known. In these tissues, the chelation of tetracycline is with calcium

orthophosphate. The volume of distribution of the tetracyclines is comparatively larger than that of body water, encouraging sequestration of the drug in some tissues. Crystalline deposits probably of a metabolite of tetracycline, have also been observed in the conjunctiva in patients on long-term therapy for acne. This highly interesting ocular side effect of tetracycline is probably seen very rarely. The efficacy of tetracycline in acne is believed to be via a decrease in the fatty acid content of sebum. The question arises as to whether there is any effect of prolonged therapy with this drug on the lipid layer of the tear film produced by the secretion of the meibomian glands.

## Cephalosporins

This is a large group of antibiotics with the same mechanism of action as the penicillins, namely inhibition of bacterial cell wall formation (**Table 1**). This effect leads to entry of water into the bacterial cell by osmosis resulting in rupture of the bacterium.

**Cephaloridine** administered systemically has been associated with hallucinations and nystagmus<sup>6</sup>.

**Cefoxitin sodium** (MEFOXIN) is a semisynthetic derivative of cephamycin c and is resistant to breakdown by beta-lactamases (see above). It is indicated for the therapy of various aerobic and anaerobic bacterial infections. Exfoliative dermatitis associated with the use of cefoxitin was reported by Kannangara et al<sup>11</sup>. As with penicillin, this can affect the eyes and the periorbital skin. This was in an 84-year old man who received **cefoxitin** at a dosage of 1.0g intramuscularly (IM) every six hours for osteomyelitis (infection of bone) of the calcaneum.

Generic name	Trade name
cefaclor	DISTACLOR
cefodizime	TIMECEF
cefotaxime	CLAFORAN
cephalexin	KEFLEX
cefoxitin	MEFOXIN
cefuroxime	ZINACEF

Table 1: Examples of cephalosporins

## Chloroquine

**Chloroquine** (NIVAQUINE) is an antimalarial drug which attacks the asexual erythrocytic forms of the malaria parasite or plasmodium, i.e. it is a schizonticide. The mechanism of this effect is unknown, but the latest theory is that it acts by converting haem in Plasmodium to a toxic product by inhibiting its binding to a histidine-rich protein<sup>12</sup> (plasmodium is a unicellular protozoan). There are four species of Plasmodium, namely *P. vivax*, *P. malariae*, *P. ovale* and *P. falciparum*, each causing a different type of malaria. Chloroquine prolongs remissions between *P. vivax* attacks

and is effective against sensitive strains of *P. falciparum*.

Chloroquine is also used to treat rheumatoid arthritis and discoid lupus erythematosus, in these cases in much higher doses, and it is in this capacity that it may (although rarely) lead to retinopathy or maculopathy. Excretion of chloroquine is slow and the drug becomes concentrated in the choroid and RPE.

Before commencing long-term therapy with chloroquine, a baseline eye examination including VA, visual fields, ophthalmoscopy and colour vision appraisal, should be carried

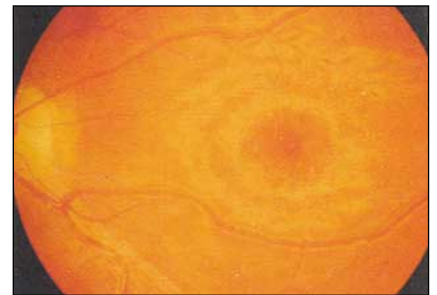


Figure 3 Bull's eye retinopathy occurring as a side effect of chloroquine therapy

out. Six-monthly monitoring is recommended thereafter, in order to screen for asymptomatic premaculopathy.

Later, loss of the foveolar reflex and pigment stippling of the RPE may occur. Blurred vision may also be reported. Chloroquine retinotoxicity is popularly known to cause bull's eye maculopathy (**Figure 3**). This consists of a central bright red circular area, surrounded by a concentric lighter, circular region which, in turn, is surrounded by a further bright hyperpigmented area.

Chloroquine can also lead to corneal deposits similar to those occurring with amiodarone, an antiarrhythmic agent<sup>13</sup>. In contrast to chloroquine retinopathy, this is not related to dosage or duration of treatment. It appears that the drug itself is deposited in the cornea, and severe deposition may lead to reduced vision or haloes.

## Suramin

This drug is useful in the treatment of trypanosomiasis (sleeping sickness), and is also currently being investigated for the treatment of various neoplasms. It can lead to many different adverse effects which vary in intensity and frequency with the nutritional status of the patient, and reactions are more severe in malnourished patients. The adverse effects of suramin on the visual mechanism may be related to an inhibition of the coupling of rhodopsin to transducin (the latter is a so-called G-protein, which is an important intermediary in the cascade reaction which multiplies the initial bleaching of the chromophore into millions of molecules of the

final product; bleaching involves the conversion of the 11-cis condition in the dark to the trans-condition by the action of photons<sup>14</sup>.

A vortex keratopathy similar to that seen with **chloroquine**, **amiodarone** (CORDARONE X) and **procaïnamide** (PRONESTYL), may also be seen<sup>15</sup>.

## Tryparsamide

This drug is also used in trypanosomiasis. Ocular side effects of **tryparsamide** are more severe and common than other side effects. Constriction of the visual fields followed by decreased vision, may progress to optic neuritis resulting in blindness if therapy is not discontinued early. 'Shimmering' or 'dazzling' of vision occurs in nearly 10% of patients taking tryparsamide.

**Metronidazole** (FLAGYL) is used to treat amoebiasis and giardiasis, other protozoal infections. One patient has been reported to experience oculogyric crises while taking this drug<sup>16</sup>.

## Anti-tuberculous drugs

**Streptomycin** is used in the therapy of several conditions, particularly tuberculosis (where two or more drugs to which the organism is sensitive should be used, to prevent development of resistance) and bacterial endocarditis. Goode et al<sup>17</sup> have studied the abolition of the vestibuloocular reflex (VOR) by streptomycin in chicks, in whom it is reversible (it is not in man). Streptomycin is reputed to be toxic to the hair cells in the vestibule. **Ethambutol** (MYAMBUTOL) is active against *Mycobacterium tuberculosis*. Numerous adverse ocular effects due to ethambutol have been reported, most being reversible. However, some irreversible effects have also been described, e.g. chiasmal demyelination.

In view of the association with optic neuritis, patients on ethambutol should be instructed on home testing of visual acuity and colour vision. If dosage exceeds 15mg/kg/day, screening of the patient every two to four weeks is recommended<sup>18</sup>.

**Isoniazid** (RIMIFON) is another drug used to treat tuberculosis. It often leads to optic neuritis<sup>19</sup> but this can be prevented by daily administration of pyridoxine, a B group vitamin. The drug has also rarely been reported to lead to production of antinuclear antibodies but very few patients develop systemic lupus erythematosus (SLE), and even fewer have ocular involvement.

Secretion of **rifampicin** (RIFADIN, RIMACTANE) or its metabolite in tears has been reported to cause orange discolouration of contact lenses<sup>20</sup>.

## Conclusion

Although certain drugs are obviously required more often in certain parts of the world, the use of antimicrobial agents is extremely widespread throughout the world. In

developed countries, antibiotics and other antibacterial agents are very commonly used; these are also used frequently in those third world countries which can afford them, but in these countries, the antiprotozoal agents and antihelminthic drugs also constitute a large proportion of drugs used. What is more, in these regions, many of these drugs are freely available to the general public without prescription.

As a result, ocular effects reported from antimicrobial drug use are numerous. For the optometrist, it will be good practice to understand the more severe side-effects described above and their early detection so that the patient can be referred before serious consequences ensue, and secondly to help this process by looking into the more interesting but perhaps less serious side effects (such as the deposition of tetracycline in the tissues of the eye) simply as an interesting clinical exercise.

With reference to general medical practitioners reading this article, it is hoped that the scale of the problem not only of ocular, but perhaps even more so of systemic side effects of antimicrobial agents, would make him/her reconsider their prescribing policies for infectious diseases. It should be reiterated here that before prescribing any drug, a doctor should, as a matter of routine, balance the possibility of side-effects against the potential consequences of the malady, if it were to be left untreated.

With the 1980s advent of AIDS, which attacks the very cells involved in cell-mediated immunity (T lymphocytes), and other generally untreatable infections like Lassa fever (which is rife in Nigeria), the need for antimicrobial agents will continue to increase and, consequently, the incidence of ocular and other side effects is also likely to rise. A reappraisal of prescribing practices is warranted to reduce the above, and to minimise the progressive emergence of resistant microorganisms.

## About the author

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