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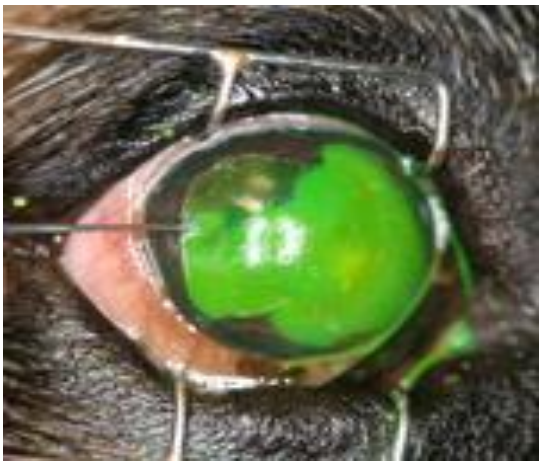
Ophthalmology Case Challenges Mini Series

Session 1: Conjunctivitis and Keratitis: Case Presentations

David Gould BSc (Hons), BVM&S, PhD, DVOphthal, DipECVO, MRCVS

RCVS and European Specialist in Veterinary Ophthalmology



David Gould BSc (Hons), BVM&S, PhD, DVOphthal, DipECVO, MRCVS
RCVS and European Specialist in Veterinary Ophthalmology
Davies Veterinary Specialists
Manor Farm Business Park
Higham Gobion
Hertfordshire SG5 3HR
Tel: 01582 883 950
djg@vetspecialists.co.uk

Feline conjunctivitis

In contrast to dogs, conjunctivitis in cats is usually primary infectious in aetiology. The two most common infectious causes are *Chlamydophila felis* and Feline Herpes Virus 1 (FHV-1). Other agents implicated in primary infectious feline conjunctivitis include *Mycoplasma* spp and calicivirus.

Other reported bacterial conjunctival isolates (which may be pathological or may represent secondary invaders) include *Staphylococcus* spp, *Streptococcus* spp, *Corynebacterium* spp and *Pseudomonas* spp. As with dogs, it should be remembered that the presence of bacterial is not necessarily pathological; bacteria can be cultured from the conjunctival sac of 4%-67% normal cats. Of these, the majority are Gram positive.

Chlamydophila felis or FHV-1?

Both these agents can cause unilateral or bilateral conjunctivitis and acute, chronic or recurrent disease. They usually, but not always, affect young or adolescent cats. They can be difficult to distinguish clinically, but a few pointers are:

- Chlamydophila usually causes conjunctivitis in the absence of any systemic signs, and the patient is usually otherwise bright and well

- FHV-1 usually causes conjunctivitis in association with upper respiratory tract signs, at least during primary infection. If a cat is sneezing, it is twice as likely to be infected with FHV-1 than *C. felis*

- FHV-1 causes keratitis (corneal ulceration or chronic keratitis), whereas *Chlamydophila* does not

Diagnosis

- PCR to identify FHV-1 or chlamydial DNA from a dry bacterial swab is the most commonly performed diagnostic test. Apply topical anaesthetic and take a vigorous swab from the conjunctival sac. The laboratory can perform PCR testing for both organisms from the same swab. If the cat has URT signs then swab the oropharynx too

    - Real-time PCR testing (e.g. Acarus laboratory, University of Bristol) is a semi-quantitative test. This is particularly useful for FHV-1, since it shows whether high levels of virus have been detected (likely to indicate active disease) or low levels (which may simply reflect a carrier status)

- Other tests such as fluorescent antibody testing or culture are rarely performed since the advent of PCR testing

- FHV-1 diagnosis can be particularly problematic since both false-positive and false-negative PCR results are common. Diagnosis may therefore rely on a 'jigsaw' approach, relying on a combination of history, signalment, ocular signs, PCR testing and response to antiviral treatment (Gould 2011).

<u>*Chlamydophila felis*</u>

C. felis is widespread in the worldwide feline population, with more than 10% of unvaccinated household cats and up to 64% of cattery cats having antibodies against *Chlamydophila*. Despite this high exposure rate, *C. felis* can be isolated from the conjunctiva of only around 6% of clinically healthy cats, thus its isolation from the conjunctiva is usually clinically significant. Studies have isolated *C. felis* from between 7% and 56% of cats with conjunctivitis (Wills et al 1988, Low et al 2007, Hartmann et al 2010).

Clinical disease is most commonly seen in cats less than 1 year of age. Clinical signs, primarily conjunctivitis, develop after an incubation period of between 2-5 days. Transient fever and inappetance may develop, but most cats remain well and continue to eat. Respiratory and other systemic signs are uncommon. However, the organism can be shed from the gastrointestinal and urogenital tracts and this may act as a source of infection to other cats (Gruffydd-Jones et al 2009).

Conjunctival shedding of *C. felis* usually stops from around day 60 post-infection, although untreated cats may shed the organism for up to 215 days and some may develop persistent infection. Host immunity involves both cellular and humoral responses, and increasing immunity is established with age.

Treatment of Chlamydophila

The infection may be self-resolving. However, if chronic or recurrent, or if infection becomes a problem within a colony or cattery, then a 3week course of antibacterials are required:

- Doxycycline 10mg/kg UID (not in kittens or pregnant queens)
- Synulox 25mg/kg BID has been reported to be effective
- Topical tetracyclines are effective, but are difficult to obtain and require frequent application (up to 6x daily). If systemic doxycycline is instigated then topical medication is not usually required, except perhaps to treat secondary or mixed infections

FHV-1

FHV-1 is a significant cause of feline morbidity worldwide. In addition to its role in feline upper respiratory tract disease it is a major cause of feline ocular disease. It is widespread in the global feline population, with reported serological prevalence rates of up to 97% (Maggs et al 1999). Following exposure, more than 80% of cats become persistently infected and, of these, 45% will subsequently shed virus spontaneously or as a result of natural stress situations, whilst around 70% will shed virus in response to corticosteroid administration (Gaskell and Povey 1977).

Primary infection occurs most frequently amongst kittens and adolescent cats, as maternal antibodies decline from around 8 weeks of age. However, even vaccinated cats remain at some risk because FHV-1 vaccines, both parenteral and intranasal, confer only partial immunity against clinical signs and no protection against reactivation/shedding. FHV-1 preferentially infects mucoepithelial cells of the tonsils, conjunctiva and nasal mucosa but there is also significant infection of corneal epithelial cells. The resultant lytic infection is characterised by rapid replication and acute cellular damage leading to cytolysis. Clinical signs develop 2-6 days after infection. Ocular signs associated with this phase are acute conjunctivitis and epithelial keratitis characterised by the formation of punctate and dendritic epithelial ulcers that persist up to 3 weeks.

Latency and recrudescent disease. During primary infection, FHV-1 virions invade sensory nerve endings of the trigeminal nerve within the host tissue and travel to the trigeminal ganglion. Here FHV-1 develops a latent state. Latent FHV-1 virus may be reactivated to cause

recrudescent clinical disease. This has been recorded spontaneously or in association with various stressor conditions including systemic corticosteroid administration, co-infection with other agents, change of housing, parturition and lactation. Recrudescence results in viral replication and migration down the sensory axons to epithelial tissues. This may result in subclinical shedding, active conjunctivitis or keratitis, or chronic stromal keratitis.

Ocular signs associated with FHV-1 include the following:

- Conjunctivitis
- Dendritic corneal ulceration
- Geographic corneal ulceration
- Chronic stromal keratitis
- It has also been linked with a number of other ocular conditions including ophthalmia neonatorum, symblepharon, keratoconjunctivitis sicca, tear film instability, eosinophilic keratitis, corneal sequestration, calcific band keratopathy, periocular dermatitis, and anterior uveitis

Treatment of FHV-1

Treatment protocol may require a multi-faceted approach tailored to the individual patient and, importantly, its owner. Factors to be considered should include:

- The stage of infection
- Severity of clinical disease
- Financial considerations and owner/ patient compliance

Key points in a treatment plan may include:

- Reduction of stress
- Symptomatic treatment if indicated (e.g. systemic antibiotics, fluids in systemically ill patients)
- Topical antivirals (see table below)
- Systemic antivirals (famcyclovir)

- Other treatments such as L-lysine and interferon are unproven and not currently recommended

Table: Antiviral drugs listed in decreasing order of *in-vitro* efficacy against FHV-1

Drug	Dosage
Trifluorothymidine (trifluridine, 5FT)	1% solution topically q4-6h for 21days
Ganciclovir	0.15% gel q4-6h topically for 21 days
Idoxuridine	0.1% ointment q4-6h topically for 21 days
Cidofovir	0.5% solution topically q12h
Famciclovir/ penciclovir	90mg/kg *per os* 3x daily for 21 days
Vidarabine	3% ointment topically 5x daily for 21 days
Aciclovir	3% ointment topically 5x daily for 21 days

Canine conjunctivitis

Viral conjunctivitis is relatively uncommon in dogs, but is seen in canine distemper, canine adenovirus-2 and canine herpesvirus-1 infections (Greene and Appel 2006, Ledbetter et al 2009).

Bacteria can be isolated from the conjunctiva of 39%-87% of normal dogs, according to different studies, with greater than two-thirds of canine isolates being Gram positive.

- Predominant Gram positive isolates: *Staphylococcus* sp, *Corynebacterium* sp, *Streptococcus* sp, *Bacillus* sp

- Predominant Gram negative isolates: *Acinetobacter* sp, *Neisseria* sp, *Moraxella* sp, *Pseudomonas* sp, *E.coli*

Because of the high bacterial isolation rate from the normal canine conjunctiva, positive bacterial culture from clinical cases does not necessarily indicate a pathological link, and this should be borne in mind when interpreting conjunctival swab results; laboratory culture reports of scanty growth or mixed growth of organisms may simply represent normal conjunctival flora and as such may not require antibacterial treatment.

Infectious canine conjunctivitis develops when the local equilibrium between host and organism alters to allow overgrowth of bacteria sufficient to cause pathological disease, which is manifest by swelling, redness and ocular discharge. Usually this is a result of local factors (e.g. trauma to the conjunctiva, reduced tear production, eyelid defects, corneal disease, foreign bodies) or systemic factors (e.g. immunosuppression, allergic disease). It follows that, in addition

to treating any pathological bacteria, any underlying cause is identified and treated simultaneously. A thorough ophthalmological examination is imperative, paying particular attention to signs of eyelid or third eyelid disease, tear film deficits, and ocular surface disease.

Suitable topical antibacterials for canine conjunctivitis include the following:

- **Chloramphenicol** is an excellent first-line treatment with a broad spectrum of activity. Of all the topical antibacterials it is the least epitheliotoxic. It is bacteriostatic rather than bacteriocidal, therefore should be used at a higher frequency of application in active infections (e.g. 4x-6x daily)

- **Fusidic acid** (Fucithalmic). A good first-line treatment, with a broad-spectrum, mostly Gram-positive range of activity. Its lubricant base and bacteriocidal mode of action gives it the advantage of requiring only once or twice daily application. However it is poorly effective against some Gram negative organisms, including *Pseudomonas* spp

- **Gentamicin** (Tiacil, Clinagel, Gentocin) (aminoglycoside) is a reasonable choice although it is poorly effective against streptococci, and is also relatively epitheliotoxic. It is particularly useful for Gram-negative infections (eg *Pseudomonas* spp)

- **Ciprofloxacin or ofloxacin** (Ciloxan, Exocin) (fluoroquinolones), are wide-spectrum although also poorly effective against streptococci. Probably best reserved as second-line antibiotics for more serious infections (e.g. corneal melts associated with Pseudomonas infection) or when culture/sensitivity results indicate that their use is appropriate

- **Double- or triple-combinations** (eg polymixin B + neomycin) with or without corticosteroids (eg Polyfax, Maxitrol). Debatable whether these should be used first-line.

Conjunctival swabbing for bacteriology culture and sensitivity is not always practical in a first opinion practice situation. However, if the conjunctivitis is persistent, severe or associated with corneal ulceration then antibacterial sensitivity testing is indicated; it is not logical simply to increase the frequency of the existing topical antibiotic (increasing fusidic acid application from 2x to 6x daily is rarely effective) or to switch randomly between different topical antibiotics. Instead, search for any underlying cause (tear film defects, eyelid disease etc) and consider submitting a conjunctival swab for bacterial culture and sensitivity testing. ***It is important that the laboratory performs sensitivity testing against commonly used topical antibiotics rather than performing a generic screen****; when submitting an ocular swab remember to state the site from*

which it was taken and ensure that the laboratory tests it against appropriate topically used antibacterials including chloramphenicol, fusidic acid, gentamicin, polymixin B, neomycin, ciprofloxacin, ofloxacin and tobramycin.

Secondary conjunctivitis

As discussed above, canine conjunctivitis usually develops secondary to other factors. Certainly, dogs should not have repeat bouts of primary infectious conjunctivitis, so consider secondary conjunctivitis if repeated episodes occur or in chronic cases. Secondary causes include:

- Keratoconjunctivitis sicca (KCS)
    - Immune-mediated lacrimal gland destruction
    - Topical immunosuppressives long-term: cyclosporine 0.2% (Optimmune), cyclosporine in corn oil (0.5%-2%), tacrolimus 0.03%
    - Long-term lubricants (see below)
    - Topical antibiotics if secondary infection
    - Consider parotid duct transposition if non-responsive
- Entropion and other eyelid defects (qualitative tear film deficits, distichiasis, ectopic cilia, ectropion, eyelid masses, third eyelid gland prolapse, blink defects)
- Conjunctival, nasolacrimal or corneal foreign body
- Keratitis/ corneal ulceration
- Local irritation (dust, smoke etc)
- Intraocular disease
- Allergic (atopic conjunctivitis)

Lubricants/ tear substitutes

Tear substitutes are one of the mainstays of treatment for all types of tear film deficits. Tear film deficits can be grouped as follows:

- Quantitative tear film deficits
    - Keratoconjunctivitis sicca (KCS): Most common form in dogs.
- Qualitative tear film deficits
    - Evaporative tear loss eg meibomian gland disease (meibomianitis)
    - Eyelid disease eg reduced blink (exposure keratitis, facial nerve paralysis) or eyelid margin disease (marginal blepharitis)

Mimicking the three layers of the tear film, the main classes of tear substitutes are lipid-based ointments, aqueous drops and mucinomimetics or combinations of these.

- *Lipid-based tear substitutes* (eg Lacrilube) such as lanolin, petrolatum and mineral oil are ointments that mimic the lipid portion of the tear film and prevent evaporation of existing tears. They have good corneal retention and so are useful when frequency of application is a problem. They are used three or four times daily. However, they may be more difficult to apply than less viscous preparations and are likely to cause blurring of vision. They are also useful as ocular protectants during anaesthesia or if eyelid paresis is present
- *Aqueous preparations* (eg Tears naturale, Liquifilm, Sno Tears, Viscotears) contain hypromellose, methylcellulose, polyvinyl alcohol or carbomer to increase viscosity and prolong corneal retention time. Despite this, they drain quickly from the ocular surface. Because they require very frequent application, they are not particularly effective as tear substitutes in veterinary species
- *Mucinomimetics* (eg Ilube, Viscotears, Hycosan, Hycare, Remend) have longer corneal contact times than aqueous tear substitutes and are more effective as tear substitutes

Corneal ulceration

The average thickness of the normal canine and feline cornea is approximately 0.6mm, and it consists of four layers:

- Corneal epithelium (10%)

- Corneal stroma (90%)
- Descemet's membrane (elastic-like layer)
- Corneal endothelium (single cell layer)

Corneal transparency is maintained by a combination of:

- Absence of blood vessels or lymphatics
- Absence of pigmentation
- Non-keratinised epithelium
- Parallel-organised collagen lamellae within the stroma with minimal cross-linking
- Paucity of cells and organelles
- Relative dehydration due to 'waterproofing' by a hydrophobic epithelium, and the presence of an endothelial Na/K ATPase pump that removes water from the stroma and returns it to the anterior chamber

Corneal ulceration develops when there is a breach in the epithelial layer, exposing the underlying stroma and sensory nerve endings. Causes include:

- External causes
    - Trauma
    - Foreign body
    - Topical irritants (eg acid, alkali)
    - Infectious (eg feline herpesvirus, canine adenovirus)
- Secondary to existing ocular or periocular disease eg
    - Eyelid defects
    - Blink disorders
    - Tear film defects
    - Anatomical eg brachcephalics
    - Intraocular disease

Ophthalmic examination when assessing corneal ulceration should include the following:

1. Hands off' assessment
2. Assess eyelid conformation
3. Schirmer Tear Test
4. Assess blink (palpebral + normal blink)
5. Examine lid margin, conjunctival fornices and behind third eyelid (topical anaesthetic)
6. Fluorescein stain
7. Swab if indicated

Management of corneal ulcers consists of assessing the depth (the key question being 'is the ulcer deep enough to warrant surgical intervention?'), identifying and correcting any underlying cause, and managing the ulcer depending on the above.

Assessing corneal thickness is most accurately achieved by use of a slit lamp. However, as a rule of thumb, if there appears to be any depth to an ulcer then it should be considered potentially deep and specialist advice should be sought.

Assessing the depth of a corneal ulcer is of course instrumental in determining the best course of treatment. As a rough guide see the table below. Remember however that any underlying cause should be identified and treated, and some types of ulcer require additional treatment (eg indolent corneal ulcers, melting corneal ulcers, feline herpes virus ulceration etc)

Depth of ulcer	**Medical treatment**	**Surgical treatment**
Superficial	Topical antibiotic + systemic analgesia ?topical analgesia ? contact lens	Third eyelid flap/ none
Less than half depth	Topical antibiotic +/- surgical + systemic analgesia ?topical analgesia ?contact lens	Third eyelid flap/ none (but careful monitoring required)
Greater than half depth	Topical antibiotic plus surgical + systemic analgesia ?topical analgesia	Conjunctival graft Corneo-conjunctival transposition

Use of topical analgesics is controversial. Topical ketorolac trometamol 0.5% (Acular eye drops) is an effective analgesic in human patients. In veterinary patients it is a good topical anti-inflammatory agent but its analgesic effects appear minimal.

Topical local anaesthetics (eg proxymetacaine drops) are excellent analgesics but should only used for examination or for short procedures (eg corneal scrapes, swabs, debridement). They are epitheliotoxic so should not be used as part of a treatment regime.

Antibiotics for corneal ulcers

All corneal ulcers should be treated with topical antibiotics to prevent infection of the ulcer site with bacteria from the surrounding local environment. For corneal ulcers where there is no evidence of active infection (ie no mucopurulent discharge or signs of corneal stromal infection) then broad-spectrum topical antibiotics requiring a low frequency of application are appropriate, such as fusidic acid or chloramphenicol. If the ulcer appears to be infected then more aggressive treatment is indicated – for example swabbing for bacterial culture/ sensitivity, application of bacteriocidal antibiotics such as topical fluoroquinolones at higher frequency of application, systemic antibacterial treatment etc.

Corneal ulcers in brachycephalic dogs

Brachycephalic breeds such as the pug, Shi tzu, French bulldog and Pekingese should be monitored particularly carefully. Their exposed cornea, poor blink reflex and reduced corneal sensitivity predisposes them to corneal ulceration that can be very slow to heal - and in these breeds ulcers can rapidly deepen to become descemetocoeles or full thickness ruptures. Early referral of brachycephalic ulcers offers the best visual outcome.

Corneal melts

Acute stromal collagenolysis (liquefactive stromal necrosis) describes a rapid and progressive corneal melt that should be treated as a medical and/or surgical emergency. It can occur when an existing epithelial erosion or ulcer:

- Becomes infected with a bacterium that releases proteases
- Is treated with topical corticosteroids

Corneal melts may also be associated with chemical injuries (especially alkali burns) and, rarely, insect bites.

The bacterial species most commonly isolated from corneal melts are *Pseudomonas aeruginosa* and beta-haemolytic streptococcus. They release a variety of proteolytic enzymes that dissolve the corneal stroma and lead to progressive deepening of the ulcer. Topical corticosteroids induce corneal melts by activating release of endogenous proteases (matrix metallo-proteases, MMP's) from keratocytes and neutrophils.

Signs of an early corneal melt include:

- A corneal ulcer with an ill-defined gelatinous rim, which may be grey, white or yellow
- Increasing ocular discomfort
- Progression from serous to mucopurulent ocular discharge
- Progressive deepening of the ulcer
- Secondary uveitis (miosis and iris hyperaemia)

Work-up and treatment

Melting ulcers should be classed as an emergency. Immediate referral should be considered. If not, animals should be hospitalised and carefully monitored. If this is not possible, then it is vital that the owner returns for regular (*at least* daily) check-ups, and is made aware of the risk of sudden globe rupture.

A typical work-up would consist of:

- History-taking (including prior ophthalmic disease, use of topical corticosteroids, exposure to chemicals)
- Thorough eye examination. Proceed carefully if the ulcer is deep. If there is a risk of imminent globe rupture it may be necessary to omit certain procedures such as STT or tonometry
- PH testing of conjunctival fornices if there is a history of acid or alkali exposure
- Fluorescein staining
- Conjunctival or corneal swab under topical anaesthesia (care!). In-house cytology can be used to identify bacterial rods or cocci, which may help in selection of antibacterials. The swab can also be sent for bacterial culture and sensitivity, which may be of retrospective use

Medical treatment consists of:

- Autologous serum q30-60mins. This has broad-spectrum anti-protease activity to help to stop the melt

- Topical antibacterials. Fluoroquinolones such as ciprofloxacin and ofloxacin are commonly used (their use should be reserved for melting ulcers). They are broad-spectrum, with good activity against Pseudomonas, *but note that some streptococci species may be resistant*

- Systemic antibacterials

- Systemic NSAID's

- Other drugs that may have anti-protease activity and might be considered include topical acetylcysteine, topical EDTA, systemic tetracycline and vitamin C

- If the melt is due to an alkali burn, then copious irrigation of the corneal surface should be performed until the normal pH (around pH7.5) has been restored. Specialist advice should be sought

Surgical intervention is often required, most commonly conjunctival grafting. Conjunctival pedicle, bridge, hood and 360^{o} grafts may be used. Conjunctival grafts not only give physical support to the weakened cornea, but also provide a blood supply, thus allowing direct access by serum anti-collagenases and systemically administered antibacterials.

<u>Indolent corneal ulcers</u>

Alternative terms include non-healing ulcer, under-run ulcer, refractory ulcer, persistent corneal erosion, recurrent epithelial erosion, basement membrane epithelial dystrophy, Boxer ulcer, spontaneous chronic corneal epithelial defect (SCCED).

A typical indolent epithelial erosion is:

- Seen in middle-aged to older dogs

- Seen in any breed of dog, including mixed breeds, although some breeds may be over-represented

- Superficial, involving the epithelium only (no stromal involvement)
- Surrounded by non-adherent epithelium
- Usually, but not exclusively, located in the axial or paraxial cornea
- Non-infected
- Associated with varying signs of discomfort
- Non-vascularized early in its course, becoming vascularized in time (NB the blood vessel response that aids healing of stromal ulcers is ineffective for indolent epithelial erosions and often complicates treatment, especially surgical intervention)
- Non-responsive to medical management

Work-up

Don't forget a detailed ophthalmic examination of both eyes to check for any underlying conditions such as KCS, Distichiasis etc

Treatment

Indolent epithelial erosions rarely heal spontaneously or with topical antibiotic therapy alone (NB note that these ulcers are not infected and topical antibiotics such as chloramphenicol BID are merely used prophylactically to prevent bacterial contamination of the ulcer. Unless the ulcer becomes infected, there is no justification in dosing at high frequency, or changing antibiotics, and in fact these approaches are more likely to inhibit healing).

Surgical options include:

- Debridement alone (approximately 50% healing rate)
- Debridement followed by grid or punctate keratotomy (approximately 70% healing rate)
- Debridement followed by phenol cautery and saline flushing (no studies of healing rate, but anecdotal reports suggest around 70%)
- Superficial keratectomy (approximately 100% healing rate)

In contrast to the first three procedures, superficial keratectomy requires general anaesthesia and the use of an operating microscope, and should be performed by an ophthalmologist. It has an excellent success rate, but if performed on a cornea that already has a marked neovascularisation response it can lead to a transient granulation tissue response that may take some weeks to resolve. To avoid this, early referral is recommended

When to refer

Consider referral to an ophthalmologist (or seek telephone advice) when a corneal ulcer is:

- Not responding to appropriate treatment
- Getting deeper
- Melting
- Down to Descemet's membrane
- Accompanied by significant corneal oedema
- Ruptured
- Likely to require microsurgery
- Attached to a pug!

References and further reading

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