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The cornea as part of the ocular surface

• The cornea cannot be considered in isolation from the other components of the “ocular surface”
• The modern view of the “ocular surface” is that of a morphofunctional unit comprising the pre-corneal tear film, lacrimal glands, cornea, limbus, conjunctiva, mucocutaneous junction, meibomian glands, and the subepithelial corneal nervous plexus.
• Corneal innervation has a trophic effect on the epithelial cells and is responsible for the normal blinking and lacrimal reflexes
• It is evident that compromise of the reflex arc involving corneal sensation – lacrimation / blinking can lead to further ocular surface disease and therefore can be seen as self perpetuating
• For example in keratoconjunctivitis sicca (KCS) the reduced aqueous tear secretion is typically viewed as the major factor leading to ocular pathology. When the above reflex is considered it is apparent that the pathology of the epithelium and subepithelial innervations will cause:
  I  reduced reflex lacrimation
  II reduced blinking and tear film distribution
  III reduced trophic effect from subepithelial innervations
• This leads to further corneal pathology and a negative loop perpetuating the progression ocular surface disease.

An approach to cases of ocular surface disease

• In all cases of surface ocular disease it is imperative that attempts are made to establish an underlying CAUSE for the disease.
• This may seem daunting due to the number of potential “causes” of surface ocular disease - to simplify ones approach to these cases, following Roman adage of “Divide and Conquer” is useful
• The possible differential diagnoses for all cases of surface ocular disease may be divided as follows:

<table>
<thead>
<tr>
<th>FAT TIM Eyelid Tumour</th>
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<tbody>
<tr>
<td>F</td>
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<tr>
<td>A</td>
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<tr>
<td>T</td>
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<table>
<thead>
<tr>
<th>Tear film deficiencies-</th>
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<tbody>
<tr>
<td>Aqueous: quantitative or poor distribution</td>
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<tr>
<td>Mucin: tear film instability</td>
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<tr>
<td>Meibum: chronic blepharitis</td>
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| I  | Infections (bacterial, fungal and viral) |
| I  | Infection – dacryocystitis |
| I  | Immune mediated disease (e.g. superficial punctuate keratitis-MLHD) |
| M  | Mechanical irritations (entropion/ distichia/ectopic cilia etc) |

| Eyelid | eyelid disease (blepharitis) extending to conjunctiva |
| Tumour | conjunctival infiltration |
### FAT TIM Eyelid Tumour – specific investigations:

<table>
<thead>
<tr>
<th>Letter</th>
<th>Description</th>
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<tbody>
<tr>
<td>F</td>
<td>Foreign body - close visual inspection including conj fornices &amp; under TEL (Bennett’s)</td>
</tr>
<tr>
<td>A</td>
<td>Allergic - history, seasonal, itchy, dermatological signs and cytology of conjunctivaj</td>
</tr>
<tr>
<td>T</td>
<td>Trauma / toxic reactions - hx exposure – severe acute signs</td>
</tr>
<tr>
<td>T</td>
<td>Tear film deficiencies</td>
</tr>
<tr>
<td>T</td>
<td>Aqueous: - STT1, corneal sensitivity and the palpebral reflex</td>
</tr>
<tr>
<td>T</td>
<td>Mucin: - TBUT normally 20-25- affected &lt; 5 s, conj biopsy fornices for goblet cells</td>
</tr>
<tr>
<td>T</td>
<td>Meibum - visual inspect meibomian glands</td>
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<tr>
<td>I</td>
<td>Infections - cytology, culture</td>
</tr>
<tr>
<td>I</td>
<td>Infection – dacryocystitis - reflux from punctae, N-L flush, cytology, culture, dacryocystorhinography</td>
</tr>
<tr>
<td>I</td>
<td>Immune mediated disease</td>
</tr>
<tr>
<td>M</td>
<td>Mechanical irritations - close visual inspection with magnification for distichia and ectopic cilia</td>
</tr>
<tr>
<td>E</td>
<td>Eyelid disease - hair plucks &amp;, sticky tape samples microscoopy,culture and histopath</td>
</tr>
<tr>
<td>T</td>
<td>Tumour conjunctival infiltration - thickening/corrugation – biopsy</td>
</tr>
</tbody>
</table>

- By remembering the mnemonic “**FAT TIM has an EYELID TUMOUR**” and using it as a checklist when you are investigating an individual case visual cause will greatly increase the thoroughness in approaching such cases and confidence that potential causes have not been overlooked.
- n.b. contrary to cats, most canine conjunctivitis are secondary (KCS, euryblepharon, entropion-ectropion etc…) in cats, most conjunctivitis cases are primary due to viral, or bacterial infections (e.g. FHV-1, *Chlamyphila felis*)

### A clinical approach to surface ocular disease: interactive examination

- **Investigation of surface ocular disease**
  - History
  - Physical examination
  - Dermatological examination
  - Ophthalmological examination
  - Patients presenting with surface ocular conditions (i.e. affecting the cornea or conjunctiva) often have concurrent disease affecting the eyelids / periocular skin
  - Part of the initial assessment should be aimed at determining if the condition is primarily ocular with secondary eyelid disease (i.e. allergic conjunctivitis leading to secondary trauma/ eyelid maceration etc), or primarily an eyelid disease
  - This distinction is not always obvious (generally the more severe the eyelid disease the more likely this is the primary disease process)

- **Investigation of eyelid disorders & periocular skin disease (specialist session)**
  - Identify eyelid disorders causing mechanical irritation of the eye (conformational eyelid disorders, distichia, trichiasis etc)
  - Search for parasites and dermatophytes
  - Determine if eyelid infection is present
  - Consider irritant / allergic disease last
  - Biopsy eyelid when there is ulceration, mass lesions or persistence despite diagnostics/ treatments

- Identify eyelid disorders causing mechanical irritation of the eye (conformational eyelid disorders, distichia, trichiasis etc)
- Gross evaluation of the patient’s eye and adnexa – once the patient is relaxed and without restraint
- Best to perform initial assessment on the floor
CASE 1: 5yo MN ECS discharging eye (OS)

CASE 2: 2yo ME G Dane discharging eye (OS)

- Investigation of surface ocular disease
- History
- Physical examination
- Dermatological examination
- Ophthalmological examination

- Investigations should include ALL of the following
- STT1 measurement:
  - Perform before any other ocular manipulation/close examination
  - It should be carried out before any drops or stains are instilled in the eye
• In dogs a reading of <12 mm is suspicious while <8-10 mm is diagnostic tear underproduction (when signs consistent KCS present)
• Cats tend to have lower normal values than dogs, especially when stressed – comparison between eyes is useful. Interpret in combination with clinical signs
• Assess other ocular reflexes
• Corneal reflex
• Palpebral reflex – also assess “completeness” of the palpbral reflex
• Examination in light with focal illumination +/- magnification
• Circular pattern of inspection
• Eyelids
• Bulbar conjunctiva (rule out deep perilimbal hyperaemia)
• Palpebral conjunctiva and third eyelid
• Upper and lower punctae
• Cornea
• Ophthalmological signs associated with surface ocular disease:
• Superficial (conjunctival) hyperaemia is superficial corneal vascularisation are indicative of surface ocular disease
• Superficial (conjunctival) hyperaemia and may involve the bulbar and / or palpebral hyperaemia) and is often more severe towards the fornices
• Other signs of surface ocular disease include:
• Discomfort (lacrimation/ blepharospasm)
• Chemosis
• Ocular discharge
  - Serous
  - mucoid
  - purulent
  - brown/black staining of hair
  - normal response to ocular irritation (conj. goblet cells)
  - bacterial infection (n.b. bacteria are present in most conjunctival sacs so a positive culture does not infer direct disease causation)

Superficial (conjunctival) hyperaemia is superficial corneal vascularisation are indicative of surface ocular disease

Blood vessels tortuous, branching & bright red
Vessels move with conjunctiva
Indicative of …. surface ocular disease

Visible as they cross the limbus
Branching pattern
Indicative of …. surface ocular disease

• Remember - always examine the palpebral conjunctiva!!!
• Hyperaemia of the palpebral conjunctiva may occur in combination with superficial bulbar hyperaemia or in isolation in certain surface ocular conditions e.g. allergic conjunctivitis
CLINICAL CASES

6yo MN Leonberger discharging eye (OS)
POH: cataract sx 6 m previous – receiving chronic
topical NSAID therapy
• Rule out foreign bodies
• Bennett’s cilia forceps used to examine the conjunctival fornices and behind the third eyelid (TEL)- when examining the bulbar aspect of the TEL never “hold” the leading edge of the TEL and ensure the limbus under the TEL is visualised

• cytology
• “cytobrush” and “Diff Quik®” staining
• This is simple to perform and provides useful information which can guide initial treatments

SUMMARY
• Investigations for ALL cases with surface ocular disease
• Examination without restraint
• STT1 measurement
• Assess other ocular reflexes
• Examination in light with focal illumination +/- magnification
• Rule out foreign bodies
• Cytology
• **Investigations for SPECIFIC cases of surface ocular disease**

  • **Testing for infectious agents**
    
    • **Bacterial culture & sensitivity, viral culture or PCR (FHV-1)**
    
    • **Fluorescein dye test (Jone’s test)**
      
      Fluorescein dye is applied to the eye – if the nasolacimal duct is patent the dye normally appears at the nose within 5-10 minutes
      
      If uniocular pathology do the affected initially – otherwise fluorescein from other eye may obscure test
      
      n.b. some dogs have openings into the nasopharynx
    
    • **Nasolacrimal cannulation & flushing**
      
      Cannulation of the nasal ostium is possible in dogs and horses
      
      Cannulation of the upper NL punctae
      
      Conscious canine (general anaesthesia for cats)
      
      Local anaesthesia
      
      Cannulate the upper puncta with a 2G nasolacrimal cannula and gentle irrigate with BSS which should exit the lower puncta
      
      Gentle digital pressure over lower punctae and continue flushing until BSS visible at nose or gagging occurs
      
      DO NOT FORCE FLUID IF RESISTANCE- CAN RUPTURE NLD
    
    • **Skull radiographs – dacryocystorhinography – plain & contrast**
      
      Plain films initially
      
      Cannulate the upper puncta (as explained before)
      
      Inject small amount iodine based contrast (0.5ml) into the upper puncta whilst occluding the lower puncta
      
      Lateral and dorsoventral views are most useful

• **Corneal ulceration – a subset of corneal pathology**

  • Simple – superficial – heal < 7 days
  
  • Complicated – persist > 7 days
  
  • Classified by depth: superficial, deep stromal, and descemetocoele
  
  • Superficial corneal ulcers or erosions can further be classified as uncomplicated, or complicated (progressive, or refractory)
  
  • Uncomplicated superficial ulcers can resolve with topical antibiotic therapy e.g. poly-pharmacy -neomycin, bacitracin, & polymixin B
  
  • As with other forms of surface ocular disease it is imperative that any underlying **CAUSE** for the ulceration is established
  
  • Differentials for corneal ulceration “**FAT TIM has an EYELID TUMOUR**”
Outline your initial approach to the examination of this eye: (i.e. investigations for all cases of surface ocular disease):

1. Examination without restraint
   Mild blepharospasm but no evidence of entropion or trichiasis

2. STT 1 measurement (and other ocular reflexes)
   STT 30mm/minute (OS) 20mm/min (OD) – other reflexes normal

3. Examination with focal illumination and magnification
   Eyelid margins NAD
   Bulbar conjunctiva (superficial hyperaemia)
   Palpebral conjunctiva (hyperaemia but no follicular reaction)
   Third eyelid – hyperaemia of overlying conjunctiva
   Nasolacrimal punctae – NAD
   Cornea – superficial ulcer (central ovoid and elongated horizontally)
   with loose non adherent edges. Mild corneal oedema in region of corneal ulceration

4. Rule out foreign bodies
   Examination with Bennett’s forceps reveals no foreign bodies in the conjunctival fornices—foreign body on bulbar surface of TEL.
5.... Cytology: Scant population of coccoid bacteria and neutrophils

Jack 4 yo MN Border Collie – 1 week pain OD: FB - posterior aspect of third eyelid

CLINICAL CASE

1.... Examination without restraint
    Mild blepharospasm but no evidence of entropion or trichiasis
2.... STT 1 measurements (and other ocular reflexes)
    STT 25mm/minute (OS) 15mm/min (OD) – other reflexes normal
3.... Examination with focal illumination and magnification
    Cornea – superficial ulcer with loose non-adherent edges.
    Mild corneal oedema in region of corneal ulceration
4.... Rule out foreign bodies
    Examination with Bennett’s forceps reveals no foreign bodies
5.... Cytology: scant population of neutrophils
Scenario 1: hx ulceration < 7 days

Treatment plan: …………………………………………………………………………………………………………………
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Scenario 2: hx ulceration > 7 days

Treatment plan: …………………………………………………………………………………………………………………
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- **Spontaneous chronic corneal epithelial defects (SCCEDs) i.e. indolent ulceration**
- Most refractory ulcers in the dog are primary, but they may be secondary:
  - Rule out underlying conditions:
    - Eyelash abnormalities
    - Entropion & poor eyelid function with CNVII paralysis or lagophthalmos
    - Abnormalities of the pre-ocular tear film (KCS & tear mucin deficiencies)
    - Neurotrophic keratitis (CNV dysfunction) → refractory ulcer without associated pain
    - Stromal edema may impair epithelial adherence → severe or chronic stromal oedema, subepithelial bullae → may rupture or lift the epithelium off the stroma
    - Generalized corneal oedema may result from glaucoma, chronic uveitis, and primary endothelial dystrophy or degeneration

- Typically middle-aged dogs of all breeds
- Boxers are over-represented
- Superficial, non-infected erosions surrounded by a zone non-adherent epithelium
- Fluorescein stain often leaks beneath the non adherent epithelium resulting in a less intense ring of staining around the ulcer
- No loss of corneal stroma
- Oedema localized to the region of the defect
**Histopathological findings**
- Include loss of the corneal epithelial basement membrane & formation of a superficial stromal hyalinized zone with abnormal nerve plexus
- These distinct stromal suggest that stromal abnormalities are crucial to the pathophysiology of this disease and may act as a barrier to the formation of normal adhesion complexes (hemidesmosomes)

**Management**
- **Medical** (often combined with corneal epithelial debridement)
  - Given that the defects are likely to be the result of a stromal defect medical therapy alone is often unrewarding
  - **Broad spectrum antibiotics**
    - SCCEDS are by definition NOT INFECTED
    - Antibiotic prophylaxis is needed - intensive treatment with frequent application of antibiotics may delay wound healing
  - **Atropine 1%**
    - Cycloplegic: to reduce intraocular pain (TO EFFECT) – be careful with KCS cases!
  - **Topical hyperosmotic agents**
    - e.g., 2-5% sodium chloride ointment
    - May reduce epithelial and subepithelial oedema & improve epithelial adherence to stroma - have been used in treatment of refractory corneal erosions with limited response
    - Hyperosmotic agents irritate the eye & may require more frequent application because of their short duration of action
    - Only used in cases were the ulceration is secondary to an underlying corneal oedema (e.g. endothelial dystrophy/ degeneration) i.e. not true SCCEDs
  - **Autogenous serum**
    - Source of fibronectin
    - Plasma glycoprotein \( \rightarrow \) stimulates cell adhesion / migration, & protein synthesis
    - It has been used in treatment of refractory ulcers and been shown to promote epithelial attachment & healing in humans & rabbits
    - Studies have shown that fibronectin is already present in SCCED patients so benefit of its use is uncertain
  - **Tetracyclines**
    - Doxycycline shown to inhibit MMP’s (matrix metalloproteinases) enzymes that degrade basement membranes and collagen
    - Recent work suggests that MMP 2 and 9 levels are not associated with SCCED

**Surgical**
- **Mechanical debridement**
  - Removal of loose epithelium +/- contact lens
  - Topical anaesthetic (proxymetacaine) and then using a cotton swab or Kimura spatula, or cilia forceps remove flaps of epithelium by pulling their edges toward the center
  - The defect is usually significantly increased in size
  - Edges should be firmly attached
  - Debridement \( \rightarrow \) repeated every week – expect gradual reduction in ulcer size
Mechanical debridement with Bennett's Cilia forceps

Mechanical debridement with a “stick” swab

- Procedures that involve modification of the corneal stroma have a higher success rate than epithelial debridement alone
- Chemical debridement
  - Remove abnormal epithelium, basement membrane (BM), & altering the anterior stroma
  - Agents used:
    - trichloracetic acid
    - Phenol
    - tincture of iodine
  - Flushing post cautery is very important
- grid keratotomy (GK)
  - Topical anaesthetic and sedation or general anaesthesia
  - A cross-hatched pattern of incisions over the ulcer bed (usually extending slightly beyond the ulcer margin) using a 22 g needle, a set depth knife or knife with a micrometer
  - Incisions should just breach the junction of the epithelial basement membrane and the normal corneal stroma
  - Post operative topical antibiotics 5-7 days
  - ~90% success within 2 weeks (longer for horses)

Grid keratotomy – 22 g needle (bevel facing up) 10 days post-operatively

- MPK: multiple punctate keratotomy (multiple anterior stromal punctures 0.2 mm) with a 20- to 23-gauge needle into the exposed stroma and 1-2 mm of healthy cornea surrounding the ulcer
CLINICAL CASES

- Tenacious adherent mucoid/mucopurulent discharge
- Corneal neovascularisation/pigmentation with chronicity - STT1 = 3

1

- Tenacious adherent mucoid/mucopurulent discharge/recurrent erosions/‘punched-out’ corneal ulceration - STT1 = 5

2

- Tenacious adherent mucoid/mucopurulent discharge / corneal thickened irregular and pigmentation - STT1 = 0

3

- What other investigations would you perform?
- What investigations would you perform?
Investigations for ALL cases with surface ocular disease

* STT1 measurement +

KCS (keratoconjunctivitis sicca)

- The aqueous portion makes up the bulk of the tear film and is produced by the lacrimal and third eyelid glands
- A STT 1 measurement of 10mm wetting/minute or less is consistent with KCS, but must always be considered in conjunction with clinical signs:
  - Congenital – usually unilateral, reported more frequently in the small breeds
  - KCS in conjunction with a curly/rough coat (ichthyosis)
  - Neurological (interruption of parasympathetic supply to lacrimal gland)
  - Drug-induced (atropine, sulphonamides, anaesthesia)
  - Distemper (viral lacrimal adenitis)
  - Obstruction of lacrimal ductules by chemosis or cicatrisation.
  - Iatrogenic (excision of the third eyelid gland)
  - Secondary to metabolic disease (hypothyroidism, diabetes mellitus)
  - Trauma to the orbit (direct lacrimal gland damage)
  - Irradiation (e.g. radiotherapy)
  - Immune mediated adenitis – most important cause of canine KCS.

- Immune-mediated cases:
  - Bilateral although frequently one eye precedes the second clinically.
  - Marked breed predisposition leading to the common assumption that the disease is at least in part inherited
  - West Highland White Terrier represents the most commonly affected breed (UK)
  - Histopathology of lacrimal tissue taken from affected cases demonstrates a progressive fibrosis and atrophy of glandular tissue.

- Therapy
  - Medical
    - Topical Cyclosporine A (Optimmune®) twice daily lifelong
    - Immunomodulating drug that acts to reduce cytokine release and activation of T helper lymphocytes
    - Treatment is most successful when initiated early and lacrimal tissue can recover some secretory function
    - Improved tear production can take 4-8 weeks to be evident
    - Oral pilocarpine – a parasympathomimetic - numerous side-effects including hypersalivation, abdominal cramps and diarrhoea
    - Topical pilocarpine -
    - False tears (hypromellose, carborner polymer, hyaluronate, paraffin-based)

- Surgical
  - Punctal plugs – plugs are placed in the lower nasolacrimal punctum to prevent drainage of tears (only really useful where some tear secretion remains)
  - Puntal ablation (cautery)
  - Permanent partial tarsorrhaphy
  - Parotid duct transposition – used as a last resort
• Superficial keratectomy if severe visual deficits associated with corneal scarring/pigmentation
• Only possible if KCS is controlled medically

• Neurogenic KCS

• Results from interruption in the parasympathetic innervation of the lacrimal gland
• It is usually seen in conjunction with an ipsilateral dry nose as the innervation to the lateral nasal gland shares the same preganglionic parasympathetic fibres proximal to the pterygopalatine ganglion.

• Treat underlying cause (e.g. otitis media, osteomyelitis of petrous temporal bone)
• Neurogenic KCS will not respond to cyclosporine A
• False tear preparations need to be given very frequently (as tear production is often zero)
• Oral pilocarpine or topical pilocarpine is useful in a few cases
• Parotid duct transposition is frequently required.