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Optimized Ophthalmics:

Advances in Medical Treatment of Ocular Disease

J. Seth Eaton, VMD, DACVO

Ocular Pharmacology

- Many factors influence action of an ophthalmic drug, independent of its mode of action
  - Mode of administration (suspension, ointment, oral)
  - Ocular surface dynamics
  - Route of absorption
  - Molecular state of the drug
  - Disease status of the treated eye

The “Perfect” Eye Drop

- pH 4.5-9.0
- Osmolality 200-600 mOsm/kg
- Uniform particle size (< 10 micron diameter)
- Not protein-bound
- Hydrophilic and hydrophobic drug states
- Balanced ionized and unionized states (pKa)

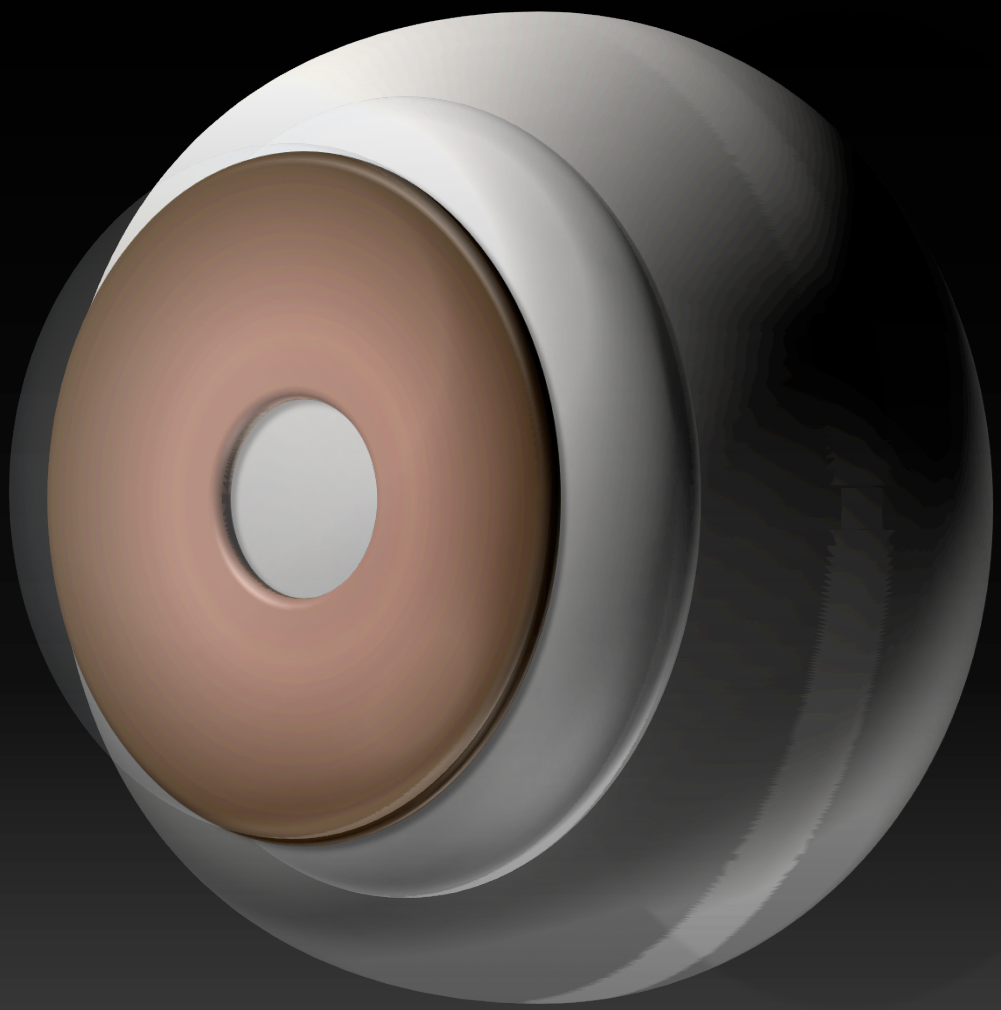
Topical Ophthalmics

Minimal Penetration

- Neomycin-polymyxin-bacitracin/gramicidin
- Aminoglycoside antibiotics
- Tetracycline antibiotics
- Antiviral medications
- Hydrocortisone
- Cyclosporine/tacrolimus

Enhanced Penetration

- Fluoroquinolone antibiotics
- Chloramphenicol
- Prednisolone acetate/ dexamethasone
- Flurbiprofen/diclofenac
- Glaucoma medications (latanoprost, dorzolamide, timolol)



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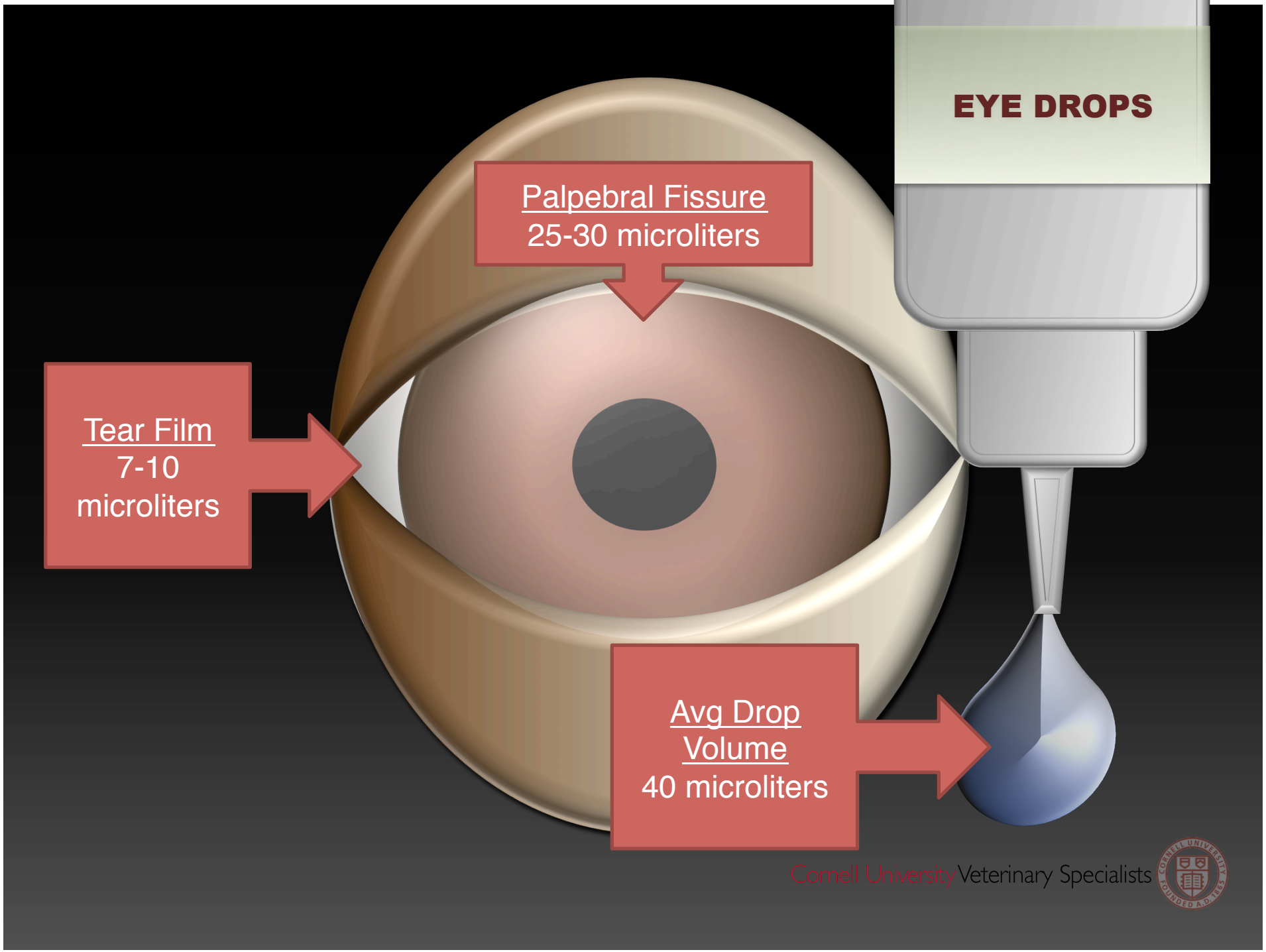
EYE DROPS
Palpebral Fissure
25-30 microliters
Tear Film
7-10
microliters
Avg Drop
Volume
40 microliters
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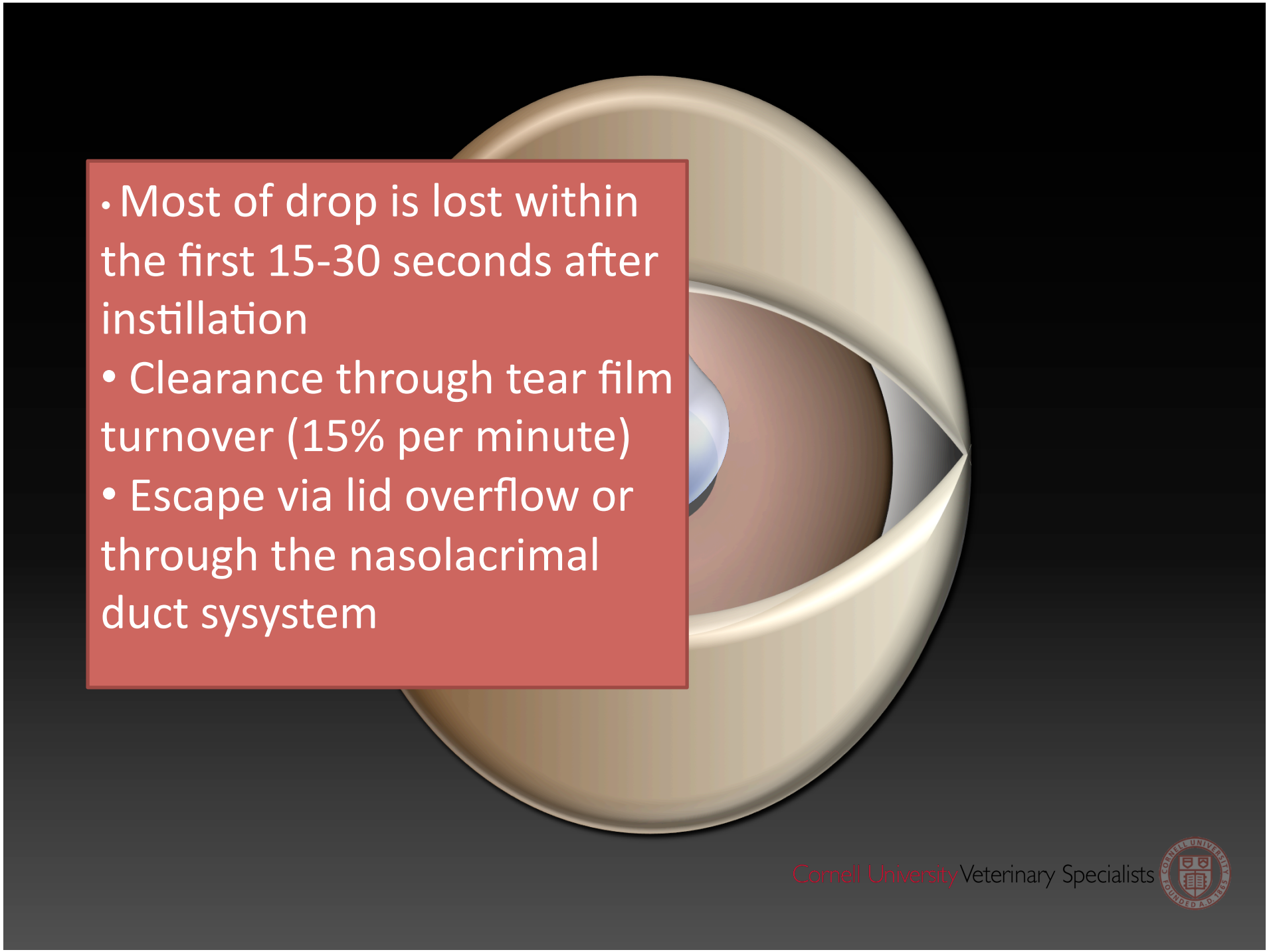
• Most of drop is lost within the first 15-30 seconds after instillation
• Clearance through tear film turnover (15% per minute)
• Escape via lid overflow or through the nasolacrimal duct sysystem
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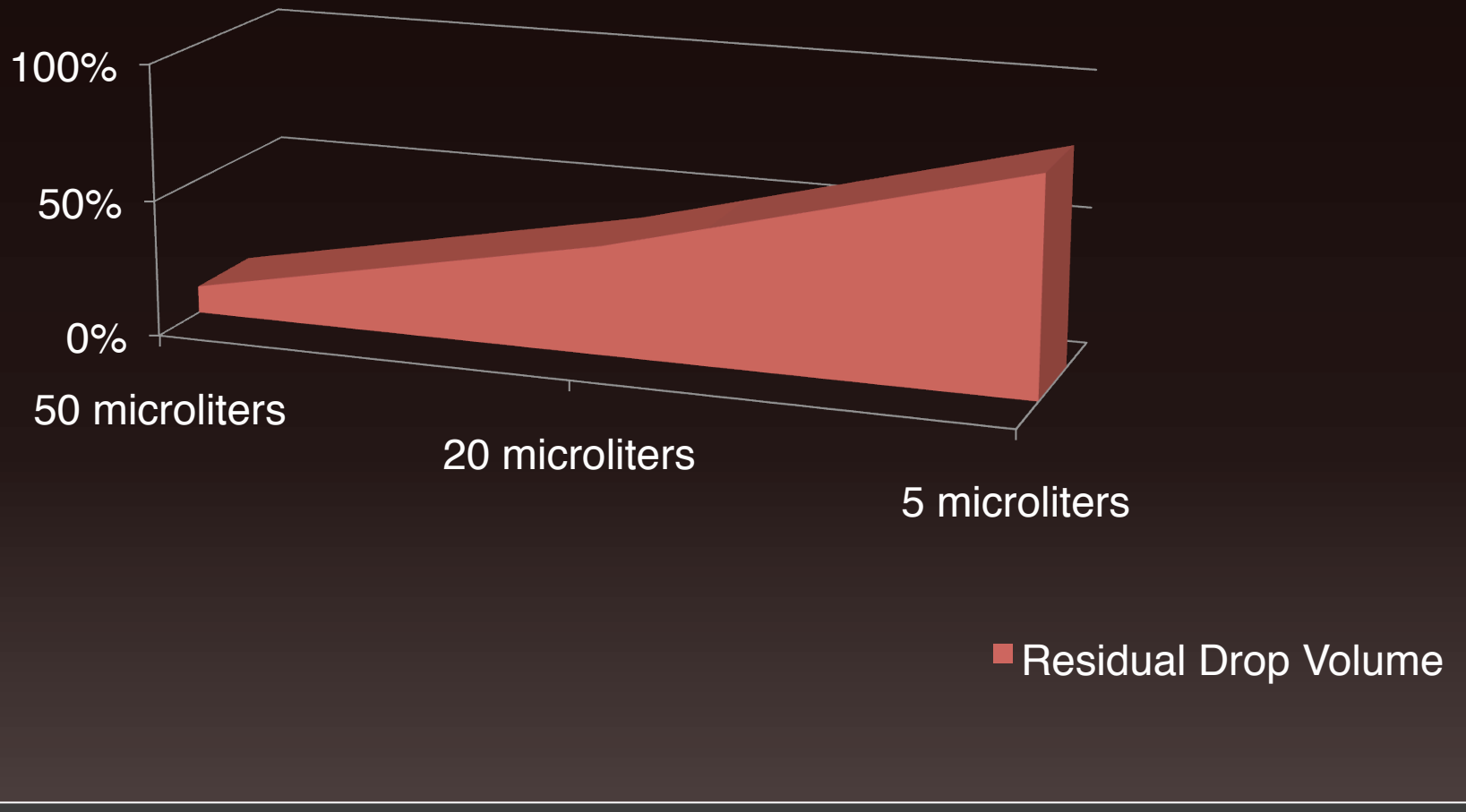
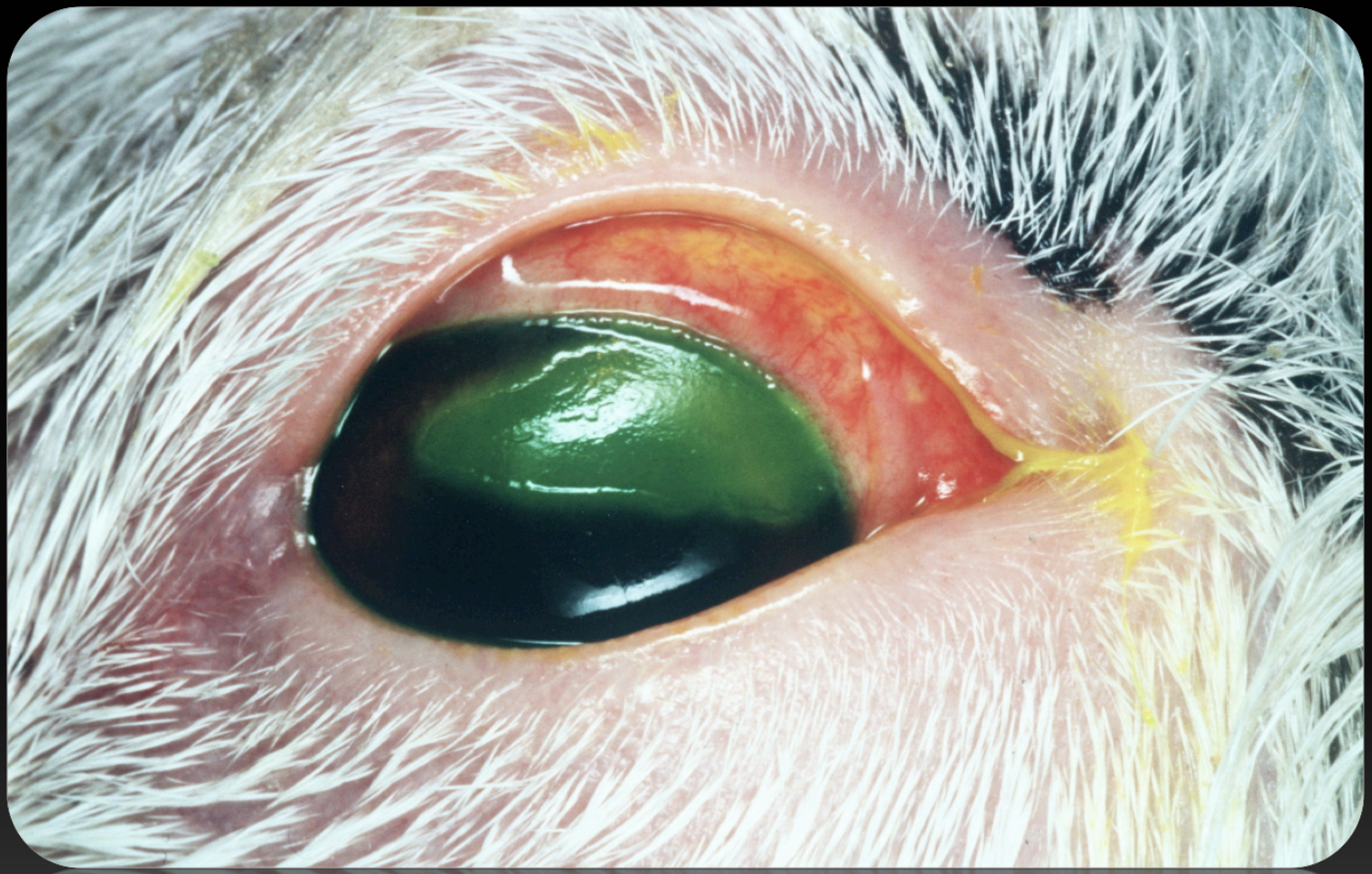
Effect of Drop Volume on Drainage Rate

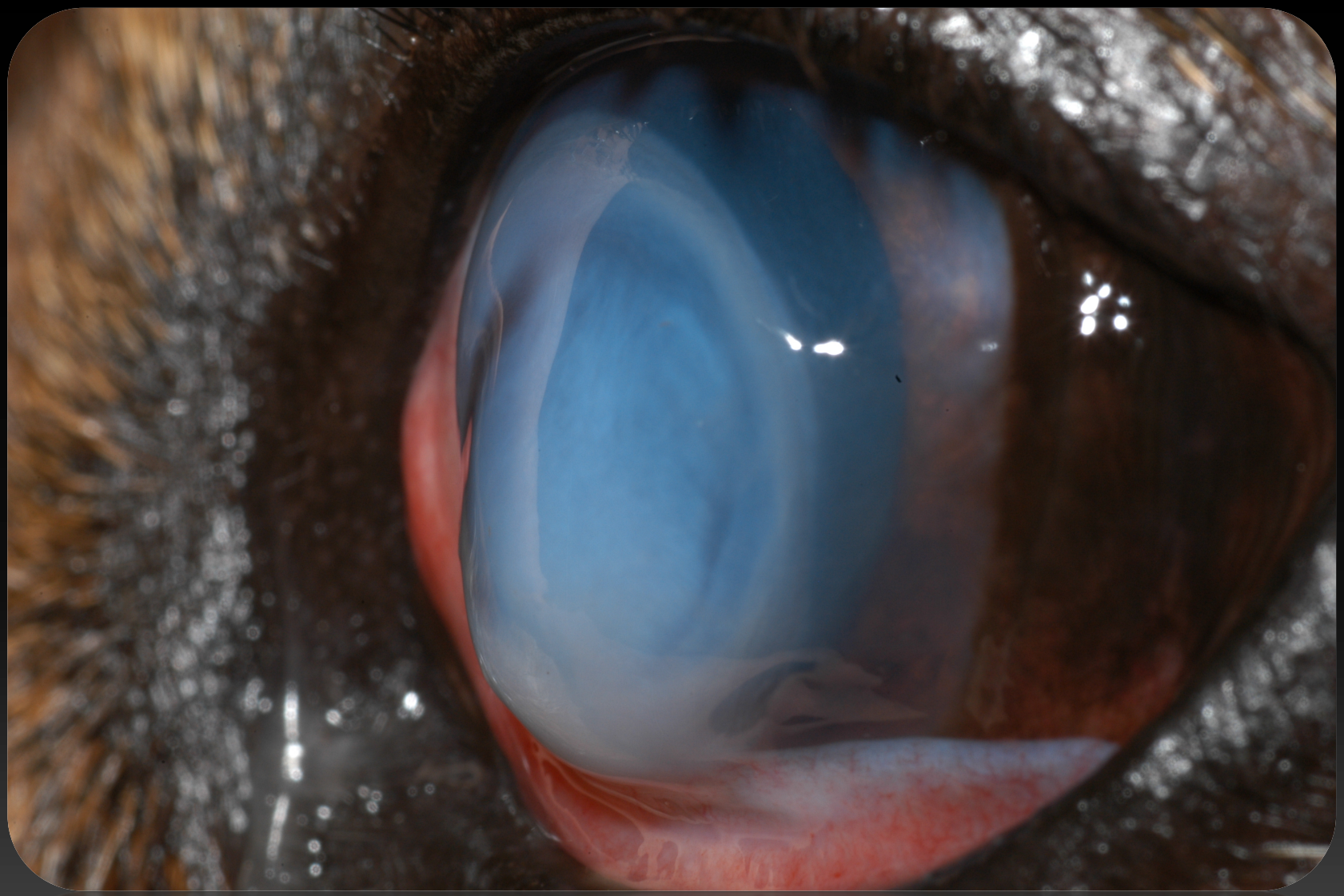


Strategies to Reduce Drainage Rate

- Control blinking frequency
- Control tear flow dynamics
- Size of drop
  - Strategy would be to reduce volume instilled to 5-15 microliters
  - **Avoid administration of consecutive drops**

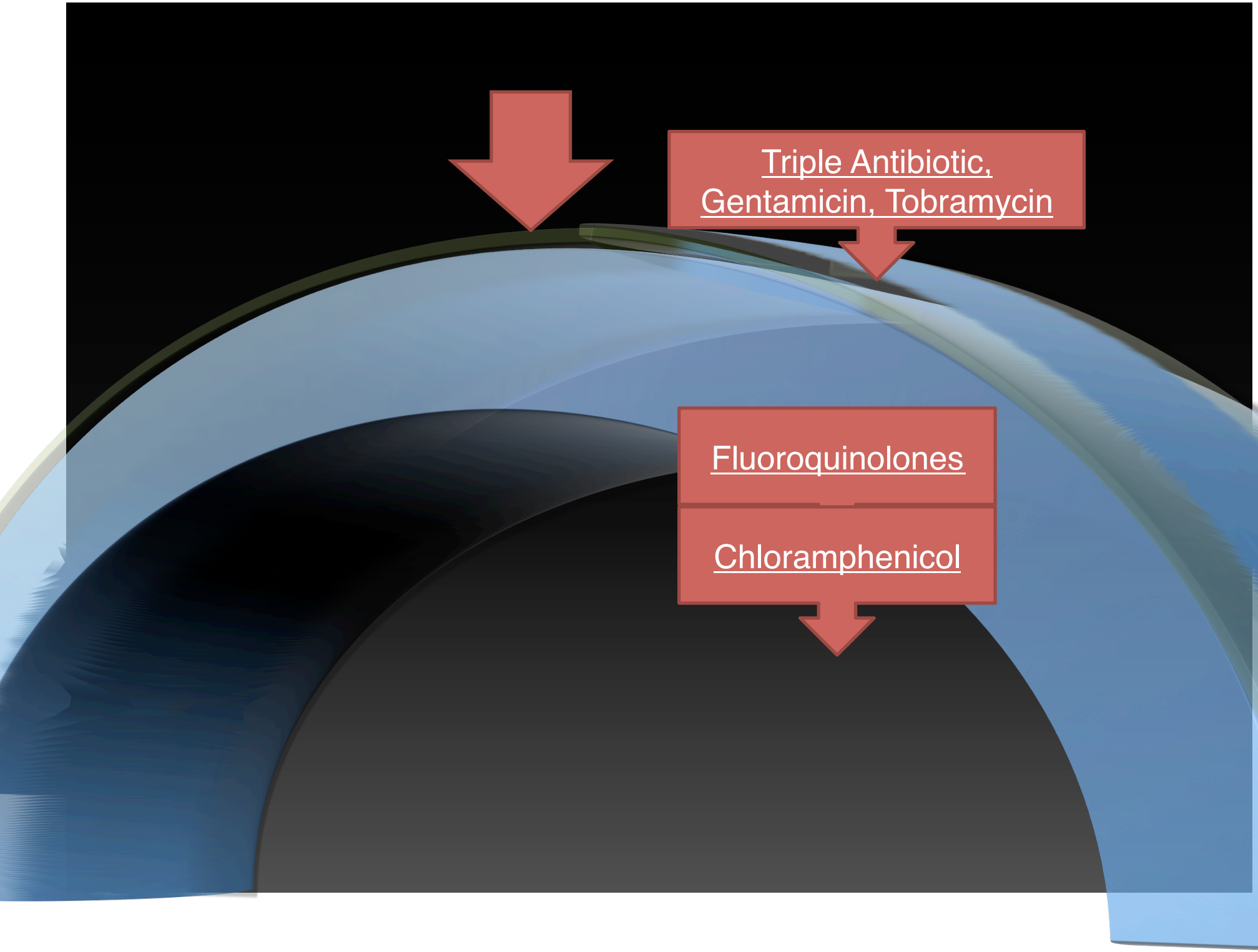
Antibiotics





Ophthalmic Antibiotics

- Antibiotic choice should be based upon:
  - Suspected contaminant or contaminant risk
  - Culture and sensitivity (if available)
  - Penetration into different tissues
  - Species or breed-specific contraindications


Triple Antibiotic,
Gentamicin, Tobramycin
Fluoroquinolones
Chloramphenicol

Ophthalmic Antibiotics

- Neomycin-polymyxin-bacitracin (ointment or solution)
- Tobramycin, gentamicin
- Chloramphenicol
- Fluoroquinolones (ofloxacin, ciprofloxacin, moxifloxacin)
  - Excellent coverage for *P. aeruginosa*
  - Excellent corneal/intraocular penetration

Ophthalmic Antibiotics

- For cats…
  - Tetracyclines (oxytetracycline)
  - Erythromycin
  - Fluoroquinolones
- Seeking coverage against pathogens such as *Chlamydophila felis* and *Mycoplasma spp.*

Journal of Feline Medicine and Surgery (2011) **13**, 744–751
doi:10.1016/j.jfms.2011.06.007

ELSEVIER

jfms

Anaphylactic events observed within 4 h of ocular application of an antibiotic-containing ophthalmic preparation: 61 cats (1993–2010)

Karen M Hume-Smith DVM[1,a], **Allyson D Groth** BVSc[1], **Mark Rishniw** BVSc, Dipl ACVIM[3], **Linda A Walter-Grimm** DVM[4], **Signe J Plunkett** DVM[5], **David J Maggs** BVSc, Dipl ACVO[2*]

- 998 survey respondents with only 8% reporting anaphylactic events
- 45 cats from surveys and 16 from Federal Drug Administration reports met the inclusion criteria
    - 87% healthy at examination, wide age range (kitten to geriatric)
- 56% experienced anaphylactic events within 10 minutes of administration
- 82% survival with supportive care
- 51% of cats had vaccinations and/or other ophthalmics at time of exams
- Oxytetracycline/polymyxin B or neomycin-polymyxin-gramidicin/bacitracin (with or without hydrocortisone) administered in 84% of reported cases
- **Polymyxin B present in 100% of reported cases**
- Limited by retrospective nature of study, varying clinical definitions of anaphylaxis

What About Oral Antibiotics?

- Barriers to ocular penetration of oral/ parenteral antibiotics
  - Blood-aqueous barrier
  - Corneal avascularity
  - Poor lacrimal availability
- Exceptions
  - Tetracyclines
    - Actively secreted by the lacrimal gland

Tetracyclines in Ophthalmology

- Limited spectrum for canine ulcerative keratitis
- **BUT…**
  - Possess anticollagenase properties
    - Chelate calcium and zinc, inhibiting metalloproteinases
  - Possess immunomodulatory properties
    - May be used in combination with systemic niacinamide
  - Effectively penetrate lipid-rich tissue
    - May be useful in cases of marginal blepharitis
  - May promote corneal wound healing
    - Chandler HL et al. J Am Vet Med Assoc 2010(4): 378-86

Anti-Inflammatory Medications

Prednisolone or Dexamethasone?

When Should I Use topical NSAIDs?

Flurbiprofen or Diclofenac (Voltaren®) ?

Indications for Anti-inflammatories

- Blepharitis
- Conjunctivitis
- Keratitis (non-ulcerative)
- Uveitis
  - Anterior, posterior, or both
  - Prophylaxis for lens-induced uveitis
- Retinal detachment
- Inflammatory orbital disease

Anti-Inflammatories

Topical

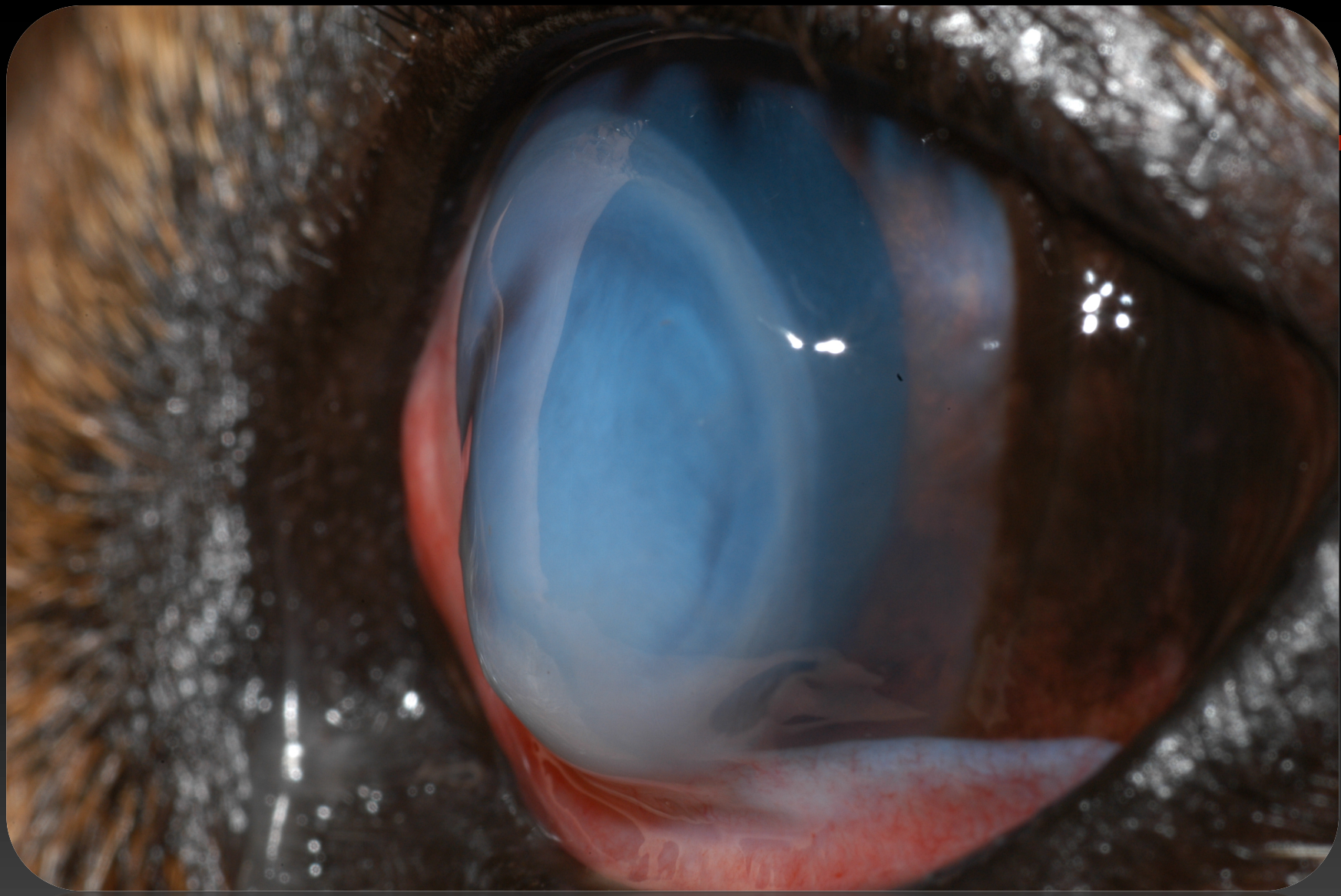
- Corticosteroids
  - Prednisolone acetate
  - Dexamethasone
  - Hydrocortisone
- NSAIDs
  - Flurbiprofen
  - Diclofenac sodium (Voltaren®)

Oral/Systemic

- Corticosteroids
  - Prednisone/prednisolone
  - Dexamethasone
- NSAIDs
  - Carprofen (Rimadyl®)
  - Meloxicam (Metacam®)
  - Deracoxib (Deramaxx®)
  - Piroxicam (Feldene®)
  - Robenacoxib (Onsior®)
  - *Tepoxalin (Zubrin®)*

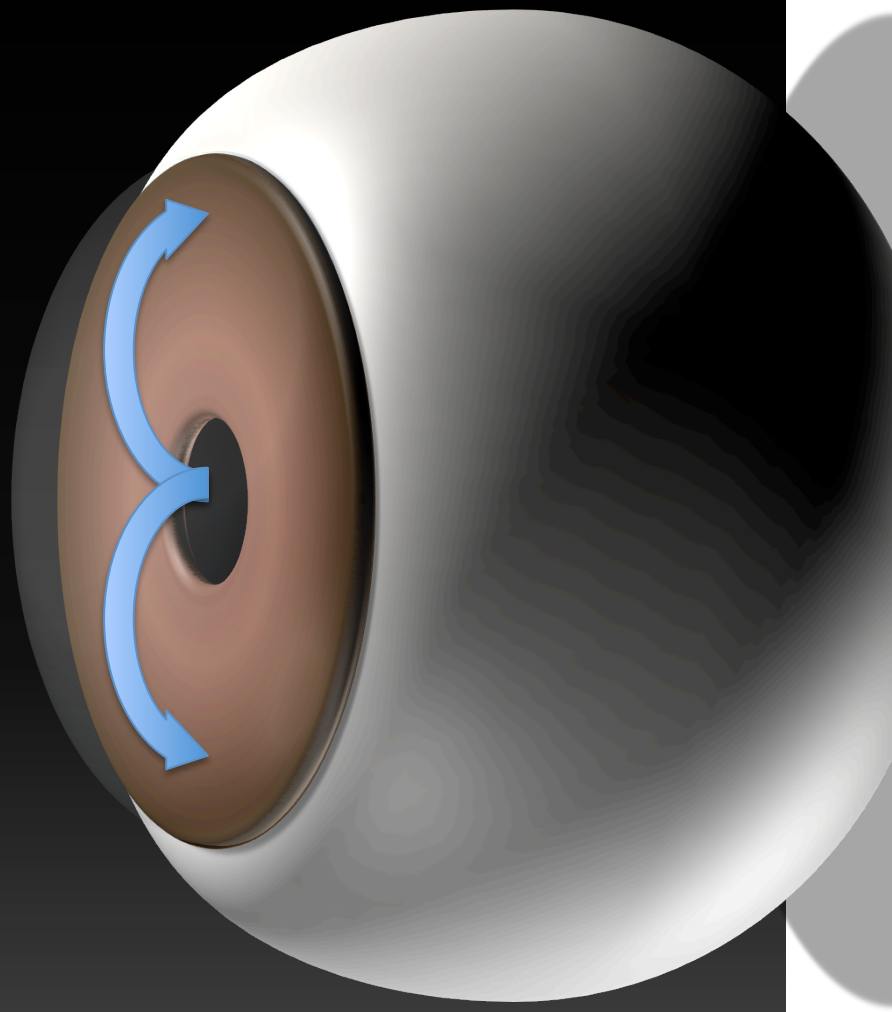
Anti-Inflammatory "Rules of Thumb"

1. Corneal ulcer?
   - NO TOPICAL STEROIDS
   - Use topical NSAIDs judiciously
2. Concurrent glaucoma or glaucoma risk?
   - Avoid topical NSAIDs if possible
3. Treating anterior uveitis?
   - Hydrocortisone is ineffective
4. Posterior segment/orbital inflammation?
   - Use oral anti-inflammatories



Adverse Effects of Topical NSAIDs

- Decreased facility of aqueous outflow
- Risk of exacerbating or eliciting glaucoma
- Judiciously used in acutely inflamed eyes (i.e. immediately following cataract surgery)
- Mechanism unknown
- Similar risk has NOT been identified with systemic NSAIDs



Topical Hydrocortisone

- Hydrocortisone is a **poor** topical anti-inflammatory
  - Poor penetration of both conjunctival and corneal tissue

Future Directions

- Enhanced penetration
  - Corticosteroids
    - Lotemax® (loteprednol)
    - Durezol® (difluprednate)
  - NSAIDs
    - Nevanac® (nepafenac)
    - Xibrom® (bromfenac)

Oral Anti-inflammatories

- Topical corticosteroids/NSAIDs will NOT reach the posterior segment (choroid, retina, optic nerve) or orbit
- In health, the blood-aqueous barrier limits intraocular drug delivery from the bloodstream
- During inflammation, blood-aqueous barrier is compromised
  - Systemic drugs have enhanced access to the intraocular environment

Presenter Indications for Topical Anti-Inflammatories

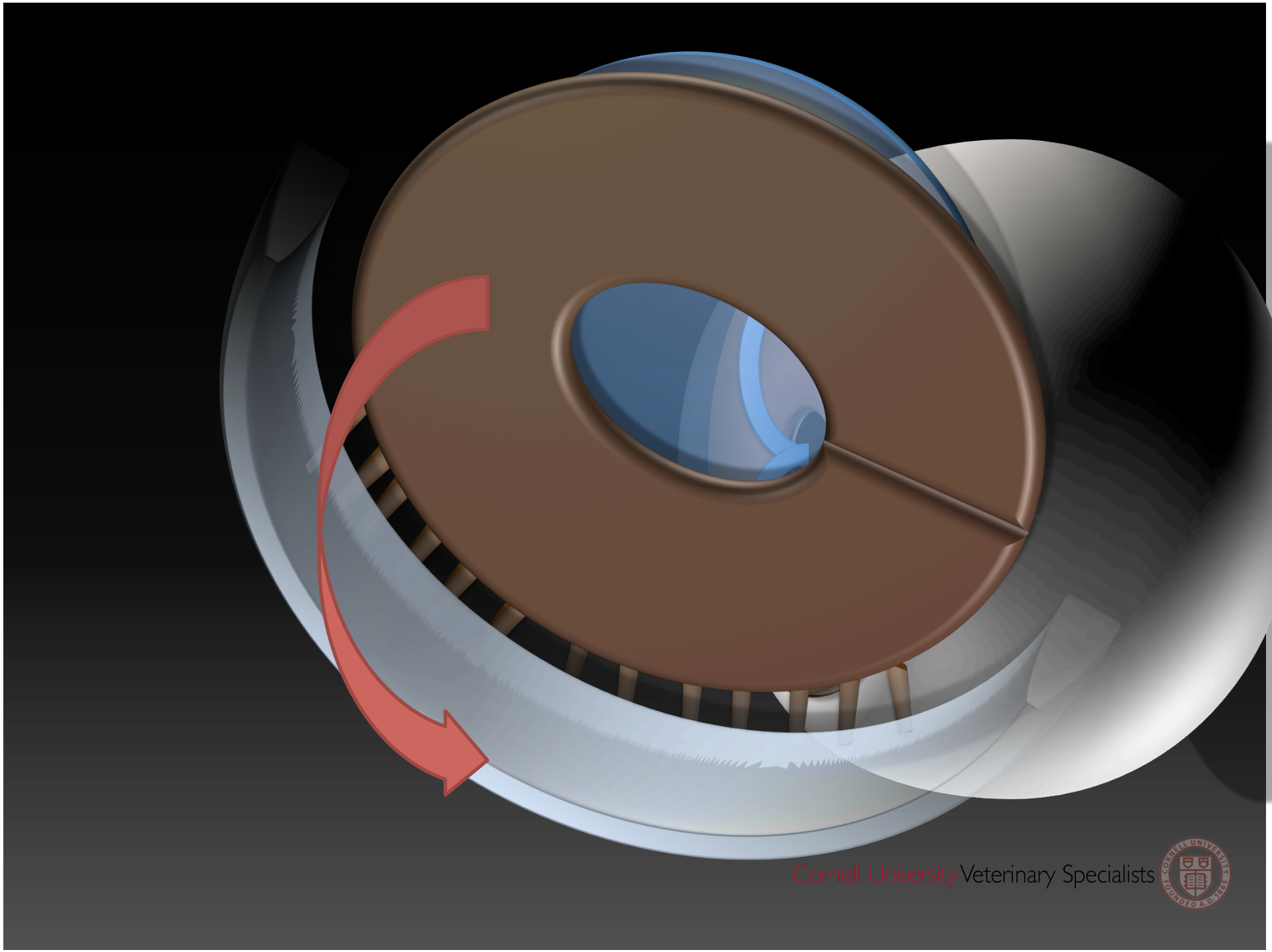
1. Treatment of anterior disease/uveitis
   - Corticosteroid is preferred in the face of secondary glaucoma or glaucoma risk
   - NSAID is preferred in patients with diabetes mellitus
   - Hydrocortisone is INEFFECTIVE

Presenter Indications for Oral Anti-Inflammatories

1. Treatment of posterior ocular inflammation
2. Treatment of uveitis/adnexal disease in the presence of ulcerative corneal disease

Concurrent use of oral NSAID and topical corticosteroid (and vice versa) is **low risk**.

Glaucoma Medications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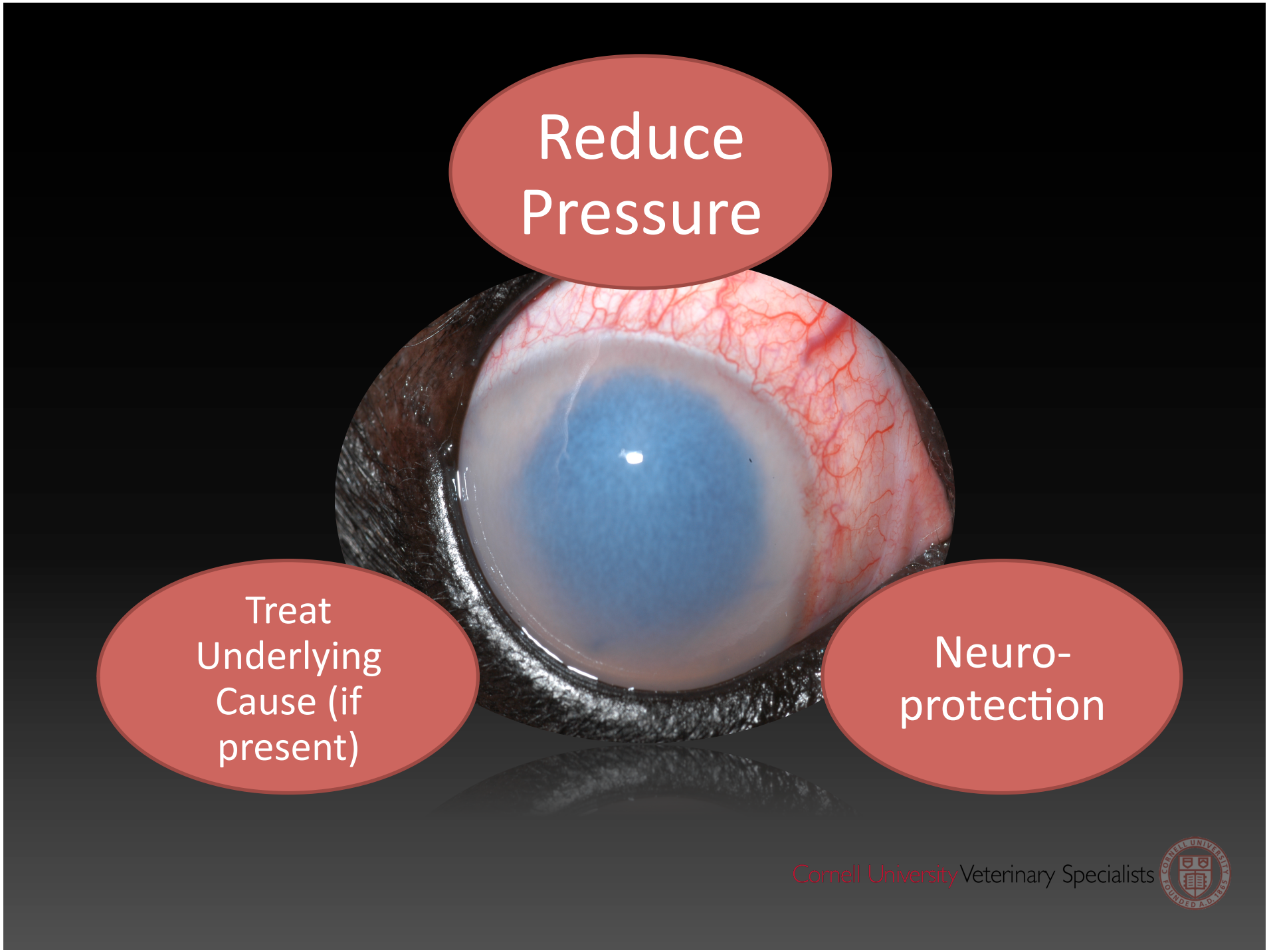
Reduce Pressure
Treat Underlying Cause (if present)
Neuro-protection
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Reducing Intraocular Pressure

ACUTE

- Osmotic agents
  - Mannitol (intravenous)

MAINTENANCE

- Carbonic Anhydrase Inhibitors
  - Dorzolamide, brinzolamide (topical)
  - Methazolamide (oral)
- Beta Blockers
  - Timolol, betaxolol (topical)

Prostaglandin Analogs

- Latanoprost (Xalatan™)
- Travoprost (Travatan™)
- Bimatoprost (Lumigan™)

Prostaglandin Analogs

- PGF2α analogs
- Encourage aqueous outflow through the **unconventional** pathway
- May also alter the trabecular meshwork within the iridocorneal angle

Prostaglandin Analogs

- Effect within 20-60 minutes
  - –May be useful in acute glaucoma therapy
  - –Commonly used as maintenance therapy
- **Ineffective in cats**
  - –Physiologic differences in intraocular receptors
  - –New evidence indicates some effect in **acute** phase of feline glaucoma

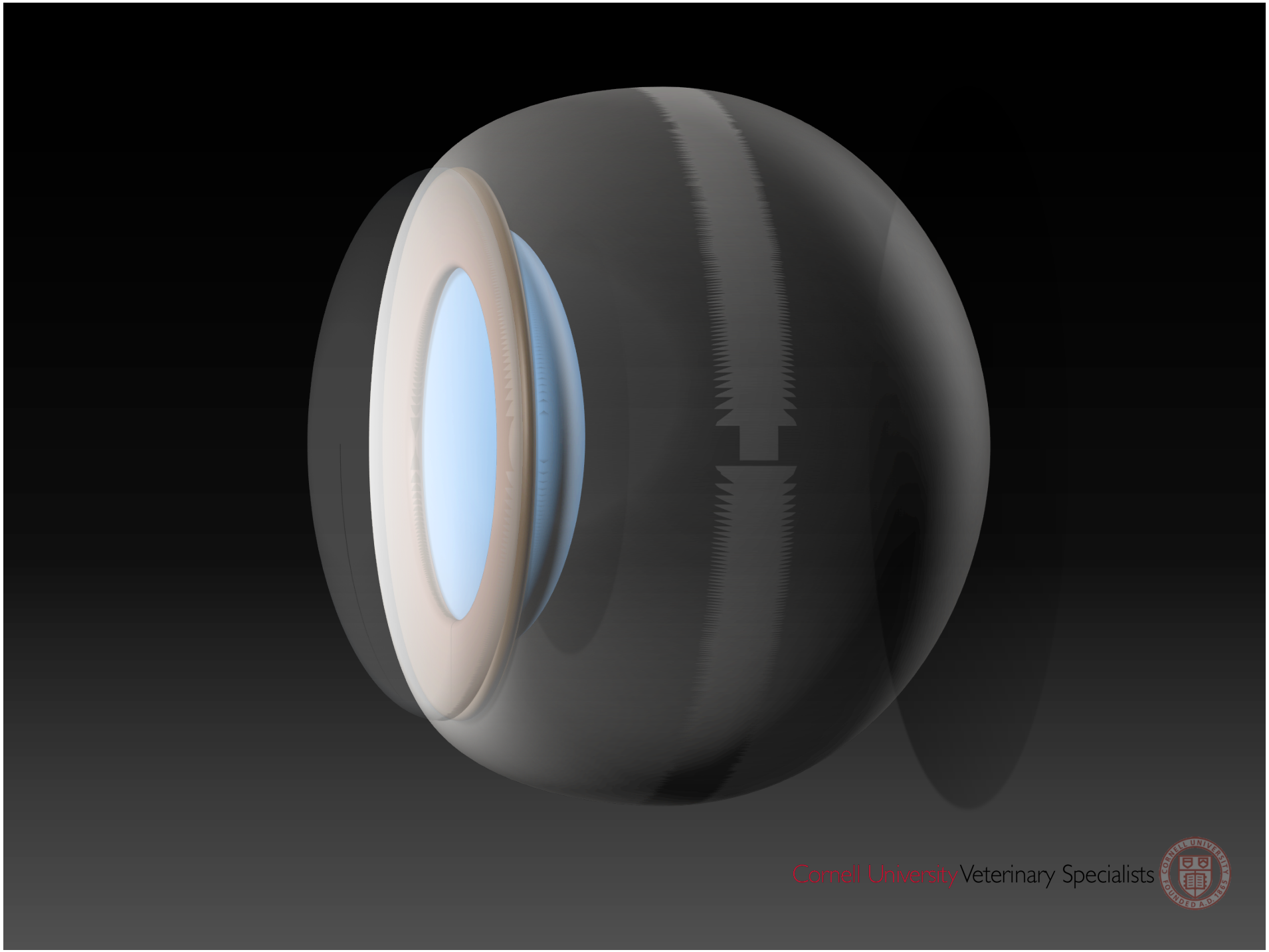
Prostaglandin Analogs

Side Effects

- Local irritation
- Blepharospasm
- Aqueous flare
- Iris color change
- Miosis
- **Beauty??** (Latisse®)

Contraindications

- Lens luxation
- Uveitis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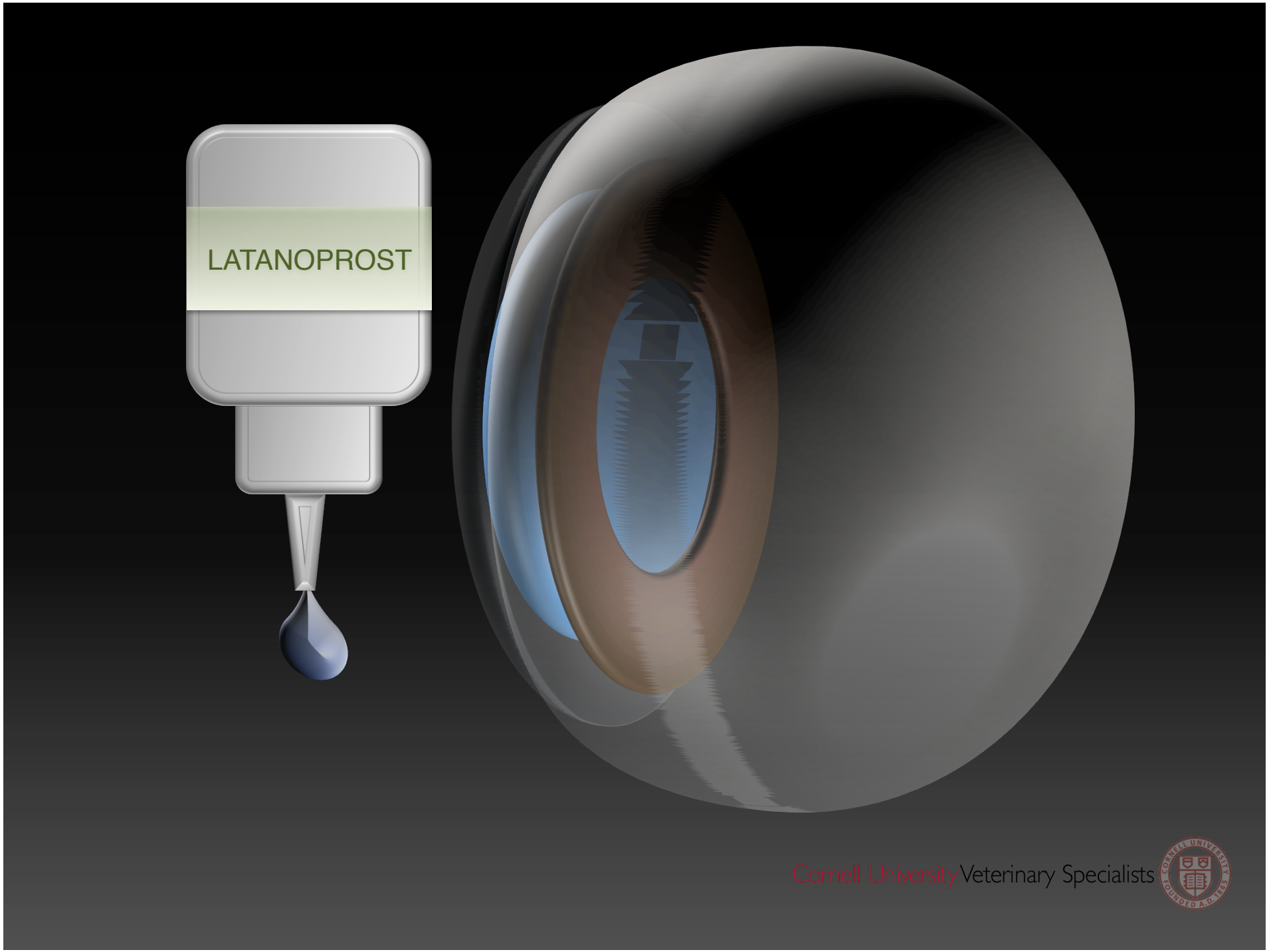
LATANOPROST
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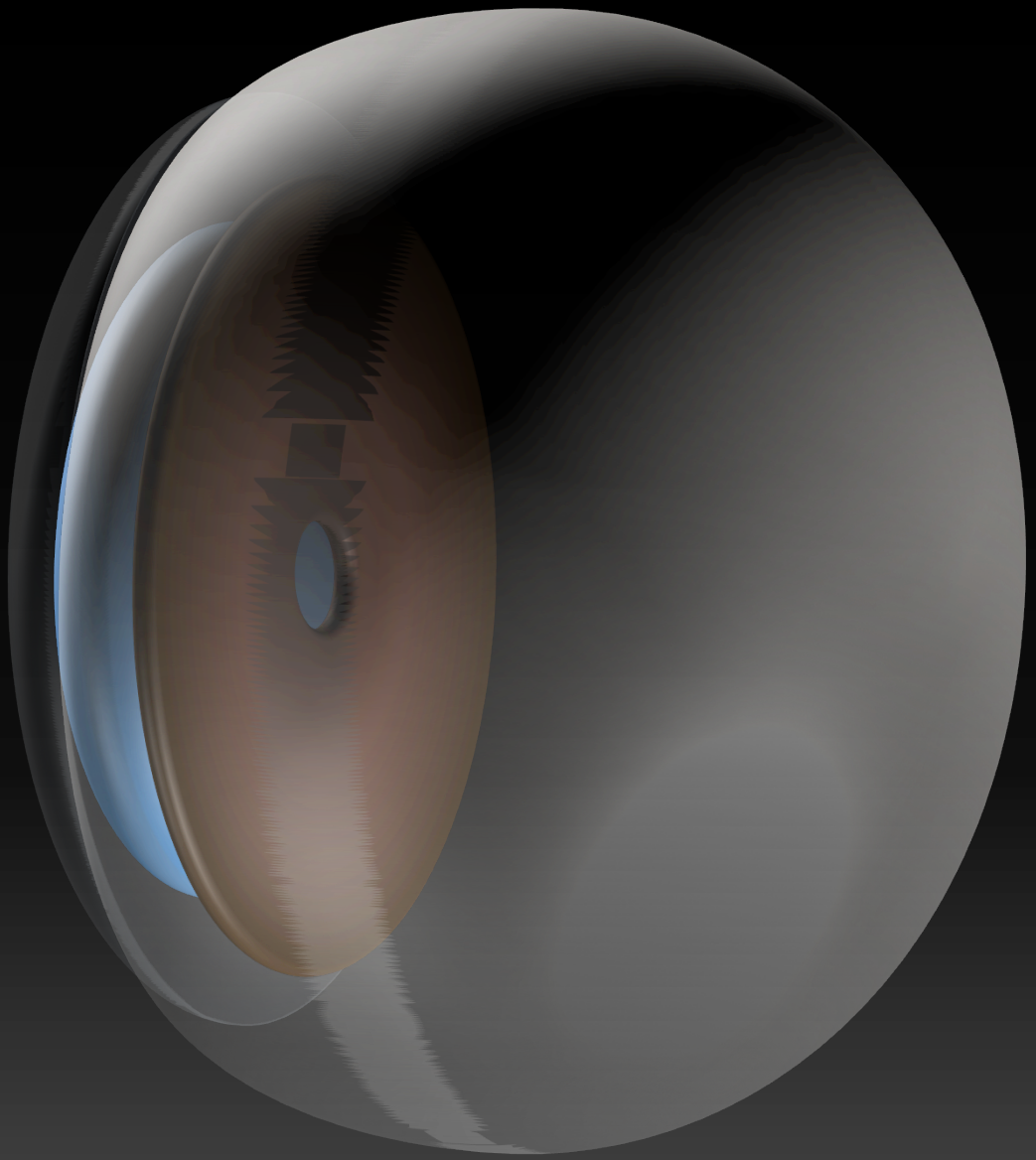

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Neuroprotection

- Mitigate ischemic damage to the optic nerve/ retina
- Mechanisms of neuroprotection
  - Vasodilation
  - Antagonism of retinal excitotoxicity
  - Antioxidant therapy
- Potential Agents
  - Calcium channel blockers (amlodipine)
  - NMDA antagonists (memantine)

Canine Glaucoma

Corneal edema
Episcleral congestion
PLR deficit/pupil dilation
IOP > 25 mmHg

Lens in anterior chamber?

Hypopyon, Hyphema, Tumor, Trauma

No additional findings

1. 1 drop **latanoprost** (0.005%)
2. Check IOP in 60 minutes
3. If IOP still > 25 mmHg, IV bolus **mannitol (1 gram/kg)** over 20 minutes
4. Dorzolamide QID and/or methazolamide PO BID-TID
5. **Latanoprost** BID
6. **Timolol** BID-TID
7. **Amlodipine**
8. Consider analgesia

1. Prednisolone acetate BID-QID
2. Dorzolamide QID and/or methazolamide PO BID-TID

- Focus on treating inflammation and/or underlying cause
- Can consider mannitol (questionable efficacy in the face of uveitis)
- Avoid use of latanoprost or prostaglandin analogs

1. No latanoprost!
2. Bolus **mannitol (1 gram/kg)** over 20 minutes
3. Dorzolamide QID and/or methazolamide PO BID-TID
4. Prednisolone acetate BID-QID

Feline Glaucoma

PLR deficit/mydriasis
IOP > 25 mmHg

Lens in anterior chamber?

No lens in anterior chamber

1. Prednisolone acetate BID-QID
2. **Dorzolamide** QID
3. **Avoid methazolamide** due to risk for systemic side effects in cats
4. **Timolol** BID

- Focus on treating the inflammation and underlying cause.
- Can consider mannitol but use with caution in cases of uveitis.
- Latanoprost is ineffective in cats!

1. No latanoprost!
2. Bolus **mannitol (1 gram/kg)** over 20 minutes
3. Check IOP in 60 minutes
4. Dorzolamide QID
5. **Avoid methazolamide** due to risk for systemic side effects in cats
6. Prednisolone acetate BID-QID

Lacrimostimulant Medications

Stimulation of Natural Tear Production

- Definitive treatment for keratoconjunctivitis sicca
- **Lacrimostimulants**
  - –Cyclosporine A (CsA)
  - –Tacrolimus (TAC)

Cyclosporine A (CsA)

- Calcineurin inhibitor
  - Binds intracellular *cyclophilin*
  - Interrupts inflammatory cell activity (T-lymphocytes)
  - Inhibits inflammation
- Stimulates tear production
  - Mechanism not well-understood
- Also stimulates mucin production

Cyclosporine A (CsA)

- Available in commercial and compounded formulations
  - –Restasis® - 0.05% suspension
  - –Optimmune® - 0.2% ointment
  - –1 and 2% compounded ointments, oil immersions, or suspensions

Cyclosporine A (CsA)

- Side effects
  - –Topical hypersensitivity
  - –Systemic absorption
    - Suppression of systemic lymphocyte activity
    - Clinical significance unknown

Cyclosporine A (CsA)

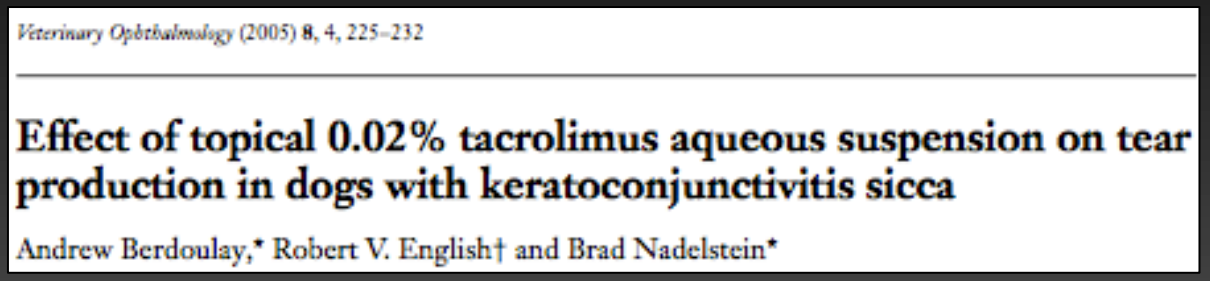
- Lesser response if STT value is **< 2 mm/min** at diagnosis
- Poorer prognosis if STT value is **0 mm/min** at diagnosis
- Maximal response may require up to 8 weeks of **compliant** treatment

Tacrolimus (TAC)

- Formerly FK 506 or fujimycin
- Also a calcineurin inhibitor
  - Mechanism different than CsA
- 10-100 times more potent effects than CsA

Tacrolimus (TAC)

- Studies support anecdotal claims
  - All dogs controlled with CsA could also be controlled with TAC
  - 25% of those dogs experienced STT increase of 5 mm/min or greater
  - 50% of dogs whom did not respond to CsA did so with TAC



Veterinary Ophthalmology (2005) **8**, 4, 225–232

Effect of topical 0.02% tacrolimus aqueous suspension on tear production in dogs with keratoconjunctivitis sicca

Andrew Berdoulay,* Robert V. English† and Brad Nadelstein*

Tacrolimus (TAC)

- No commercial ophthalmic available
- Compounded into 0.02/0.03% concentration preparations
- Long-term ophthalmic side effects not documented

Tacrolimus (TAC)

- Dermatologic side effects
  - Protopic®
  - Reports of neoplasia (lymphoma, squamous cell carcinoma) with long-term use

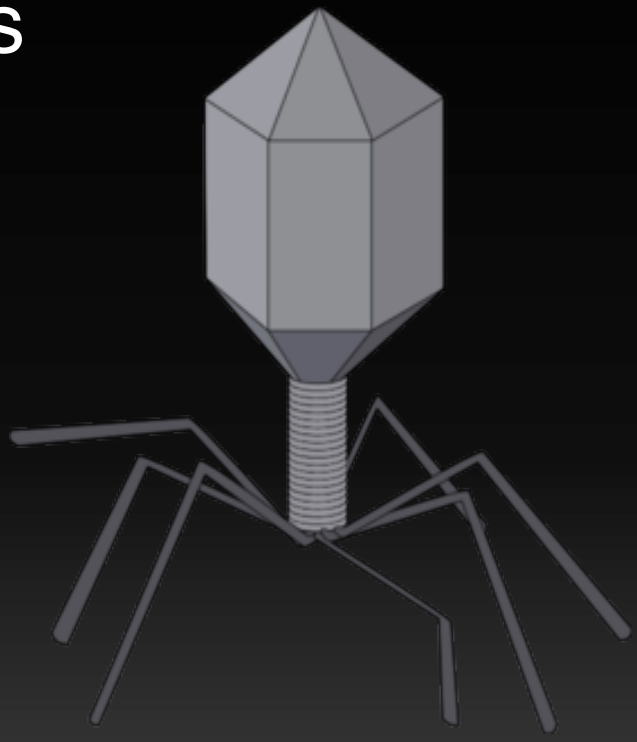
Use of Lacrimostimulants

- Cyclosporine is the first-choice for treatment of canine KCS
- Tacrolimus should be reserved for particularly severe or refractory KCS
  - May also be considered in dogs with pigmentary keratitis
  - May inhibit/partially reverse corneal melanosis

Antiviral Medications

Antiviral Agents

- Mostly nucleoside analogs
  - Interfere with viral DNA replication in infected cells
- Act at **cytoplasmic** level
  - Risk of toxicity to non-infected cells



Antivirals in Veterinary Medicine

- Most agents are “virostatic”
  - Topicals historically require **frequent application**
- Poor compliance can prevent effective treatment

Antivirals in Veterinary Medicine

- In vitro and in vivo studies support clinical use
- Not all drugs equally effective against FHV1
- Significant differences
  - Safety
  - Bioavailability
  - Effective route of administration

Acyclovir (Zovirax®)

- Commonly employed in human medicine (HSV-1)
- Pharmacology
  - Must undergo activation via **viral enzymatic phosphorylation**
- Associated with lower toxicity to non-infected cells

Acyclovir (Zovirax®)

- Does not reach effective serum concentrations in cats after systemic administration
- Associated with side effects:
  - Bone marrow suppression
    - Leukopenia
    - Anemia (non-regenerative)

Valacyclovir (Valtrex®, Zelitrex®)

- Ester pro-form of ACV
- 2.3-fold greater bioavailability in cats, but…

Associated with severe bone marrow suppression, hepatic necrosis, and renal tubular epithelial necrosis

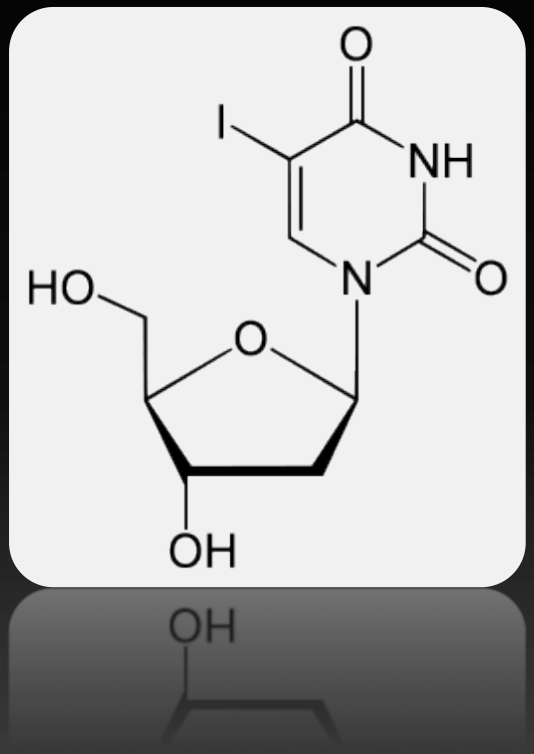

VALTREX®
Cornell University Veterinary Specialists

Topical Antiviral Agents

- Idoxuridine
- Trifluridine (Viroptic®)
- Cidofovir

Idoxuridine and Trifluridine

- Effective against FHV1
- Do **not** require viral enzyme activation
  - Less specificity for infected cells
- Frequent reports of severe ocular irritation with trufluridine



Idoxuridine and Trifluridine

- Idoxuridine compounded into 0.1% formulations
- Trifluridine available as Viroptic®
- Frequent administration is required for efficacy
  - **At least 5 times daily**

Cidofovir

- No viral enzyme activation required
- Requires **twice daily** application
- Well-tolerated and effective in a recent in vivo study
- Compounded into 0.5% aqueous formulation

Penciclovir

- Commercially available in pro-drug form as **famciclovir (Famvir®)**
- Structurally similar to ACV
  - Requires viral enzyme activation
- Subject of recent in vitro and in vivo investigation

Famciclovir (Famvir®)

- Atypical pharmacodynamics
  - Complex, non-linear metabolism and distribution in cats
  - Fails to reach effective concentrations in plasma in cats after administration of human dose (15 mg/kg)

UCDAVIS VETERINARY MEDICINE

Thomasy SM et al. Am J Vet Res. 2007 Nov;68(11):1252-8

Famciclovir (Famvir®)

- Oral doses of 90 mg/kg TID achieved therapeutic plasma concentration
  - Reduced FHV1 antibody detection
  - Clinically reduced signs of conjunctivitis and rhinitis
  - Did not produce adverse side effects

UCDAVIS VETERINARY MEDICINE

Thomasy SM et al. Am J Vet Res. 2011 72(1):85-95

Famciclovir (Famvir®)

- High-dose therapy can be costly (even with generic famciclovir)
- Anecdotally, reported effective at lower doses (Plumb's Veterinary Formulary)
- Subsequent study confirmed efficacy at 40 mg/kg PO BID

UCDAVIS VETERINARY MEDICINE

Thomasy SM et al. Am J Vet Res. 2012 (7):1092-9

Famciclovir (Famvir®)

- Oral administration of 40 mg/kg to 7 client-owned cats with characteristic ocular signs of FHV1
- Results
  - **Tear** penciclovir concentration that approximated plasma concentration
  - **Tear** penciclovir concentration exceeding the MIC for FHV-1

UCDAVIS VETERINARY MEDICINE

Thomasy SM et al. Vet Ophthalmol 2012 (5):299-306.

Famciclovir (Famvir®)

- Available in 125 mg and 250 mg tablets
- Presenter's preferred dosage:
  - 40-50 mg/kg BID
- Safe dose has not yet been determined for kittens < 6 mos

Severe Herpetic Disease

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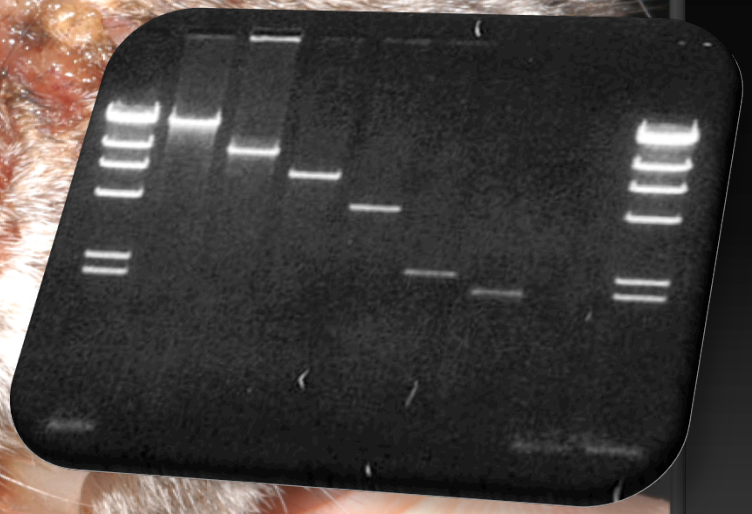
Keratitis
Conjunctivitis
Blepharitis
Dermatitis



UCDAVIS VETERINARY MEDICINE

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Severe Herpetic Disease

UCDAVIS VETERINARY MEDICINE

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2 Weeks of Famciclovir Therapy (90 mg/kg BID)

UCDAVIS VETERINARY MEDICINE

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2 Weeks of Famciclovir Therapy (90 mg/kg BID)

UCDAVIS VETERINARY MEDICINE

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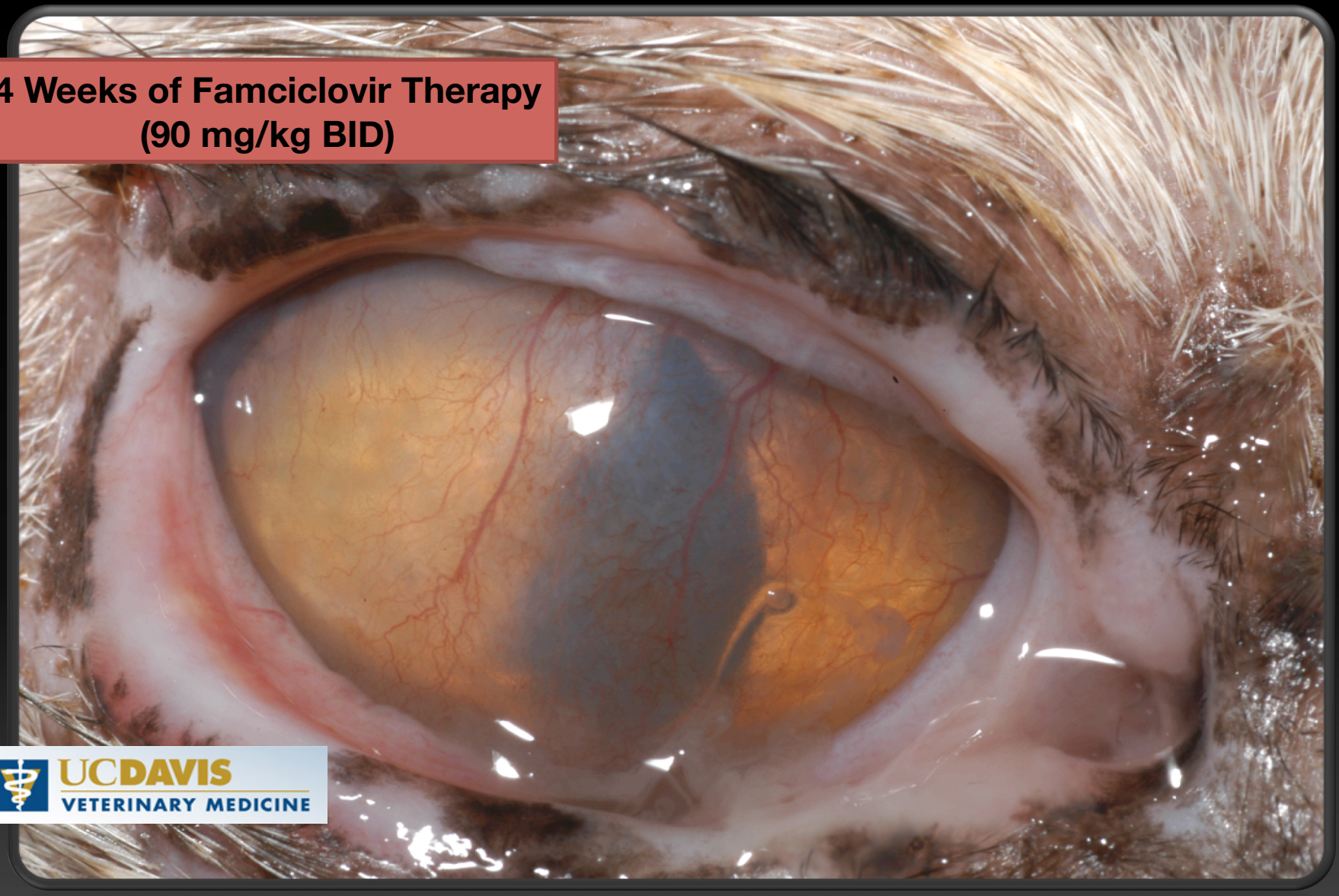
4 Weeks of Famciclovir Therapy
(90 mg/kg BID)
UCDAVIS
VETERINARY MEDICINE
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Medical Treatment for Cataracts?

No medication has been proven to **reverse** cataract development or improve vision in patients with progressive cataracts

Veterinary Ophthalmology (2006) 9, 5, 311–316

CLINICAL ARTICLE

The effect of a topical antioxidant formulation including N-acetyl carnosine on canine cataract: a preliminary study

David L. Williams and Patricia Munday

Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge, CB3 OES, England, UK

- Thirty dogs treated for at least 2 months
- Reduction of lens opacity in dogs with immature cataract or nuclear sclerosis
- Owner reports "suggested" improved visual behavior in 80% of cases

Effect of grape polyphenols on oxidative stress in canine lens epithelial cells

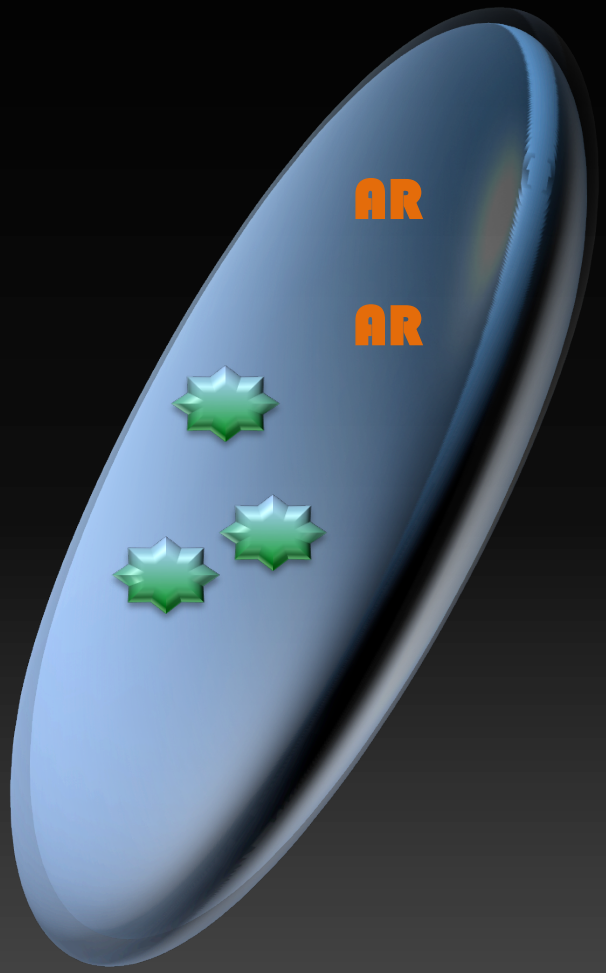
Curtis A. Barden, MS; Heather L. Chandler, PhD; Ping Lu, MD, PhD, MPH; Joshua A. Bomser, PhD; Carmen M. H. Colitz, DVM, PhD

AJVR 2008

- In vitro
- Grapeseed extract
- Significant inhibition of mechanisms of oxidative stress
- In vivo studies not yet presented

Medical Treatment for Cataracts

- Aldose reductase inhibition
  - Recent prospective study of Kinostat®
  - Demonstrated significant delay of cataract onset and progression in client-owned diabetic dogs



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Topical KINOSTAT™ ameliorates the clinical development and progression of cataracts in dogs with diabetes mellitus

Peter F. Kador,*† Terah R. Webb,‡ Dineli Bras,‡ Kerry Ketring§ and Milton Wyman*‡¶

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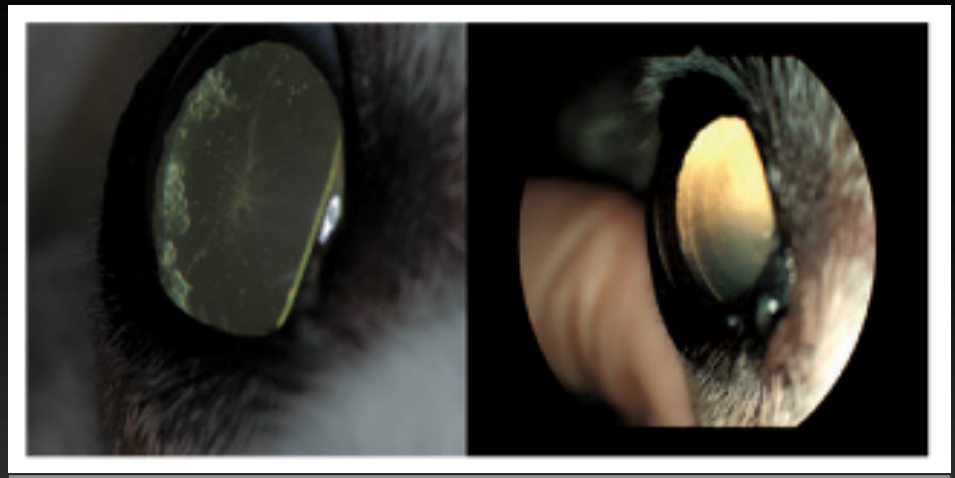
- Controlled study
- 12 months
- Drop given TID OU
- Significant inhibition of cataract **when given at time of DM diagnosis**



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