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Retroillumination is a simple and useful technique for:

- Assessment of aqueous flare
- Focal illumination or transillumination
- Tonometry (measurement of intraocular pressure)
- 4. Tonometry (measurement of intraocular pressure)
- 3. Assessment of aqueous flare
- 2. Focal illumination or transillumination
- 1. Retroillumination

Mastering 4 skills will permit a very thorough examination of the anterior segment:

1. Retroillumination
2. Focal illumination or transillumination
3. Assessment of aqueous flare
4. Tonometry (measurement of intraocular pressure)

To perform a thorough ophthalmic examination, you need:

1. The patient and veterinarian at eye level with each other
2. Dim ambient light
3. A bright, focal light source
4. A source of magnification
5. An orderly and complete approach

All small animal patients should be examined on a table. The veterinarian should be seated in front of them; ideally on a wheeled stool. Since the eye exam relies upon being able to look inside a dark chamber (the eye) and judge optically clear surfaces, the eye exam must be done in a darkened room with a bright and focal light source. Detection of minute but important pathology necessitates use of magnification. This combination can best be provided using an Optivisor® head loupe and Finoff® transilluminator or an otoscope used without the plastic cone. The ophthalmic examination should be carried out in a repeatable and sequential manner to ensure that nothing is overlooked. Examining the unaffected eye first in animals with unilateral disease ensures that it is not forgotten and provides information on the individual patient’s normal ocular appearance. A prepared exam sheet reminds the practitioner to perform all necessary tests in the correct sequence. An obvious method is to begin at the front and progress to the back of the eye, while simultaneously beginning peripherally and working axially: eyelids (periorcular skin, eyelid margin, and cilia), conjunctiva (nasolacrimal puncta, third eyelid, bulbar, and palpebral conjunctival surfaces), sclera, cornea (tear film and particularly the limbus), anterior chamber, iris, and lens. Anterior segment examination should be initiated prior to pupil dilation so that the iris face is easily examined; however complete examination of the lens requires full dilation.

Focal illumination or transillumination

This step requires a source of focal illumination and magnification as discussed earlier. To maximize the benefits of focal illumination, the light source should be directed from an angle that differs from the observer’s viewing angle. Varying the viewing and lighting angles relative to each other permits the examiner to utilize parallax, reflections, perspective, and shadows to gain valuable information regarding the depth within the eye and the 3-dimensional character of lesions. The anterior segment should be examined sequentially from multiple angles using this technique.

Assessment of aqueous flare

Aqueous flare is a pathognomonic sign of anterior uveitis and is due to breakdown of the blood-aqueous barrier with subsequent leakage of proteins into the anterior chamber. Aqueous flare is best detected using a very focal, intense light source in a totally darkened room. The passage taken by the beam of light is viewed from an angle. In the normal eye, a focal reflection is seen where the light strikes the cornea. The beam is then invisible as it traverses the almost protein- and cell-free aqueous humor in the anterior chamber. The light beam is visible again as a focal reflection on the anterior lens capsule and then as a diffuse beam through the body of the normal lens. If uveitis has allowed leakage of serum proteins into the anterior chamber, then these will cause a scattering of the light beam as it passes through the aqueous. Aqueous flare is therefore diagnosed when a beam of light is seen traversing the anterior chamber and joining the focal reflections on the corneal surface and the anterior lens capsule. The beam produced by the smallest circular aperture on the direct ophthalmoscope held as closely as possible to the cornea in a completely darkened room and viewed transversely with a source of magnification will also provide excellent results. Assessment of flare may be easier after complete pupil dilation due to the apparent dark space created by the pupil.
Tonometry
Assessment of intraocular pressure (IOP) - or tonometry - is essential for differentiation of the two major, vision-threatening conditions in which red-eye is the hallmark feature – uveitis and glaucoma. The Tonopen® (http://www.danscottandassociates.com/) makes measurement of IOP easier in all species. Unlike the Schiotz tonometer, the Tonopen measures IOP directly and does not require any conversion. It can also be held horizontally and allows measurements to be performed with the patient’s head held in a normal, relaxed position. Finally, it has a small probe that permits easy measurement of IOP in even the smallest feline and pediatric canine eyes.

Across large populations, normal canine and feline IOP is reported as approximately 10-25 mmHg. However, significant variation is noted between individuals, technique, and time of day. Comparison of IOP between right and left eyes is therefore critical to interpretation of results. A good rule of thumb is that IOP should not vary between eyes of the same patient by more than 20%. The obvious application for tonometry is the diagnosis of glaucoma where IOP is generally elevated. However tonometry is also used to diagnose uveitis; in which IOP is lowered. Perhaps the most important role for tonometry is the monitoring of progress of these diseases and the adjustment of medications based on these data.

WHAT’S NEW IN OCULAR PHARMACOLOGY?
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What route when?
Three anatomic features determine ocular drug penetration:
1. The cornea - Few topically applied drugs penetrate the cornea. Those that do penetrate do not “reach” the vitreous, choroid, retina, optic nerve or orbit.
2. The blood-ocular barrier prevents most systemically administered drugs from entering intraocular tissues other than the uvea.
3. The avascular structures of the eye - Systemically administered drugs “reach” only vascular areas of the eye.

The Golden Rules of Ophthalmic Drug Delivery
1. Some drugs that are unsafe topically can be given safely via a systemic route
2. Some drugs that are unsafe systemically can be given safely topically
3. Otic and dermatologic preparations should never be used ophthamically
4. Topical drugs should never be administered subconjunctivally
5. Drugs required in high concentration in the cornea/conjunctiva are best administered by frequent topical application.
6. Drugs required in high concentration in vascular components of the eye usually are best administered systemically.
7. Increased “dose” of topically applied drugs is achieved by increasing drug concentration; increasing frequency of application; or increasing contact time
8. Systemic absorption of drugs from the conjunctival sac following topical application may result in notable blood concentrations in small patients
9. Ointments increase contact time, provide lubrication, and protect against desiccation
10. Ointments should not be used when corneal rupture is present/likely or prior to ocular surgery
11. Subconjunctival injection permits a portion of the administered drug to bypass the barrier of the corneal epithelium and penetrate transcellerally. However, a notable proportion of the injected drug leaks back out the injection tract and is absorbed as if it was administered topically.
12. Always administer one drop
13. Always leave 5 minutes between drops of a different type
14. Always work “up” in viscosity when applying two or more different drops or ointments to the same eye

Ophthalmic Antibiotics
Triple antibiotic (neomycin, polymyxin B, and bacitracin or gramicidin) has a broad-spectrum, particularly against many Gram positive organisms of the conjunctiva flora. Additionally, polymyxin B is effective against Pseudomonas spp. therefore triple antibiotic is a very good choice for prophylaxis.

Chloramphenicol is a broad-spectrum, well-tolerated bacteriostatic antibiotic. However, when drugs are applied directly onto the ocular surface, concentrations achieved are so high that even minimally susceptible bacteria in vitro are often susceptible when “bathed” in the drug following topical application. Additionally, chloramphenicol will penetrate intact corneal epithelium and is good for treating deep stromal keratitis.

Gentamicin is widely used and inexpensive; however bacteria in infected ulcers are frequently resistant. Gentamicin also has relatively poor efficacy against
conjunctival flora. It is not ideal for broad-spectrum prophylaxis. Tobramycin has been less widely used, is available as an ointment or a solution, is inexpensive, and retains good Gram-negative spectrum.

The fluoroquinolones (ciprofloxacin, ofloxacin, etc) are broad-spectrum antibiotics with excellent corneal penetration. Widespread use of fluoroquinolone drugs for prophylaxis in non-infected ulcers is actively discouraged.

**Topical Anti-inflammatory Agents**  
There are two major considerations when choosing an ocular anti-inflammatory agent: 1) which agent and 2) which route of administration?

Corticosteroids are more potent inhibitors of inflammation (and of healing!) than are nonsteroidal anti-inflammatory agents (NSAIDs). Therefore, when significant control of inflammation is required, a steroid should be chosen. When there is a concern regarding local immunosuppression, an NSAID is a preferred choice. Hydrocortisone is a relatively low potency, non-penetrating steroid. Topical dexamethasone and prednisolone are very potent and penetrate an intact cornea. Topical NSAIDs (flurbiprofen, suprofen, diclofenac, and ketorolac) may delay corneal healing and have been associated with ulcer progression and rupture in some infected ulcers and are contraindicated in such situations.

**Glaucoma Medications**  
The large range of glaucoma medications can be daunting. However, all work by one of (or sometimes a combination of) three mechanisms:
1. Decrease aqueous production (carbonic anhydrase inhibitors; beta-blockers; sympathomimetics)
2. Promote aqueous outflow (parasympathomimetics; prostaglandin analogues)
3. Dehydrate the vitreous body (mannitol)

**Some general rules apply for small animals:**
- Dogs seem to tolerate these drugs better than do cats.
- Topical drugs seem to be less potent but carry fewer side effects than systemic agents.
- Expect primary glaucoma to be initially controlled but later need alternate or additional (synergistic) drugs.
- Drugs designed for human (typically open angle) glaucoma; do not work predictably on dogs or cats with (typically closed angle) glaucoma.
- Apraclonidine 0.5% causes systemic toxicity in cats and should NOT be used. It has cardiac side-effects in some dogs. There are better (safer) agents available.

**Carbonic anhydrase inhibitors (CAIs)**
CAIs lower IOP by reducing aqueous humor production. Methazolamide (2-5 mg/kg PO BID – TID) and dichlorphenamide (2-5 mg/kg PO BID - TID) appear to be the best-tolerated systemic CAIs. However they can cause GI upset, hypokalemia, or acidosis with secondary tachypnea, especially in cats. Side effects are rapidly reversible with reduction in dose or frequency. Topical CAIs such as dorzolamide or brinzolamide and a dorzolamide/timolol (beta-blocker) combination provide a means to reduce IOP without systemic side effects. These require application q 8 hours in dogs but may be effective q 12 hours in cats. The major role of the topical CAI’s appears to be maintenance of lowered IOP, rather than management of acute congestive crises.

**Synthetic Prostaglandins**
Latanoprost is most studied of a new class of drugs that lower IOP in humans by promoting non-conventional (uveoscleral) outflow has been developed. In dogs, these drugs produce marked miosis and may also act via increasing conventional outflow and/or alteration of iris plane position. These drugs have very potent IOP-lowering effects in normal and glaucomatous dogs but appear ineffective in cats. Since they are prostaglandins, these drugs contribute to breakdown of the blood aqueous barrier and their use in animals with coexistent glaucoma and uveitis appears unwise. Their effect may be reduced by simultaneous application of a corticosteroid or NSAID.

**Keratoconjunctivitis sicca – beyond cyclosporine**
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Keratoconjunctivitis sicca (KCS) or “dry eye” is often considered as simply an aqueous tear deficiency. However, the tearfilm relies on a complex secretory, distributional, and drainage system which must act together to protect the corneoconjunctival surface. In most KCS cases, treatment with cyclosporine is curative. Unresponsive cases require further discussion.

**The five main treatment goals:**
1. **Resolve the underlying cause.** Although autoimmune dacryoadenitis is most common, consideration of the “damnit” list, careful assessment of history and clinical signs, and appropriate diagnostic testing will facilitate recognition of other causes, expedite treatment, and improve prognosis.
2. **Minimize further tear loss and maximize tear production.**
distribution. Dogs with marginal tear production can be made more comfortable by correction of mild entropion or entropion, removal of distichia, or reduction of palpebral fissure size.

3. Stimulate tear production. Tear replacement is no substitute for increased tear production. Cyclosporine (CsA) is an effective drug for this purpose, reduces immune-mediated destruction of the lacrimal gland, is directly lacrimogenic, and promotes mucin production. These three functions and knowledge that immune-mediated dacryoadenitis is the most common cause of KCS make treatment with CsA the first choice. Its direct lacrimogenic effect relies on frequent application, while immunosuppression and remodeling of glandular tissue require more chronic use. Therefore, in most cases this drug should be instituted twice daily and the patient rechecked in approximately 2 weeks. The client should be instructed to apply CsA until the time of recheck examination.

4. Supplement the tearfilm. “Artificial tears” provided as aqueous solutions, viscous polymer or methylcellulose solutions, and petrolatum ointments do not replace all functions served by tears and can dilute naturally-produced tears. These products and their preservatives also can cause surface irritation. Until CsA improves clinical signs, I use preservative-free hyaluronic acid (http://www.imedpharma.com/), which is mucinomimetic and extremely well tolerated in dogs and cats.

5. Treat secondary infection Secondary infection is common when tear quality or quantity declines and can be treated with a well-tolerated, broad-spectrum antibiotic that controls overgrowth of gram-positive flora. Triple antibiotic ointment is an excellent choice. This should be discontinued as soon as clinical signs improve.

What do I do when CsA fails?

1. Reassess cause
If, after 2-4 weeks, a poor clinical response to cyclosporine is noted, the primary cause should be reconsidered. Autoimmune dacryoadenitis is a diagnosis that can be reached only after thorough attention to the DAMNIT list has permitted rejection of all alternate causes such as:

Developmental KCS (acinar hypoplasia) is seen in small breeds, can be unilateral, and is often associated with absolute sicca (STT = 0). It is unlikely to respond to topical CsA and may require parotid duct transposition.

Autoimmune destruction of the lacrimal glands is the most common etiology in dogs. The stimulus for this disease is unknown. These cases are most likely to respond to CsA.

Metabolic causes of KCS are controversial with some studies showing an association between KCS and endocrine disorders. Concurrent treatment of the endocrinopathy might improve prognosis.

Neoplasia of the lacrimal glands is rare; however KCS is seen in association with orbital disease.

Infectious etiologies such as canine distemper virus and feline herpesvirus cause KCS but ocular signs are usually overshadowed by systemic signs. Tear production usually resumes if the infectious etiology resolves. Severe bacterial blepharoconjunctivitis or orbital cellulitis may also affect the lacrimal glands or their ductules producing temporary KCS. Iatrogenic KCS is associated with removal of the third eyelid gland.

Trauma to the lacrimal gland is uncommon; however damage to its innervation (CN V or VII) does occur with coincident dysfunction of eyelid movement and/or neurotrophic keratitis. Concurrent desiccation and crusting of the ipsilateral nostril strongly suggests neurogenic dysfunction. Some advocate oral administration of ophthalmic pilocarpine titrated to just below systemic toxicity in such cases. Signs of toxicity include vomiting, diarrhea, and bradycardia. One dosage recommendation is to use 1% pilocarpine in dogs < 4 kg, 2% in dogs 4-20 kg, and 4% pilocarpine in dogs > 20 kg. The initial dose is one drop PO BID for three days. This dose is increased by one drop every three days until the earliest signs of toxicity are observed. The drug is discontinued for 24 hrs or until gastrointestinal signs abate and then re-instituted at the highest dose which did not produce signs of toxicity. CsA should also be used since it acts via an alternate mechanism and has additional desirable effects.

Toxic causes of KCS are well-described; especially sulfas drugs, atropine, etodolac, and general anesthesia/sedation.

2. Increase CsA dose or frequency
When 0.2% CsA fails, I prefer to try an increased dose (up to 2%) or frequency (up to 4 times daily) before trying alternate drugs.

3. Use alternate immunosuppressive agents
Tacrolimus acts by a different receptor and is more potent than CsA, and may be effective in some patients that are unresponsive to CsA. Safety and efficacy of a 0.02% aqueous suspension have been reported and are very promising. However, an FDA alert regarding
the potential for this drug to cause cancer, especially in children recommends that tacrolimus is used only when other drugs have failed. Topical dexamethasone or prednisolone may reduce dacyroadenitis and keratoconjunctivitis but requires caution in eyes prone to ulceration.

4. Consider qualitative tearfilm disturbances
Qualitative deficiencies result from altered mucin or lipid composition of the tearfilm. Close examination of the meibomian glands and lid margins is recommended. If meibomitis is present, then a protracted course (6-10 weeks) of systemic antibiotics appropriate for deep dermatitis is recommended; sometimes with 1 week of systemic prednisolone (1 mg/kg).

Parotid duct transposition (PDT) involves redirection of parotid saliva to the ventral conjunctival fornix. This is reserved for patients in which no cause is found and which have not responded to protracted and multiple medical therapies. Saliva differs from tears in many ways; especially increased mineral content and higher pH. Common complications of PDT include corneal mineralization and blepharitis secondary to overflowing saliva.

CORNEAL ULCERS – THE GOLDEN RULES OF MANAGEMENT
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A corneal ulcer is characterized by loss of corneal epithelium. With progression, especially in the presence of enzymes with collagenase activity, the corneal stroma becomes involved. Ultimately, corneal perforation and intraocular involvement with visual loss are possible. The golden rules of ulcer management are designed to prevent this progression.

1. Find and remove the primary cause
All patients with ulcers should undergo a very thorough examination aimed at determining and removing/correcting/treating the cause. Failure to do so is one of the most common reasons for an ulcer not to heal or to heal but recur. Because corneal epithelium is constantly being abraded and desiccated but is protected from excess abrasion by the eyelids and tears, ulcers may be thought of as arising when this situation becomes unbalanced. I.e., there is decreased corneal epithelial protection (tear film or eyelid dysfunction) or increased corneal abrasion (exogenous or endogenous friction). Therefore, causes can be divided into those explained by eyelid, eyelash, or tear abnormalities, foreign bodies, exogenous trauma, or a very limited number of microorganisms.

2. Exogenous trauma is a diagnosis by exclusion
Because of the long list of possible causes, ulceration due to unwitnessed exogenous trauma should be diagnosed only after exclusion of all other potential causes. This requires Schirmer tear testing, assessment of palpebral reflexes, thorough examination of lid and conjunctival anatomy and function (including the posterior face of the third eyelid), and consideration of infectious causes.

3. Other than herpesvirus, infection does not cause ulceration
Although secondary bacterial infection is one of the most feared ulcer complications, no bacteria initiate corneal ulcers in small animals. In dogs and cats, the only organisms known to initiate ulcers are feline and canine herpesviruses. Treatment of these ulcers is addressed by the first rule: “find and treat the primary cause”.

4. Bacterial infection makes ulcers deeper or gelatinous or green
Once the corneal epithelium is breached, bacteria (including those that are part of the normal flora) can complicate and cause rapid worsening of corneal ulcers. In particular, Gram-negative organisms cause stromal collagen damage through collagenase production. Hallmark signs of infection include corneal stromal loss (deepening of the ulcer); “melting” or malacia; or infiltration with white blood cells causing the corneal stroma to become greenish-yellow. Ulcers showing these signs should be assessed by cytologic examination of corneal epithelial samples, along with aerobic bacterial culture and sensitivity testing.

5. Know the speed and mechanisms of normal corneal wound healing
Rate of corneal wound healing depends upon the corneal layer involved. Epithelial healing occurs within hours to days and should leave no long-term scar. Stromal healing requires activation of resting kerocytes into active fibroblasts and sometimes fibrovascular ingrowth. This may take weeks to months for a deep ulcer and gray wispy scars are expected. Endothelial cells are post-mitotic in adult animals and regeneration is extremely limited with persistent focal corneal edema resulting following deep ulcers.

6. Prior to therapy, characterize ulcers as “simple” or “complicated”
Simple ulcers, by definition, are superficial and present
less than 7 days. If the ulcer fails to fit either of these criteria then it is defined as complicated. Complicated ulcers need only be present more than 7 days or deep. Complicated ulcers should be further defined as indolent (in dogs only), infected (in cats or dogs), or having their primary cause still present (in cats or dogs). Each of these has a characteristic appearance. Indolent ulcers are also known as refractory or Boxer ulcers, recurrent erosions, or superficial chronic corneal epithelial defects (SCEDs) are seen in dogs only, are superficial, uninfected, chronic or likely to be come chronic, and have a lip of redundant non-healing corneal epithelium that is easily debrided with a cotton-tipped applicator. This lip often produces a characteristic “halo” fluorescein staining-pattern due to leakage of stain under the non-adherent lip. They arise from a failure of replicating and migrating epithelium to complete the final step in healing – to adhere to the underlying stroma via the epithelial basement membrane. They are seen in older dogs of any breeds and younger dogs of a limited number of breeds, especially corgis and boxers. Diagnosis is assumed that the wrong antibiotic was chosen and a different one is tried. This has led to the trite but true saying: “When a superficial ulcer doesn’t heal in 7 days, change your diagnosis, not your antibiotic”. Ulcers in which the primary cause is still present typically appear like simple ulcers but remain chronic. That is, they don’t necessarily worsen; they just don’t heal. Infected ulcers are described above as having stromal loss, malacia, or white blood cell infiltration.

Treatment of Superficial Ulcers
The basic tenets for treatment of superficial ulcers are identification and treatment/correction of the primary cause, along with institution of broad-spectrum topical antibiotic therapy approximately 2-3 times daily. Systemic antibiotics are not indicated since they do not reach an avascular cornea. Prevention of self-trauma and induction of mydriasis are considered on an individual basis. A recheck examination should always be scheduled for inside 7 days. Uncomplicated, superficial ulcers treated in this manner should have healed by 7 days. If they have not, then they have, by definition, become complicated ulcers for one of the three reasons discussed above. One of the most common errors in ulcer treatment is frequently made at this point. It is assumed that the wrong antibiotic was chosen and a different one is tried. This has led to the trite but true saying: “When a superficial ulcer doesn’t heal in 7 days, change your diagnosis, not your antibiotic.”

Treatment of infected ulcers
The same basic tenets apply to treatment of deeper stromal (and typically infected) ulcers: identification and treatment of the primary cause, broad-spectrum topical antibiotic therapy, prevention of self-trauma, and induction of mydriasis. However, antibiotic therapy needs to be more aggressive (up to hourly) and typically is based upon cytology and/or culture results. Arresting corneal malacia requires topical application of anti-collagenase products. Acetylcysteine was once widely advocated for this purpose. More recently, autologous serum has been promoted as a preferred product. In addition to its broad-spectrum anti-collagenase properties, benefits are presumed to arise from numerous growth factors contained in serum. A venous blood sample is collected aseptically and allowed to clot in a sterile tube. After centrifugation, serum is separated and stored in a sterile multidose vial or commercially available eye-drop container (http://www.medi-dose.com/). Autologous serum can then be applied to the infected eye as needed (as frequently as q 1 hour for a rapidly melting corneal ulcer). Serum should be stored in the refrigerator and replaced every few days.

Ulcers that are rapidly progressive, have obvious areas of melting, or are deeper than half corneal thickness, are likely to benefit from surgery. This is because the corneal stroma has only a limited ability to regenerate, and healing is slow, often requiring fibrovascular infiltration. This may take weeks if it occurs spontaneously from the limbus, but can be rapidly provided by conjunctival grafting. In addition, conjunctival grafts provide mechanical support for a weakened cornea, a continuous supply of serum, which contains anti-collagenases and growth factors, an immediate source of actively replicating subconjunctival fibroblasts for collagen regeneration in the stroma, and a route for systemic antibiotics to be delivered to the corneal ulcer.

Temporary Tarsorrhaphy or Third Eyelid Flap?
Third eyelid flaps have been used widely for treatment of ulcers. While they do provide a “bandage” which reduces desiccation and frictional irritation of the cornea by eyelids, they are associated with some unwanted and potentially deleterious effects. Penetration of medications through or around the third eyelid to the affected cornea is questionable at best. Rather, the anterior face of the third eyelid provides a slick, and direct “chute” to the nasolacrimal puncta. Inability of the owner and clinician to monitor progress, or more importantly worsening, of the ulcer behind the third eyelid is another serious limitation of this technique. By comparison, a temporary lateral tarsorrhaphy is extremely easy to perform, provides adequate corneal protection, and allows medication and monitoring of the ulcer. A temporary tarsorrhaphy is performed using 3-0 or 4-0 Vicryl® on a 3/4- or ½- curved, cutting micropoint needle, and 3-5 X magnification. The upper eyelid is grasped gently with fine tissue forceps and the needle is passed through the skin, entering at the haired-non-haired junction approximately 3 mm from the eyelid margin and emerg-
Treatment of Canine Indolent Corneal Ulcers

All indolent ulcers should be debrided with a dry cotton-tipped applicator following application of topical anesthetic. This is part of the diagnostic and therapeutic processes. The epithelial lip surrounding these ulcers is very easily debrided, and sometimes results in an extensive ulcer. Occasionally, epithelium can be debrided out to the limbus. However, this is a necessary first step and inadequate debridement is one of the more common reasons for treatment failure. A simple (non-indolent) ulcer cannot be debrided in this fashion. Debridement alone resolves some indolent ulcers. However, many will not resolve without a grid keratotomy (GK). First, any redundant, non-adherent epithelium is debrided with a dry cotton-tipped applicator. Then a GK is performed by making linear striations in the cornea in a “cross-hatch” or grid pattern using the tip of a 25-gauge needle. A tuberculin syringe seems to be the “handle” for directing the needle. Striations need to extend from normal adherent epithelium, through the ulcer bed, and emerge in normal adherent epithelium on the opposite side of the ulcer. They must be multiple and deep enough to create obvious, visible score marks in the corneal stroma. General anesthesia or sedation is recommended for fractious dogs and when learning this technique. With compliant animals and an experienced operator, topical anesthesia and good restraint or sedation may be all that are required. Medical therapy is continued as for any superficial ulcer. A single dose of atropine postoperatively is usually necessary to control reflex uveitis. Topical application of hyperosmotic (5%) sodium chloride ointment at least 4 times daily is recommended if corneal edema is marked as this may further decrease already impaired epithelial adhesion. A success rate of approximately 80% can be expected using GK alone. Treatment failures tend to arise when patients are “under-treated” by inadequate debridement, or too few, too superficial, or too short score marks in the cornea. Indolent ulcers that have not healed 10-14 days after an initial GK should have the procedure repeated. Grid keratotomy is a potent treatment for indolent ulcers in dogs; however it is contraindicated in all other ulcer types in dogs. Indolent ulcers have not been proven to occur in cats and GK is absolutely contraindicated in this species since it is a very “reliable” means of inducing a corneal sequestrum.

Knowledge of just a few key virological points is essential before making rational suggestions to owners regarding diagnosis and treatment of FHV-1-infected cats:

1. **FHV-1 infection (but not necessarily disease) is common.** Over 90% of cats are seropositive to this virus.
2. **FHV-1 establishes lifelong latency** within neural tissues in about 80% of infected cats.
3. **FHV-1 reactivates from latency** commonly with or without obvious cause and with or without clinical evidence of reactivation.
4. **FHV-1 is associated with recrudescence disease in only a small percentage of cats.**
5. **FHV-1 produces disease by (at least) two very different mechanisms** that require markedly different therapeutic approaches:
   6. **Cytolytic (ulcerative) infection** occurs during initial (primary) infection or following viral reactivation from latency. Cells rupture due to active viral replication and therefore therapy should involve an antiviral agent. Immunomodulation at this point is contraindicated.
   7. **Immunopathological (non-ulcerative) inflammation** where immune-mediated disease may involve no or low-grade viral replication. At this stage, antiviral agents alone may not be effective and coincident anti-inflammatory therapy may be indicated.

**Diagnosis**

Because intermittent viral shedding occurs in normal cats and because vaccine virus can become latent and reactivate, the diagnosis of FHV-1 in individual cats is
extremely difficult. When virus is detected in a cat with disease its presence may be coincidental (unrelated to the primary disease process), a consequence of the primary disease process (because stimulation of sensory nerves may cause reactivation), or the cause of the primary disease process. Only the last circumstance is one where viral detection by virus isolation, immunofluorescent antibody assay, or polymerase chain reaction (PCR) is actually useful. However, even then, no test currently differentiates vaccine- from “wild-type”-virus. Because there is no reliable test for FHV-1, I tend to rely on the paradigm that “most feline keratoconjunctivitis is infectious; with Chlamyphila felis and FHV-1 being common”. This is in sharp contrast to dogs where primary infectious keratoconjunctivitis is rare. I then use observations like degree of chemosis (often greater with C. felis) and hyperemia (often greater with FHV-1), presence of keratitis (not a sign of C. felis infection), dendrites (pathognomonic for FHV-1), and upper respiratory signs (more severe in primary FHV-1 infection) to help me make a clinical judgment as to likely cause.

Treatment
I consider therapies for FHV-1-related syndromes under three general headings:

Supportive Therapy
Supportive therapy is the mainstay of treatment for kittens undergoing primary FHV-1 infections since these are usually self-limiting. Major goals are prevention of secondary bacterial infection, especially lower respiratory involvement, and maintenance of adequate nutrition, hydration, and patient comfort. A warm, relatively humid, and well-ventilated environment is essential. For comfort and to improve penetration and efficacy of topical medications, eyes and nostrils should be kept clear of discharge. Nebulization, steam inhalation, and adequate hydration will aid in the loosening and expectoration of secretions. Appetite may be stimulated by offering warmed, strongly flavored, and aromatic foods. Systemic antibiotics should be considered to control secondary infection and to limit chronic sequelae. Topical antibiotics should be used whenever corneal ulceration is present. At this phase of disease, corticosteroids have several deleterious effects such as deeper and more persistent corneal ulcers, corneal edema, corneal vascularization, and sequestrum formation, and should not be used. They may also extend the period of viral shedding. The effect of non-steroidal anti-inflammatory agents and cyclosporine on acute FHV-1 infections has not been examined, however whenever ulceration or other evidence of active lytic infection is observed, anti-inflammatory medications of any type would appear to be ill advised as they may potentiate antigen penetration into and persistence in the corneal stroma.

The use of corticosteroids in chronic recurrent cases of herpesvirus infection in cats is controversial. They seem to reduce conjunctivitis but also may allow the virus to become more established with a rebound of clinical signs when they are stopped. However, they are sometimes necessary for patients with immune-mediated disease such as feline eosinophilic keratoconjunctivitis, even when FHV-1 is suspected of being involved. In these cases, I begin the steroids in the middle of and coincident with a longer course of a topical or systemic antiviral agent.

Antiviral Agents
A large variety of antiviral agents exists for oral or topical treatment of cats infected with FHV-1. However, some general comments regarding these agents are possible:

No antiviral agent has been developed for FHV-1. Agents highly effective against closely-related human herpesviruses are not necessarily or predictably effective against FHV-1 and all should be tested in vitro before they are administered to cats. In vitro potency is described as the drug concentration at which viral replication is suppressed by 50% (or IC50). Therefore, a more potent drug will have a lower IC50.

No antiviral agent has been developed for cats. Agents with a reasonable safety profile in humans are not predictably non-toxic when administered to cats and all require safety and efficacy testing in vivo.

Many antiviral agents require host metabolism before achieving their active form. These agents are not reliably or predictably metabolized by cats and pharmacokinetic studies in cats are required.

Antiviral agents tend to be more toxic than do antibacterial agents since viruses are obligate intracellular organisms and co-opt or have close analogues of the host’s cellular “machinery”.

All antiviral agents currently used for cats infected with FHV-1 are virostatic. Therefore, they typically require frequent administration to be effective.

Efficacy, pharmacokinetics, safety, and efficacy of the following antiviral drugs have been studied to varying degrees:

Idoxuridine is effective against FHV-1, with a reported IC50 of 4.7 μM. It has been used as a topical (ophthalmic) 0.1% solution or 0.5% ointment. Systemic therapy is not possible, and corneal toxicity can occur with topical use although it is usually well tolerated. It should be applied
It is available as a dermatologic cream for humans that shed FHV-1 more often than unsupplemented cats. It is supplemented cats demonstrated more severe disease and change in plasma arginine concentration; however supplementation with L-arginine and plasma lysine concentrations were increased to levels similar to that with bolus administration without change in plasma arginine concentration; however supplemented cats demonstrated more severe disease and shed FHV-1 more often than unsupplemented cats. It is should not be applied to the eye. We are currently investigating its safety and pharmacokinetics in cats but, at this time, its use cannot be recommended.

**Famciclovir** is a prodrug of penciclovir used to enhance bioavailability; however metabolism of famciclovir to penciclovir in humans is complex and requires di-deacetylation, predominantly in the blood, and subsequent oxidation to penciclovir by aldehyde oxidase in the liver. Unfortunately, hepatic aldehyde oxidase activity is nearly absent in cats. Data suggest that the pharmacokinetics of this drug are extremely complex and likely result from nonlinear famciclovir absorption or metabolism, perhaps in association with nonlinear penciclovir elimination. Despite this, there is evidence that 90 mg/kg famciclovir PO three times daily is effective in cats with herpetic disease despite this dose failing to achieve target plasma concentrations.

**Adjunctive therapies**

Because some cats experience frequent herpetic recurrences, investigation of adjunctive therapies safe for longer term use and able to minimize severity, frequency, and duration of recurrent outbreaks is important.

**Lysine** limits in vitro replication of FHV-1 only with concurrent depletion of arginine. In vivo, once-daily oral administration of 400 mg lysine to latently infected cats reduced viral shedding and twice-daily oral administration of 500 mg lysine in cats undergoing primary FHV-1 reduced severity of conjunctivitis. In both studies, plasma arginine concentrations remained normal and toxicity wasn’t observed. However, no treatment effect was noted in cats within a shelter administered oral boluses of 250 mg (kittens) or 500 mg (adult cats) of lysine once daily for the duration of their stay. Because bolus administration of lysine is often impractical, we investigated safety and efficacy of a 5% lysine-supplemented diet. No signs of toxicity were observed and plasma lysine concentrations were increased to levels similar to that with bolus administration without change in plasma arginine concentration; however supplemented cats demonstrated more severe disease and shed FHV-1 more often than unsupplemented cats. It is
possible that bolus administration is necessary or that lysine is ineffective in large multicat populations.

**Lambda-carrageenan** is a red seaweed extract with in vitro activity against FHV-1 when used prior to viral adsorption. However, it was ineffective when a 250 μg/mL solution was applied topically 4 times daily beginning before experimental infection of cats.

**Leflunomide** is an immunosuppressive agent that has some in vitro effects against FHV-1. The proposed method of action is through inhibition of viral outer tegument formation. In vivo studies are required.

**The interferons** are cytokines with diverse physiological roles in viral infections; however in vitro and clinical trials have produced conflicting results. In vitro, human IFN alpha and feline IFN omega had activity against FHV-1 and human IFN alpha permitted an eightfold increase in acyclovir IC50 especially with treatment before infection. However, in vivo, no benefit was demonstrated with a regimen of 10,000 IU feline IFN omega OU BID along with 2,000 IU administered PO SID for 2 days before inoculation. By contrast, 2 other IFN alpha regimens (10⁸ IU/kg subcutaneously BID beginning 1 day before inoculation and 5 or 25 IU PO q 24 hrs given after inoculation) reduced clinical scores in experimentally infected cats.