UVEITIS. IT IS AN OCULAR LYMPHADENOPATHY.
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INTRODUCTORY PHILOSOPHY
The uvea contains familiar tissues and cell types (lymphocytes, smooth muscle, and blood vessels, for example), is inflamed by familiar antigens (infectious agents, neoplasia, auto-antigens) and reacts with the 5 cardinal signs of inflammation seen elsewhere (heat, pain, swelling, etc.). This review aims to aid diagnosis and therapy of uveitis by likening it to inflammation elsewhere (because it is more similar than it is different) while highlighting differences (because these are helpful). For further information, please refer to a review article from the Journal of Feline Medicine and Surgery upon which these notes are based (2009 Mar;11(3):167-82). Although it focuses on cats, there are more similarities than there are differences between dogs and cats.

CLINICAL SIGNS
Active (acute) uveitis has few pathognomonic signs and these are notably more subtle in cats than they are in dogs. Therefore, uveitis in cats often goes undetected by owners and untreated by veterinarians until potentially blinding sequelae such as glaucoma, cataracts, and retinal detachment or degeneration occur. For these reasons, clinicians must maintain a high index of suspicion regarding uveitis in all cats with ocular disease and even those with nonspecific signs such as lethargy, “hiding”, anorexia, or fever.

Uveitis, like inflammation elsewhere, is evident as one or a combination of the 5 cardinal signs of inflammation: heat, pain, swelling, redness, and loss of function. One just has to think about how these are best seen:

- **Intraocular pain**: blepharospasm or epiphora; however cats seem more likely to show subtle and less localizing signs such as lethargy or anorexia
- **Iridal swelling** requires that the eye is examined using a source of magnification (such as the **Optivisor®**) in association with a bright and focal light source (such as the Finoff transilluminator®) directed very obliquely across the globe. Look for a loss of the normal "texture"
- **Redness** evident as scleral injection is typically evident in dogs but can be particularly subtle in many cats. The tendency to diagnose any redness of this region as conjunctivitis must be avoided. Redness of the iris usually indicates neovascularization and not congestion and is discussed below under chronic changes.
- **Dysfunction**: Given the diverse range of critical functions of the uvea, loss of function produces an important series of clinical signs evident as breakdown of the blood aqueous barrier (BAB), miosis, corneal edema, and hypotony. Of these BAB breakdown is pathognomonic and so the anterior chamber is worthy of special attention since the aqueous humor is equivalent to the interstitial space. In particular look for **hypopyon** (white blood cells), **hyphema** (red blood cells), and **fibrin, aqueous flare** (albumin and other small proteins) and **keratic precipitates** (white blood cells and inflammatory proteins clumped against the corneal endothelial surface).

Chronic uveitis and its sequelae are associated with scarring (fusion of one tissue to another and cicatrization), chronic dysfunction, and neovascularization evident as **glaucoma** (due to scarring or clogging of the iridocorneal angle), **anterior or posterior synechia** (adhesions between the iris and corneal endothelium or lens, respectively), **phthisis** (globe contracture) or **retinal detachment** (due to contraction of vitreous fibrin). Altered aqueous humor composition and circulation also causes a relative malnutrition of the lens (evident as **cataract**) and inner cornea (evident as corneal edema, vascularization, fibrosis etc.). **Lens luxation** may occur due to enzymatic lysis or phagocytosis of the lens zonules, secondary to cataract development, or as a sequela to buphthalmos due to secondary glaucoma. Neovascularization of the face of the iris (**rubeosis iridis**) is a pathognomonic sign of subacute or chronic active uveitis. It is one of the signs that is seen more easily in cats than in dogs due to the typically lighter iris color of cats.

DIAGNOSIS
Having a high degree of clinical suspicion and performing a targeted clinical examination with appropriate ocular diagnostic testing (Box 1) will ensure that uveitis is diagnosed when present. However, detecting uveitis is the beginning of the diagnostic process; not the end. Confirming or eliminating all suspected etiological diagnoses is the essential next step. By conducting an excellent general physical and ophthalmic exam as well as gathering a focused history, the initial goal is to establish whether further diagnostic testing is strongly supported. I do this by categorizing the uveitis as present in a well or systemically ill patient, unilateral or bilateral; exogenous or endogenous; acute or chronic; and as involving the anterior uvea, choroid, or both.

**Box 1. Essential diagnostic tests to detect evidence of uveitis (Tests should be conducted in this order)**

<table>
<thead>
<tr>
<th>Ophthalmic test</th>
<th>Look for:</th>
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<tbody>
<tr>
<td>Retroillumination</td>
<td>o Anisocoria (especially due to miosis)</td>
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<tr>
<td></td>
<td>o Dyscoria</td>
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<td></td>
<td>o Corectopia</td>
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<td></td>
<td>o Iridal atrophy</td>
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<td></td>
<td>o Opacities in the clear ocular media (KPs, hypopyon, hyphema, vitreous debris, posterior synechia, secondary cataract)</td>
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<td>Oblique illumination of eye</td>
<td>o Corneal edema</td>
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<td></td>
<td>o Iridal swelling/nodules</td>
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<td></td>
<td>o Iridal thinning/atrophy</td>
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<td></td>
<td>o Rubeosis iridis</td>
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<td></td>
<td>o Posterior synechia</td>
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<td></td>
<td>o Iris bombé</td>
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<tr>
<td></td>
<td>o Hypopyon</td>
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<td></td>
<td>o Hyphema</td>
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<td></td>
<td>o AC fibrin</td>
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<tr>
<td>Tonometry (IOP assessment)</td>
<td>o Decreased or low-normal in uncomplicated uveitis</td>
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<tr>
<td></td>
<td>o Elevated or high-normal when complicated by glaucoma</td>
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<tr>
<td>Pupil dilation</td>
<td>o Resistance to dilation</td>
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<td></td>
<td>o Snow banking</td>
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<tr>
<td>Assessment of aqueous flare</td>
<td>o Signs of posterior uveitis (Retinal detachment or degeneration, chorioretinal granulomas, hemorrhage, edema)</td>
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<tr>
<td></td>
<td>o Vitreous debris/infiltrates</td>
</tr>
<tr>
<td></td>
<td>o Snow banking (cats)</td>
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<tr>
<td>Fundic examination</td>
<td>o Serum proteins in the AC due to BAB breakdown</td>
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<tr>
<td>Application of fluorescein stain</td>
<td>o Corneal ulceration suggests exogenous (axonal) uveitis</td>
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<tr>
<td></td>
<td>o Corneal ulcers preclude use of topical corticosteroids</td>
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</tbody>
</table>

IOP = intraocular pressure; KPs = Keratic precipitates; AC = Anterior chamber; BAB = Blood-ocular barrier

**Etiology**

An etiologic diagnosis should then be pursued through a diagnostic workup identical to that employed for a cat with lymphadenopathy. Consider CBC, Biochemistry, urinalysis, serology, chest and abdominal imaging, etc. as appropriate for the following agents. The known causes of endogenous anterior uveitis in cats are expanding but still too few to explain the majority (~ 70%) of cases.
### Viral
- FIP
- FeLV
- FIV
- FHV
- CDV
- CAV

### Bacterial
- Bartonella spp.
- Mycobacterium spp.
- Ehrlichia spp.
- Borrelia burgdorferi
- Brucella
- Leptospira

### Fungal/Algal
- Cryptococcus neoformans
- Histoplasma capsulatum
- Blastomyces dermatitidis
- Candida albicans
- Coccidioides immitis
- Aspergillus spp.

### Parasitic
- Cuterebra larval migrans

### Protozoal
- Toxoplasma gondii
- Leishmania spp.

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*Via immunosuppression or oncogenesis; † Chorioretinitis predominates; ¥ Seroprevalence data only; no clinical evidence

The most common primary intraocular neoplasm is melanoma; however this typically causes little or no uveitis. By sharp contrast, the most common metastatic ocular neoplasm – lymphoma – tends to be associated with marked breakdown of the BAB with hypopyon formation, fibrin exudation into the anterior chamber, and hyphema. One of the curious observations with this disease is that the degree of apparent pain often seems less than might be expected from the severity of other signs of intraocular inflammation. The exception to this is when secondary glaucoma occurs, which can be quite frequent due to the highly cellular and fibrinous nature of the anterior chamber exudate. Lymphoma can cause unilateral uveitis sometimes without extraocular involvement. If the tumor cannot be diagnosed from an extraocular site, detection of neoplastic lymphocytes in an aqueocentesis sample may be helpful. Diagnostic testing aimed at discovering evidence of the tumor elsewhere should be performed first for staging the disease and because it is less invasive. Despite the severity of intraocular inflammation in many of these patients, this is often one of the more rewarding forms of uveitis to treat. If the patient’s tumor is one that readily undergoes remission when chemotherapy is initiated, then simultaneously there is usually a dramatic reduction in the degree of uveitis. Topical application of corticosteroids as an adjunct to systemic chemotherapy is wise. Mean survival time after diagnosis in one study was 14 months.

### TREATMENT
Treatment of anterior uveitis must be tailored to the individual case based on proven or suspected cause, severity, anatomical location, chronicity, and presence of systemic or other intraocular disease. Regardless, some general therapeutic guidelines are possible. Optimal treatment relies upon identification and removal or reduction of the causative antigen; however this is rarely possible. Additionally, all patients with uveitis need their intraocular inflammation controlled rapidly and completely, since it is painful and produces vision-threatening sequelae. Thus, immunomodulating drugs form the mainstay of therapy for uveitis. The major decisions are therefore which immunomodulating drugs should be given, via what route and, at what dose.

### Immunomodulatory therapy
Corticosteroids are highly potent, available in topical or systemic forms, relatively inexpensive, generally well tolerated by cats and – to a lesser extent - dogs, and can be administered at anti-inflammatory or immunosuppressive dosages. For these reasons, they are commonly used for uveitis. Their systemic use should be reserved until a definitive cause responsive to corticosteroids has been found or, failing this, until causes known to be worsened by glucocorticoids have been adequately eliminated. In particular, the systemic mycoses must be adequately eliminated as potential causes. Likewise, patients in which lymphoma is possible and which would benefit from a multidrug chemotherapeutic regimen should not be treated with systemic corticosteroids alone. By contrast, topical administration of corticosteroids may be employed safely even when an infectious or neoplastic cause might prevent systemic administration of the same drugs. This is possible because systemic effects are insignificant with short-term topical application. It is possible that topically administered corticosteroids may alter cytologic findings and so, if safe, their use should perhaps be delayed until after ocular centesis is performed. Topical corticosteroids...
should never be used in the face of corneal ulceration because they can be associated with rapid worsening of the ulcer due to superinfection, collagenvolysis, local immunosuppression, and delayed wound healing. Prednisolone acetate (1% or 0.125%) and dexamethasone (0.1%) will penetrate intact corneal epithelium and reach the anterior uveal tract. Hydrocortisone (as found in many combined antibiotic–corticosteroid ophthalmic preparations) does not penetrate intraocularly and should not be used. The frequency of application should be tailored to the severity of the uveitis; starting as frequently as q 2 hours and tapering as a clinical response is noted. When safe, corticosteroids should be administered systemically for posterior uveitis and when more significant immunomodulation is necessary, or when corneal ulceration prohibits their topical use. Typical doses of prednisolone range from 1 mg/kg q 12 hours when notable inflammation is present to 0.5 mg/kg once daily when a more moderate anti-inflammatory effect is desired. As with topical corticosteroids, dose and dose frequency of systemically administered glucocorticoids should be carefully reduced based entirely upon clinical evidence of waning disease. In cats with acute or subacute uveitis, this can be fairly rapid. Animals with chronic idiopathic (immune-mediated) uveitis require slow tapering (perhaps a halving of dose or dose frequency every 2-3 weeks), with the expectation that inflammation may return below a critical dose. In these patients, returning to the previously effective dose will be necessary. Some cats will suffer herpetic recrudescence when receiving corticosteroids, regardless of route.

Compared with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) are not immunosuppressive, and may be more expensive, sold in smaller volumes (as topical ophthalmic solutions), and sometimes unavailable in ointment form. These limitations must be borne in mind for dogs cats with uveitis; however they may be preferred over corticosteroids in patients with diabetes or other endocrinopathies in which corticosteroid use may not be wise. They can also be administered systemically instead of corticosteroids when systemic infectious disease is suspected or proven, or until lymphosarcoma is eliminated as a differential consideration. And they may be given in conjunction with a topical steroid. As such, they may make an excellent choice for initial control of inflammation while likely causes are being ruled in or out. The same general comments regarding dose frequency and route made for corticosteroids apply equally to NSAIDs.

Iridocycloplegic agents

Atropine has multiple favorable actions in eyes with uveitis. It paralyzes the iris sphincter and ciliary body muscles causing mydriasis and cycloplegia, respectively. Pupil dilation reduces leakage of vascular elements into the aqueous humor by causing blood vessels within the iris to “concertina” upon themselves (providing a physiological tamponade); decreasing iris surface area (from which inflammatory mediators and vascular components originate); reducing uveal vascular endothelial permeability; and by reducing chances and consequences of posterior synechiation. However “bunching” of the iris in the periphery does increase the chance of anterior synechia and potentially obstruction of the iridocorneal angle. Cycloplegia reduces ocular pain but also increases resistance to aqueous outflow. Therefore, pupil dilation and cycloplegia are desirable in all cases of uveitis except those where secondary glaucoma is present or likely. Depending on the severity of uveitis, once to twice daily application for the first day or two may be needed to open the pupil. Subsequently, once to twice weekly application will often keep the pupil mydriatic.

Monitoring and Sequelae

The most common sequelae in cats) include cataracts in 20-36% of eyes, lens luxation in 11-18%, glaucoma in 16-46% and enucleation in 29%. Many patients experience more than one of these sequelae. For these reasons, frequent and careful monitoring of a patient with uveitis is essential. This should be performed as for patients with immune-mediated disease elsewhere with gradual tapering of medications and re-examination at doubling intervals presuming there is improvement; more often if there is not. Re-examination and tapering of medications should be continued until there is complete resolution of every clinical sign of active uveitis. I believe that tonometry is the most sensitive test with which to monitor uveitis during treatment because subtle hypotony (sometimes only relative to the contralateral eye) can continue long after other more overt signs have normalized.

REFERENCES
