BLEPHARITIS - IT IS NOT A FOCAL DERMATITIS

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INTRODUCTORY PHILOSOPHY
External ocular disease (i.e., pathology involving the eyelids, cornea, or conjunctiva in any combination) is now an area of subspecialty within physician ophthalmology due to the close anatomical and physiological relationships between these 3 tissues, and the frequency with which such patients present. It is also advantageous to consider these tissues jointly since primary disease in any one of them frequently leads to secondary involvement of one or both of the other 2 tissues. And of course, blepharitis may simply be an ophthalmically notable sign in a patient with generalized dermatitis. Therefore a complete discussion of blepharitis and periocular dermatitis should include all causes of generalized dermatitis, as well as the specific causes of primary blepharitis, conjunctivitis, and keratitis. Clearly this goes beyond the scope of our single session today (let alone beyond the speaker’s expertise!). Instead, I will aim to present an ophthalmologist’s view of the eyelids and periocular skin focusing especially on those diseases where skin elsewhere on the body is uninvolved; and noting potential causes, my diagnostic approach, and some broad therapeutic options. Underpinning this is an understanding of what makes eyelids and blepharitis different from skin and dermatitis elsewhere.

CLINICALLY RELEVANT ANATOMY & PHYSIOLOGY
Although eyelids are covered with skin and are susceptible to skin conditions, there are a number of anatomic and physiologic peculiarities of eyelids that cause them to respond in ways that would be unexpected in skin elsewhere in the body. For example, the eyelids are:

- Highly vascular and tend to become more dramatically and/or more rapidly inflamed in response to insults that may produce more minor dermatitis elsewhere.
- Richly innervated and susceptible to intensely painful or pruritic dermatitis, which is, in turn, prone to exacerbation due to self trauma.
- A readily observed mucocutaneous junction that is often noticed by owners of animals with immune-mediated dermatitis before they see disease at other mucocutaneous junctions.
- Lined on their inner surface by conjunctiva, which is a richly vascular mucus membrane that swells and bleeds readily and is the source of mucoid discharge. Conjunctiva is also part of the mucosally-associated lymphoid tissue (MALT) system and, so, has resident lymphoid populations that can become more organized, follicular, or generally enlarged.
- Responsible for protection of the cornea; therefore blepharitis can cause intensely painful and potentially vision-threatening secondary keratitis.
- Subject to secondary dermatitis as a result of ocular discharges sometimes worsened by overgrowth of conjunctival flora (principally Gram-positive bacteria; but also Gram-negative bacteria, Mycoplasma spp., Chlamydyophila felis, viruses, fungi, and yeasts). Patency of the nasolacrimal apparatus can have dramatic secondary effects on the periocular skin.
- Invested with meibomian glands which are susceptible to impaction (chalazia), highly targeted and apparently immune-mediated inflammation (meibomitis/pyogranulomatous blepharitis), or neoplasia (adenoma), all of which may cause glandular rupture and subsequent lipogranulomatous blepharitis.

DIAGNOSTIC APPROACH
When attempting to make an etiological diagnosis in patients with blepharitis or periocular dermatitis, I initially try to divide cases into those where I believe the dermatitis (blepharitis) is primary versus those were it is secondary to another ocular cause (especially conjunctivitis or keratitis). This requires a full ocular surface examination including:

- Assessment of the palpebral reflex to verify function of cranial nerves V and VII, and quantify any lagophthalmos, especially in breeds which are conformationally predisposed to this.

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Careful examination of the periocular skin as you would with skin elsewhere but with particular attention to any skin folds, areas of depigmentation or maceration, source of hairs that are reaching the cornea or conjunctiva, and the character and position of any ocular discharge.

Careful examination (with magnification) of the eyelids, with particular attention to the margin, any thickenings (nodular or generalized), entropion or ectropion, misdirected hairs (distichia, trichiasis, ectopic cilia), the meibomian gland orifices (neoplasia, discharge), and the medial caruncle (depigmentation, maceration, length and direction of hairs).

Thorough assessment of the tear film.

Careful examination (with magnification) of the conjunctiva, especially the nasolacrimal puncta (discharge, patency), the meibomian glands (usually visible in profile subconjunctivally), presence of conjunctival follicles, and degree of chemosis and hyperemia. [While doing this try to think of yourself looking at the eyelid skin from beneath the dermis!]

Careful examination (with magnification) of the cornea, with particular attention to the regularity and moistness of the surface, and any other signs of keratitis.

Application of fluorescein stain with observation of corneal or conjunctival retention (ulcers), overflow over the eyelids, and appearance at the ipsilateral nostril or mouth (“Jones’ test”).

In some patients, further dermatologic testing is required, as it would be for patients with dermatitis elsewhere. Eyelid skin may (and should) be scraped, biopsied, cultured and have hairs plucked in a normal fashion with the only difference being that it is essential that the eyelid margin is not damaged since it is the “windshield wiper” or “squeegee” for the cornea. In addition, meibomian glands may be gently expressed and their secretions examined cytologically and microbiologically.

Based upon the results of a full ophthalmic and dermatologic examination as described, an attempt should be made to categorize the patient’s periocular dermatitis or blepharitis as one of the following:

- Primary dermatitis with associated blepharitis
  - I.e., involvement of eyelid skin and skin elsewhere (with or without secondary conjunctival or corneal involvement)
- Primary blepharitis
  - I.e., involvement of eyelid skin but not skin elsewhere, and with no or mild secondary conjunctival and/or corneal involvement (i.e., blepharoconjunctivitis).
- Primary corneal, conjunctival, or nasolacrimal disease with secondary blepharitis
  - I.e., Eyelid skin disease due to immediately subjacent (and likely confluent) conjunctival inflammation (i.e., conjunctivoblepharitis), and/or secondary to ocular discharge. In these cases, there will not be involvement of skin elsewhere.

Separating these latter two categories can appear complicated at first. However, as a rule, primary blepharitis typically is severe before it causes notable secondary conjunctivitis, and typically involves the eyelid margin before it causes notable secondary keratitis. Similarly, primary ocular disease must produce copious and usually chronic ocular discharges before it causes secondary and generalized blepharitis. Therefore, making the distinction between primary and secondary blepharitis relies upon judgment of the relative severity and chronicity of ocular discharge, conjunctivitis, keratitis, and the eyelid dermatitis itself.

**SOME SPECIFIC CAUSES OF BLEPHARITIS & PERIOCULARDERMATITIS**

**Infectious blepharitis** – Just as for dermatitis elsewhere, primary infectious blepharitis may occur as a result of many organisms, with dermatophytes, *Malassezia, Histoplasma, Leishmania* spp., feline leprosy, and *Demodex* perhaps being better described. While the eyelids can be more notably involved in these conditions, they are almost always part of a more generalized dermatitis. Bacterial blepharitis is typically secondary to another insult. The exception is perhaps *Staphylococcus* spp., which may induce hypersensitivity and a very severe periocular dermatitis, especially involving the meibomian glands (discussed below). The other primary pathogen of the cat eyelids and periocular skin appears to be feline herpesvirus (FHV-1). Cats with herpetic dermatitis have a marked ulcerative and proliferative dermatitis involving the nose and periocular skin. This is typically chronic and unresponsive to antibiotics or corticosteroids. Histologically, herpetic keratitis is necrotizing and often eosinophilic. Inclusion bodies are sometimes seen but can be absent or missed; however the diagnostic utility of PCR is high for this disease. When results of histologic examination were used as the gold standard, sensitivity and specificity...
of one PCR assay were 100% and 95%, respectively. Famciclovir has been highly effective for herpetic dermatitis (and other herpetic disease) in cats. We use 90 mg/kg PO BID.

Immune-mediated blepharitis – Immune mediated diseases targeting mucocutaneous junctions (the pemphigus group, etc.) or melanocytes (Vogt-Koyanagi-Harada or uveodermatologic syndrome), and those causing vasculitis are often more notable or more severe at the eyelid than elsewhere. Of these, the one most localized to the eyes and eyelids is uveodermatologic syndrome. As the name suggests, the sites of inflammation are the skin (especially the nose and periorificial skin), and the uveal tract (iris, ciliary body, and choroid) all of which have a rich population of melanocytes. The resulting clinical signs include poliosis, vitiligo, severe anterior uveitis (corneal edema, episcleral injection, blepharospasm, miosis, aqueous flare) often with secondary glaucoma, and chorioretinitis often with secondary retinal detachment. The ocular signs are typically more devastating and noticeable for the owner than are the skin signs as they are painful and often blinding. However, there is nothing pathognomonic about the uveitis seen and so a skin biopsy (with characteristically large, pigment-laden macrophages) is often used for diagnosis.

Meibomitis (sometimes called meibomian or tarsal adenitis, or marginal blepharitis) is a complex of disease entities where the inflammatory process seems to be highly targeted at the meibomian glands. While some causes are recognized, there is much still to learn and be better defined about this “grab-bag” term. Clinical signs include variable erythema and swelling of the eyelid margins, pruritus, blepharospasm, chemosis, and mucoid to mucopurulent ocular discharge. In its mildest form, however, it is sometimes simply a cause of epiphora. In more severe cases though there is marked disturbance of the eyelid, and often rupture of the glands with associated leakage of meibum into the surrounding tissues this often induces a marked lipogranulomatous blepharitis. Staph. hypersensitivity may also be involved in some cases.

In cats, there seems to be a different variant of meibomitis which has been called lipogranulomatous conjunctivitis. It appears to arise from the meibomian glands and manifests as a nodular conjunctivitis on the inner eyelid surface. As for dogs, ruptured glands cause a marked lipogranulomatous reaction. The upper eyelid is involved more commonly than the lower eyelid, and actinic radiation may be important in the pathogenesis of these lesions because they have been reported more commonly in white-skinned cats and sometimes in association with SCC. Surgical extirpation of glandular material and associated granulomatous infiltrate has been recommended for this condition, but concern remains as to the effects of such surgery on the lipid component of the tear film. I prefer to use warm-packing as well as systemically administered antibiotic and corticosteroids as described in the therapy section below. Because the meibomian glands (regardless of species) secrete the lipid layer of the tear film, which is critical to tear function, meibomitis almost certainly causes tear film alterations through altered lipid quantity or quality, as well as release of inflammatory mediators and lipid oxidation/breakdown products onto the ocular surface. As such, associated corneal and conjunctival disease should be expected or at the very least prophylactically and pre-emptively treated in dogs and cats with meibomian gland disease.

Allergic conjunctivoblepharitis. Ocular immune responses in humans are categorized using the classic Gell and Coombs system in which 5 classes of immunologic hypersensitivity reactions are recognized. Two forms of allergic conjunctivitis are recognized. True allergic conjunctivitis is defined as a Type 1 (immediate) hypersensitivity reaction mediated by IgE; mast cells and then histamine and related mediators. By contrast, contact dermatitis (blepharitis) and topical drug allergies (blepharitis, conjunctivitis and keratitis) are categorized as Type IV (delayed-type) hypersensitivity. While there is no doubt that veterinary patients with allergic dermatitis can present with eyelid involvement, I also see some patients with eyelid and/or conjunctival signs that I believe may be allergic but in which the lack of general skin involvement is notable. I think of these cases as allergic conjunctivoblepharitis and approach them as I would allergic conjunctivitis.

Allergic conjunctivitis in humans is defined as a non-contagious conjunctivitis with nonspecific signs of conjunctivitis (hyperemia, chemosis, epiphora and mucoid ocular discharge) but also often associated with the formation of a corrugated conjunctival surface (papillary conjunctivitis) and an itching and burning sensation, which may be relieved by use of antihistamines, mast cell stabilizers, or by identification and
removal of the allergen. Known allergens include pollens, animal skin and secretions such as saliva, perfumes and cosmetics, skin medicines, air pollution, and smoke. There is a familial tendency and the disease is often seasonal. Eosinophils may be identified on scrapings or swabs.

The most important thing to consider when treating presumed ocular surface allergy is to find and remove the allergen. However, as with allergic dermatitis, this is not always easy or possible. The exception is the patient receiving a topical ophthalmic medication. I am always highly suspicious that this may be the inciting allergen and will always try to cease or at least change that medication. Certainly, as I choose medications to treat suspected allergic conjunctivitis, I am conscious that my medication choice could make the clinical signs worse in an immunologically “turned on” animal. Immunomodulatory therapy is discussed below.

**EMPIRICAL MANAGEMENT OF BLEPHARITIS**

Like every disease, the very best treatment for blepharitis and periorcular dermatitis involves rapid diagnosis and correction of the primary cause. Often this is not possible and, even when it is, empirical or supportive care is also needed. The following are some general principles I use when treating blepharitis in dogs and cats.

**Warm-packing, blinking exercises, and tear replacement** (in that order) form the foundation of therapy for most patients I treat with blepharitis. The warm packing is intended to liquefy and facilitate expression of altered and stagnant meibum. I do not encourage owners to use cloths warmed with hot water as the heat emitted by these does not persist for a sufficiently long period. Rather, I recommend use of commercially available moist heat warm packs for humans. These are re-useable, washable, and are warmed in a microwave oven. They maintain their warmth sufficiently long that clients can be asked to warm-pack the eyelids for 5-10 mins twice daily. Based on advice I received from Akihiko Saito and our other Japanese colleagues, I am now a firm believer in the value of blinking exercises for patients with meibomian gland disease. This should be done immediately following warm packing when the meibum has been liquefied and can be expressed. Forceful (manually assisted) eyelid closure is intended to express as much meibum as possible. Eyelid disease can cause altered quality and quantity of all 3 tearfilm components as well as altered blink rates and evaporative stress, and release of lipid breakdown products and other inflammatory mediators across an already susceptible ocular surface. Therefore, I use hyaluronates for mucin and aqueous replacement and petrolatum for lipid replacement. In severe cases I avoid preserved products.

**Antibiotic therapy** is often unnecessary. When needed, I typically avoid topical application as this runs the risk of adding antigens to an already “immunologically charged” situation. Systemically administered antibiotics also likely provide better concentrations within the deep eyelid tissues and conjunctiva. Whenever possible selection should be guided by culture and sensitivity testing, especially in resistant and chronic disease. I often recommend tetracyclines because they penetrate into lipids so well and because of their myriad of effects additional to their antimicrobial action. Protracted therapy is often necessary as with deep pyoderma elsewhere.

**Immunomodulatory therapy.** If there is a notable inflammatory response (especially lipogranulomatous inflammation secondary to meibomian gland rupture, allergy, or hypersensitivity to staphylococcal antigens administration of a corticosteroid is typically required. As for antibiotics I prefer systemic administration for treatment of dermatologic disease (assuming it is safe).

Topical immunomodulation may be very useful in milder cases, when conjunctival inflammation dominates dermatologic inflammation (conjunctivoblepharitis), or as systemic agents are tapered. I recommend dexamethasone or prednisolone without antibiotic to reduce chances of hypersensitivity. Hydrocortisone is a relatively low potency corticosteroid and not preferred. You could also consider using proprietary Optimmune® since many of the compounded products are dissolved in potent allergens (peanut oil, olive oil, corn oil, etc.) Topical NSAIDs, antihistamines (often with vasoconstrictive sympathomimetic agents), and mast cell stabilizers have been used in humans, but I unaware of any specific veterinary studies.

**REFERENCES**