

Autoimmune and Immune-Mediated Skin Disorders

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Outline

- Overview
- Specific Diseases
 - Cause and Pathogenesis
 - Clinical signs
 - Differentials
 - Diagnosis
 - Prognosis
- Treatment Overview
- Questions and Answers

Overview

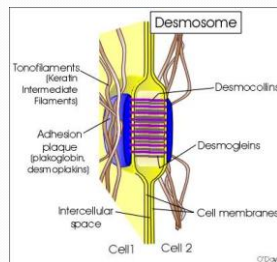
- Estimate: 1.4 and 1.3% of canine and feline dermatoses examined by dermatology service at a university
- Primary or autoimmune:
 - Antibodies or activated lymphocytes against normal body constituents
 - Mechanisms linked to autoimmunity development
 - Cytokine and chemokine environment
 - Maturation state of dendritic cells presenting self-antigen
 - Inflammatory status of peripheral tissues
 - Theme within these: breaking of tolerance by presentation of self-antigens in an inflammatory cytokine-rich context

Overview

- Secondary or immune-mediated
 - Diseases where the tissue destruction due to an immunologic event not directed against self-antigens
- Antigen foreign to the body
 - Drugs, bacteria, viruses: stimulate immunologic reaction that causes host damage

Pemphigus Complex

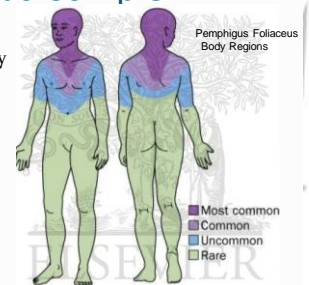
- Vesicobullous to pustular disorders of the skin or mucous membranes characterized by acantholysis
- Pathogenesis
 - Autoantibodies to components of keratinocyte desmosome



<http://www.utm.utoronto.ca/~w3bio315/lecture3.htm>

Pemphigus Complex

- Pathogenesis
 - Clinical lesions: severity and location relate to which desmosome component targeted
 - Regional variation in expression of pemphigus antigens



www.elsevierimages.com/images

Pemphigus Complex

- Pathogenesis
 - Formation of blisters/pustules/vesicles
 - Pemphigus antibody binding antigen
 - Internalization of antibody and fusion with lysosomes
 - Activation and release of a keratinocyte proteolytic enzyme
 - Hydrolyzes adhesion molecules
 - Loss of intercellular cohesion
 - Acantholysis and blister formation within epidermis

Pemphigus Complex

- Causes
 - UV light irradiation exacerbates acantholysis
 - Genetic factors: breed predispositions and familial cases
 - Drug provocation
 - Can activate proteolytic enzymes in the skin
 - Can stimulate development autoantibodies against desmosomes
- Associate with history of chronic skin disease



<http://pethealthlibrary.purinacare.com/articles/dogs-articles/the-itchy-dog/>

Pemphigus Foliaceus

- Most common form of pemphigus and likely most common immune-mediated dermatosis in dogs and cats
- Pathogenesis
 - People
 - Autoantibody target: desmoglein-1 in the desmosome
 - Additional autoantigens
 - Desmocollin-1
 - Nondesmosomal adhesion protein: E-cadherin
 - Dogs
 - Desmoglein-1 only targeted in 6% patients
 - Desmocollin-1 may be major autoantigen

Pemphigus Foliaceus

- Signalment
 - Any age, sex, or breed
 - Akitas and Chow Chows may be predisposed
- Clinical Signs
 - Erythematous macules progress to pustular stage
 - May see hairs protruding from pustules
 - May only see crusts, as pustules fragile
 - Superficial disease: ulcers rare
 - Usually bilateral and symmetric
 - Pruritus variable and often secondary to lesions

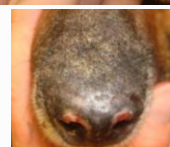
Pemphigus Foliaceus

- Clinical signs
 - Systemic signs
 - Fever
 - Lethargy
 - Anorexia
 - Lymphadenopathy
- Areas affected
 - Usually begin on face
 - Dorsal muzzle, planum, periocular skin, ears (esp. concave pinnae)
 - Generalize or regionalize
 - Widespread erythema and exfoliation
 - Footpads
 - Rarely, affect just pads in dogs
 - Lameness and hyperkeratosis
 - Onychodystrophy



<http://fusiondogs.com/Akita.html>

Pemphigus Foliaceus



Pemphigus Foliaceus

- Clinical signs
 - Cats
 - Suppuration and crusts on or around footpads or unguis folds of claws
 - Onychodystrophy can occur
 - Involvement of the nipples



Pemphigus Foliaceus

- Differential diagnosis
 - Infectious causes
 - Bacterial folliculitis
 - Acantholysis due to production of exfoliative toxin
 - Dermatophytosis
 - *Trichophyton* sp.
 - PAS stain on histopathology or macerated tissue culture



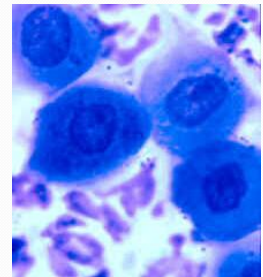
Pemphigus Foliaceus

- Others:
 - Demodicosis
 - Pemphigus erythematosus
 - Discoid or systemic lupus erythematosus
 - Dermatomyositis
 - Cutaneous adverse drug reaction
 - Zinc-responsive dermatosis



Pemphigus Foliaceus

- Diagnosis
 - Clinical history, physical exam
 - Cytology of a pustule or under a crust
 - Nondegenerate neutrophils and acantholytic keratinocytes

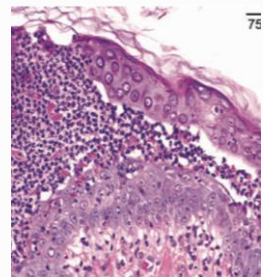


Pemphigus Foliaceus

- Diagnosis
 - Histopathology
 - Ideally pustules
 - Crusts
 - May have micropustules underneath
 - Do not scrub, gently clip
 - Biopsy without being on glucocorticoids
 - May want to biopsy while on antibiotics
 - Submit to dermatopathologist with history and description

Pemphigus Foliaceus

- Diagnosis
 - Histopathology
 - Subcorneal pustules with neutrophils and acantholytic keratinocytes, sometimes eosinophils
 - Prognosis
 - Fair to good
 - Most require life-long immunosuppressive therapy



Veterinary Dermatology, Oct. 2009, Olivry et al.

Pemphigus Foliaceus and Promeris®



Pemphigus Foliaceus and Promeris®

- Small number of dogs treated with Promeris have developed crusted and pustular skin lesions extending from application site
- Lesions clinically and histologically resemble spontaneous PF
- Study of 22 dogs with Pemphigus foliaceus-like reaction at Promeris application site (Oberkirchner, et al., 2010)
 - 8 localized, 14 had lesions at distant sites too
 - 1 or up to 10 applications
 - 13 dog required immunosuppression, 6 required continuous immunosuppression
- Likely a unique contact drug induced PF

Pemphigus Erythematosus

- People: controversial clinical heterogeneous entity: discoid lupus and superficial pemphigus
 - Current concept: human PE a variant of PF
- Dogs and cats controversial: separate entities, variant PF, actual crossover with PF and DLE
- Pathogenesis
 - People: Major autoantigen desmoglein-1: main PF antigen
 - Also targeting of basement membrane zone antigens
 - Dogs and Cats:
 - Immunofluorescence shows immunoglobulins in the intercellular epidermis and basement membrane
 - Not all dogs have the basement membrane immunoreagent deposition (the lupus-like component)

Pemphigus Erythematosus

- Signalment: No age or sex predilections
 - Scarcity of information of canine and feline PE: detailed info on breed, age, sex predisposition can't be provided
 - Possibly Collies and GSD's predisposed



<http://www.typesofdogs.org/collie.html>

Pemphigus Erythematosus

- Clinical signs:
 - Pustules, erosions, and crusts of face and pinnae
 - Depigmentation, erythema, erosion/ulceration of nasal planum and dorsal muzzle
 - Bridge of nose, peri-ocular
 - Rarely have nonfacial lesions
 - Hyperkeratotic footpads
 - Usually healthy otherwise



Pemphigus Erythematosus

- Differential Diagnosis:
 - Bacterial folliculitis
 - Demodicosis
 - Nasal pyoderma
 - Dermatophytosis
 - Discoid lupus erythematosus or systemic lupus
 - Pemphigus foliaceus-facial
 - Dermatomyositis
 - Drug reaction
 - Uveodermatologic syndrome
 - Nasal solar dermatitis
 - Zinc-responsive dermatosis

Pemphigus Erythematosus

- **Diagnosis**
 - Clinical history, physical exam
 - Cytology of a pustule or under a crust
 - Nondegenerate neutrophils and acantholytic keratinocytes
 - Histopathology
 - Same as PF except often has a lichenoid infiltrate of mononuclear cells, plasma cells, neutrophils, or eosinophils, or both

Pemphigus Erythematosus

- **Diagnosis**
 - ANA may be positive (not unique to PE, up to 30% dogs with various pemphigus phenotypes have low-titers of serum IgG targeting nuclear antigens)
 - Supportive, not pathognomonic for PE
- **Prognosis**
 - Good
 - Without treatment, often remains benign and localized

Discoid Lupus Erythematosus

- 2nd most common immune-mediated canine dermatitis, rare (not diagnosed convincingly) in cats
- **Cause and Pathogenesis**
 - Relatively benign variant of systemic lupus
 - Systemic lupus etiology multifactorial: genetic predilection, immunologic disorder, viral infection, and hormonal and UV light modulation playing roles
 - Sun exposure exacerbates disease in about 50% cases
 - Humans: T cells predominate the infiltrate
 - Dogs: Plasma cells prominent, thus B lymphocytes may be important

Discoid Lupus Erythematosus

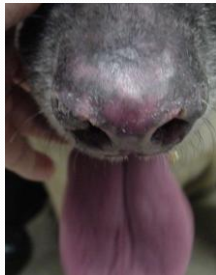
- **Signalment**
 - No sex or age predilection
 - Collies, German Shepherds dogs, Shetland sheepdogs, Siberian huskies, Brittany spaniels, German Shorthair Pointers
- **Clinical signs**
 - Initially
 - Depigmentation, erythema and scaling of nose
 - Early depigmentation: slate blue or gray
 - Nasal planum becomes smooth



<http://puppydogweb.com/gallery/collies/e.htm>

Discoid Lupus Erythematosus

- **Clinical signs**
 - Later lesions
 - Erosion, ulceration, crusting
 - Nasal involvement becomes more extensive and may spread up bridge of nose
 - Less often
 - Periocular, pinnae, distal limbs, genitalia, lips
 - Hyperkeratotic footpads and oral ulcers rarely



<http://my-pet-medicine.com/pet-gallery/canine-discoid-lupus-image.html>

Discoid Lupus Erythematosus

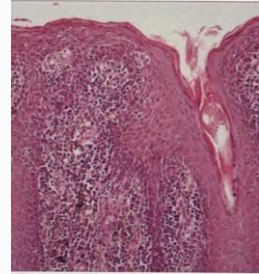


Discoid Lupus Erythematosus

- Differential Diagnosis
 - Mucocutaneous pyoderma
 - Demodicosis
 - Dermatophytosis
 - Pemphigus erythematosus or foliaceus
 - Dermatomyositis
 - Uveodermatologic syndrome
 - Nasal solar dermatosis
 - Nasal depigmentation
 - Vitiligo-like disease
 - Systemic lupus erythematosus
 - Epitheliotropic lymphoma
 - Drug Reaction

Discoid Lupus Erythematosus

- Diagnosis
 - Clinical history, physical exam
 - ANA titer: generally negative
 - Histopathology
 - Hydropic or lichenoid interface dermatitis, focal thickening of the basement membrane zone, pigmentary incontinence, apoptotic keratinocytes



Color Atlas and Text of Surgical Pathology of the Dog and Cat, Yager and Wilcock,

Discoid Lupus Erythematosus

- Prognosis
 - Good, often need lifelong treatment
 - Permanent scarring and leukoderma
 - Rarely squamous cell carcinoma develops from chronic DLE skin lesions

Cutaneous Vasculitis

- Inflammatory disease of blood vessels, secondary to immune complex deposition in vessel walls
- Often associated with:
 - Infection (bacterial, rickettsial, viral, fungal)
 - Malignancy
 - Food hypersensitivity
 - Drug reaction
 - Rabies vaccination
 - Metabolic disease (diabetes mellitus, uremia)
 - Systemic lupus erythematosus
 - Exposure to cold
 - Insect bites

Cutaneous Vasculitis

- Pathogenesis
 - Assumed to involve Type III hypersensitivity reaction
 - Soluble antibodies bind antigens: immune complexes
 - Type I hypersensitivity reactions may be important in initiation of immune complex deposition
 - Immediate hypersensitivity reaction

Cutaneous Vasculitis

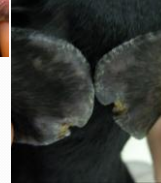
- Breeds predisposed
 - Jack Russell terriers
 - Scottish terriers
 - German shepherd dogs
 - Dachshunds
 - Rottweilers
- Vaccine reactions
 - Poodles
 - Silky terriers
 - Yorkshire terriers
 - Pekingese
 - Maltese
 - Bichon



Cutaneous Vasculitis

- Clinical Signs
 - Purpura
 - Necrosis
 - Punctate ulcers
 - Plaques
 - Bullae
 - Acrocyanosis of extremities
- Lesions often in areas of pressure, normal "wear and tear" areas, and skin covering extremities
 - Pinnae, tip of tail, scrotum, footpads
- Urticarial vasculitis: erythroderma with coalescing erythematous wheals
- Possible anorexia, depression, fever, arthropathy, myopathy, pitting edema of extremities

Cutaneous Vasculitis



- Specific types
 - Proliferative thrombovascular necrosis of the pinnae
 - Apical margins of pinnae, wedge-shaped
 - Elongated necrotic ulcer centrally

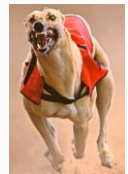
Cutaneous Vasculitis

- Specific types
 - Rabies vaccine-induced
 - Focal area of alopecia at site of vaccination
 - 1-5 months later may see multifocal lesions
 - Variable alopecia, crusting, hyperpigmentation, erosions, ulcers on pinnal margins, periocular areas, skin over bony prominences, tip of tail, footpads
 - May see lingual erosions and ulcers



Cutaneous Vasculitis

- Specific types
 - Cutaneous and renal glomerular vasculopathy
 - "Alabama rot"
 - Greyhounds
 - Reddened areas that become dark red to black and slough
 - Limbs, groin, trunk
 - Pitting edema
 - Pyrexia, lethargy, PU/PD, vomiting, acute renal failure
 - Verotoxin from *E.coli*



<http://bestbetfairbettingsystems.com/best-greyhound-laying-system-review/>

Cutaneous Vasculitis

- Specific types
 - Familial cutaneous vasculopathy of German shepherd dogs
 - Puppies
 - Pyrexia and lethargy
 - Swollen, depigmented foot pads
 - Alopecia, crusts, ulceration: pinnae, tail, nasal planum



Cutaneous Vasculitis

- Differential Diagnoses
 - Coagulopathy
 - Systemic lupus
 - Erythema multiforme
 - Toxic epidermal necrolysis
 - Frostbite
 - Drug reaction
 - Bullous pemphigoid
 - Pemphigus vulgaris
- Disseminated intravascular coagulation
- Ear pinnal lesions only: ear margin dermatosis

Cutaneous Vasculitis

- **Diagnosis**
 - Look for underlying etiologic cause
 - Ex. Tick titers
 - **Diascopy:** should not blanch
 - **Histopathology**
 - Neutrophilic, eosinophilic, or lymphocytic vasculitis
 - Ischemic dermatopathy (ex. Rabies vaccine-induced): follicular atrophy, hyalinization of collagen, cell-poor interface dermatitis, mural folliculitis
- **Prognosis**
 - Variable



http://www.medscape.com/viewarticle/448502_2

Cutaneous Drug Reaction

- Cutaneous or mucocutaneous reactions to a drug (topical, oral, or injectable)
- One to many treatments, even years of treatment
- **Cause**
 - Any drug
 - Some more associated with reactions
 - Topicals
 - Sulfonamides
 - Penicillins
 - Cephalosporins

Cutaneous Drug Reaction

- **Pathogenesis**
 - Predictable
 - Related to pharmacologic action of the drug
 - Ex. Immunosuppressive drugs: poor wound healing
 - Unpredictable or idiosyncratic
 - Dose-independent and related to patient's immunologic response or genetic differences in susceptibility
 - Often related to metabolic or enzymatic deficiencies
 - Involve all hypersensitivity reactions

Cutaneous Drug Reaction

- **Signalment**
 - No age or sex predilection
 - Breed predispositions
 - Doberman pinschers: sulfonamides
 - Miniature Schnauzers: sulfonamides, gold, and shampoo (superficial suppurative necrolytic dermatitis)
 - Literature review Scott et al., 1999: Shetland sheepdog, Dalmatian, Yorkshire terrier, miniature Poodle, Australian shepherd, Old English Sheepdog, Scottish terrier, wirehaired Fox Terrier, Greyhound

Cutaneous Drug Reaction

- **Clinical signs**
 - No specific reaction is related to only 1 drug
 - Certain reactions more common with certain drugs
 - Ex. Superficial suppurative necrolytic dermatitis of miniature Schnauzers: only associated with shampoos
 - Cutaneous and systemic signs within 48-72 hours
 - Papules and plaques that develop to pustules
 - Necrosis and ulcerations
 - Systemic signs: pyrexia, depression, neutrophilia
 - Regress spontaneously 1-2 weeks later

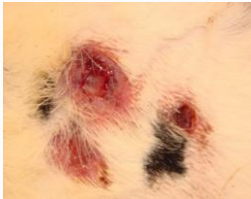


<http://www.allsmalldogbreeds.com/miniaure-schnauzer.html>

Cutaneous Drug Reaction

- **Clinical Signs**
 - Variable
 - Papules, plaques, pustules, vesicles, bullae, purpura, erythema, urticaria, angioedema, alopecia, scaling, exfoliation, erosions, ulcerations
 - Localized, multifocal, diffuse
 - Pain and/or pruritus
 - Systemic signs: pyrexia, lameness, depression

Cutaneous Drug Reaction



Cutaneous Drug Reaction

- Differential Diagnosis
 - Mimic many other dermatoses
 - Differentials depend on clinical presentation
- Diagnosis
 - History of recent drug administration
 - Usually within 1-3 weeks of starting drug
 - Prior exposure may have been tolerated well
 - CBC: anemia, thrombocytopenia, leukopenia or leukocytosis
 - Biochemistry: abnormalities related to organ damage

Cutaneous Drug Reaction

- Diagnosis
 - Dechallenge
 - Resolution 1-2 weeks after drug discontinued
 - Occasionally persist weeks to months
 - Rechallenge
 - Reaction reproduced by administration of small doses
 - Not recommended
 - Histopathology
 - Variable, reflect gross lesions

Cutaneous Drug Reaction

- Treatment
 - Discontinue offending medication
 - Symptomatic therapy
 - Glucocorticoids may be helpful
 - Prednisone 1-2mg/kg/day: dogs, PO
 - Prednisolone 2-4mg/kg/day: cats, PO
 - Until lesions resolve, then taper
 - Avoid chemically related drugs
 - Prognosis: good unless other organ involvement or extensive epidermal necrosis

Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

- Reaction pattern of multifactorial etiology
- Subcategorization confusing and controversial
 - Erythema multiforme minor: target lesions, no more than 10% body affected, no more than 1 mucosal surface affected
 - Erythema multiforme major: more than 1 mucosal surface affected, 10-50% body affected, less 10% epithelial detachment
 - Stevens-Johnson syndrome: severe EM, >50% body affected, 10-30% epithelial detachment

Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

- Toxic epidermal necrolysis
 - Generalized disease, more than 30% epithelial detachment
- Some believe TEN and EM 2 distinct syndromes, others suggest different severity of same syndrome
- Categorization of triggers controversial
 - Conversely to people, popular belief is EM often associated with drug hypersensitivity in small animals
 - Neoplasia (rarely seen with humans)
 - Infection
- Pathogenesis: not fully understood

Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

- Clinical signs
 - Often on dorsum
 - Mucocutaneous junctions, oral cavity
 - Often acutely develop and multifocal to diffuse
 - EM: papules to macules, or plaques that spread (target lesion), generalized scaling, crusting, erythema, and alopecia
 - TEN: painful vesicles, bullae, ulcers, necrosis, concurrent systemic signs



<http://blogs.babble.com/famecrawler/2011/01/06/million-dollar-money-drop-target-logo-orkin/>

Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis



Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

- Differential Diagnosis
 - Thermal or chemical burn
 - Bullous pemphigoid
 - Deep infection
 - Urticaria
 - Pemphigus vulgaris
 - Systemic lupus
 - Vasculitis
 - Epitheliotropic lymphoma
- Drug Eruption
- Demodicosis
- Dermatophytosis



Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

- Diagnosis
 - History and physical exam
 - Histopathology
 - Damage to epidermis with apoptosis of keratinocytes or full-thickness necrosis of epidermis
- Prognosis: Fair to good with EM, poor to guarded with TEN

Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

- Toxic Epidermal Necrolysis



Treatments

- Treat secondary pyoderma
 - Dogs treated during induction phase of immunosuppressive therapy with antibiotics (PF) had higher survival rates (Gomez, et al., 2002)
- Symptomatic therapy: to remove crusts
- Supportive care if necessary
- Avoid sunlight, use sunscreens (esp. with PE, DLE)
- Look for underlying cause (vasculitis, drug reaction, EM, TEN)
- Consider GI protectants

Treatments



- Immunosuppressive therapies: Glucocorticoids
 - Prednisone: Dogs, 2 mg/kg/day PO
 - Prednisolone: Cats, 4 mg/kg/day PO
 - Methylprednisolone: Dogs, 1.6 mg/kg/day; Cats, 3.2 mg/kg/day
 - Remember 4mg methylprednisolone = 5mg prednisone
 - Cats may require dexamethasone or triamcinolone
 - Triamcinolone: 0.3-1 mg/kg PO q 12-24 hrs
 - Dexamethasone: 0.1-0.2 mg/kg PO q 12-24 hrs
- Taper when lesions resolve, ideally to lowest possible alternate-day dosage that maintains remission

<http://orderprednisone.com/>

Treatments

- Immunosuppressive therapies: Nonsteroidals
 - When to add?
 - If no improvement noted with glucocorticoids
 - Undesirable glucocorticoid side effects
 - Cyclosporine
 - PF, PE, DLE, Cutaneous vasculitis, EM, TEN
 - 5 mg/kg/day (may need higher dose)
 - Atopica or solution (Neoral)
 - Gingival hyperplasia, papillomatosis, vomiting, diarrhea, anorexia



<http://www.us.atopica.com/just-For-Vets/just-For-Vets.htm>

Treatments

- Other non-steroidal treatments
 - Tetracycline/Niacinamide
 - PE, DLE, Cutaneous Vasculitis
 - Dogs >10kg, 500 mg of each TID
 - Dogs <10kg, 250 mg of each TID
 - Azathioprine
 - Dogs, 1.5-2.5 mg/kg PO, q 24-48 hrs
 - PF, PE, Cutaneous Vasculitis, EM, TEN
 - Anemia, leukopenia, thrombocytopenia, vomiting, hypersensitivity reactions (esp. liver), pancreatitis, elevated alkaline phosphatase, skin rashes, alopecia

Treatments

- Other non-steroidal treatments
 - Chlorambucil
 - PF, PE, Cutaneous vasculitis
 - Helpful in cats because do not tolerate azathioprine well
 - Cats (or dogs): 0.1-0.2 mg/kg PO q 24 hrs
 - Myelosuppression, anorexia, vomiting, diarrhea
 - Pentoxifylline
 - Cutaneous vasculitis
 - Dogs: 10-15mg/kg PO q 8 hrs

Treatments

- Topical options: PE, DLE
 - Topical glucocorticoid
 - Begin with potent topical: betamethasone, flucinolone q 12 hrs until lesions resolve, then decrease frequency and potency
 - Tacrolimus
 - 0.1% q 8-12 hrs, taper frequency with resolution
 - Consider ophthalmic glucocorticoids and tacrolimus for peri-ocular lesions
- Other options: PE, DLE
 - Fatty acids: 180mg EPA/10mg PO daily
 - Vitamin E: 400 IU PO daily

Treatments

- Complications of therapy
 - Adverse drug effects (ex. PU/PD with glucocorticoids)
 - Immunosuppression-induced infections, demodicosis
- Regular monitoring
 - Clinical signs: helps to determine when to taper (both glucocorticoids and nonsteroidals)
 - Frequent telephone updates
 - CBC, biochemistry
 - UA with culture

Concluding Remarks

- Always consider clinical history in making diagnosis
- Consider dermatopathologist
 - Search dermatopathologist on VIN
- Treatment varies by animal
 - Requires frequent rechecks to help determine how to alter medications
 - Certain drugs take longer amounts of time to see effects
 - Ex. Cyclosporine, Azathioprine: try to wait to decrease steroid dosage and frequency
 - In general: slow taper

Questions?

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