**Common Immune Mediated Skin Diseases**
- Pemphigus foliaceus
- Discoid (cutaneous) lupus
- Juvenile cellulitis
- Vasculitis

**Pemphigus Foliaceus**
- Over 50% of canine cases display symptoms before five years of age.
  - Spontaneous
  - Drug induced
  - Chronic skin disease higher risk? Disease process or the many drugs used?
  - Sunlight exacerbates autoantibodies
  - Paraneoplastic (rare)

**Pemphigus foliaceous presenting as multiple epidermal collarettes**
Collarette-form variants

Pemphigus Foliaceus

Erosions and ulcers from ruptured pustules and yellow crusts = leucocytes

Pemphigus Foliaceus - Scale predominating
Pemphigus Foliaceus

“Tyson”
**Pemphigus Foliaceus - Feet**

**Pemphigus Foliaceus in the Cat**

Head is affected in about 80% of cases.
Medial pinae increase suspicion
Trunk and belly often bilaterally symmetrical.
Nail folds and nail bed => caseous material with many acantholytic cells.
DDX includes allergic skin disease, skin parasites, dermatophytosis

**Pemphigus foliaceus cat**
Pemphigus Diagnosis
Sample intact pustule by needle puncture (best) or collect impression smear from under crusts.

Acantholytic keratinocytes may be present in lower numbers in pyoderma or ringworm. DDX immature keratinocytes

If severe & highly suspect, biopsy NOW. Otherwise 2-3 week antibiotic course to eliminate pyoderma as a Dx and histopathological complication.

Pemphigus cytology

Remember: With the exception of discoid lupus (+/-) P. foliaceus, autoimmune disease is rare!

Stuff that looks like autoimmune disease

Pyoderma
Other Immune mediated diseases
- Vasculitis
- Drug reactions
Cutaneous neoplasia: Lymphoma, MCT
Metabolic diseases
- Zinc responsive dermatosis
- Metabolic epidermal necrolysis (hepato-cutaneous syndrome)
Collarettes & pustules in pemphigus foliaceus and superficial pyoderma

Hepato-cutaneous syndrome: scale and necrosis

Principals of therapy of immune mediated disease

- Eliminate common differentials first
- Never diagnose or attempt to treat autoimmune disease without histopathological confirmation.
- Treatment is mostly life-long with dangerous drugs that require monitoring although some cases undergo spontaneous remission
- Many cases of pemphigus foliaceus will be euthanased within 12 months due to adverse reactions/cost of treatment.
- Avoid sun exposure
Principals of immunosuppressive therapy (cont)

- Ulceration and erosion => secondary infection. Requires antibiotics.

- Use the least potent drug or combination of drugs that control the conditions. Combination therapy is generally preferable to minimize the side effects.

- Monitor the patient for side effects related to the drug(s). An apparent deterioration in a patient’s condition may be
  - An exacerbation of the original disease
  - Complication of the immunosuppressive therapy. Eg demodecosis, yeast/fungal infections and bacterial infection

- Demodicosis is a common complication of immunosuppressive therapy.
We take lots of prednisolone

Corticosteroids
First choice for initial treatment of severe immune autoimmune disease
Wide range of immunosuppressing effects and short lag time.
Doses are higher (2-3x) than for the management of allergy. 2-3mg/kg initially then tapering
Combination therapy usually needed to prevent side effects
Monotherapy acceptable management in only 35-40% of dogs.

Corticosteroids in Cats
Prednisolone at double the dog dose rates 4mg/kg +
Triamcinolone (0.6 to 2 mg/kg daily) in refractory cases
In cats that resist ingesting tablets, injectable dexamethasone can be administered orally/in food
Monotherapy more successful than dogs
Don’t use azathiaprine. Can use chlorambucil

Diabetes – Type II !!!!
Azathioprine (Imuran)

Inhibiting nucleic acid synthesis.

Bone marrow suppression

Hepatopathy

Occasional pancreatitis

Profile at 2 weeks then every 3-4 weeks until a maintenance dose is reached and then every two months.

If ALT increasing, neutropaenia or thrombocytopaenia, the drug should be suspended for 2 weeks and then restarted at a lower dose rate with fortnightly monitoring.

Azathioprine

Non-enzymic

6-mercaptopurine

Thioguanine nucleotides (TGNs)

INACTIVE metabolic pathways

INACTIVE

Methyl mercaptopurine nucleotides

TPMT, thiopurine methyltransferase

Genetically induced variations in humans

Probably similar in dogs
Azathioprine (Imuran)
Drug of choice in dogs for combination with corticosteroids. Much lower range of side effects and easy to monitor.
2 week + lag phase so need to begin with a corticosteroid at full immunosuppressive doses.
Initial dose = 2mg/kg SID. Maintainance = 1-2mg/kg EOD
Aim is to withdraw or minimise the corticosteroid BEFORE reducing the dose of azathioprine.
Divide tablets for owner...BIOHAZARD. Advise gloves.
Dogs only. Fatal bone marrow suppression in cats.

Chlorambucil can be used in cats (and in dogs that don’t tolerate azathioprine) at an initial dose of 0.1-0.2 mg/kg) using the same protocol.

Cyclosporine in Pemphigus Therapy – limited data

<table>
<thead>
<tr>
<th>CsA Monotherapy</th>
<th>CsA / AZA and KTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td><strong>Initial</strong></td>
</tr>
<tr>
<td>CsA 5 to 15mg/kg</td>
<td>Ketoconazole at 2.5 – 5mg/kg</td>
</tr>
<tr>
<td>Pred 1 to 2.5 mg/kg q24h</td>
<td>AZA 1.5 – 2.5 mg/kg q24h</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td><strong>AZA and KTZ</strong></td>
</tr>
<tr>
<td>CsA 3 to 5 mg/kg q 48hrs</td>
<td>Ketoconazole 2.5 – 5mg kg-1 q48h</td>
</tr>
<tr>
<td>Pred 1 – 2.5 mg/kg q 48hrs</td>
<td>AZA 1.5 – 2.5 mg kg-1 q48h</td>
</tr>
</tbody>
</table>

Glucocorticoids were completely stopped within 3 – 12 weeks after the addition of cyclosporine.
Rosenkranz WS et al. Cyclosporine, ketoconazole and azathioprine combination therapy in three cases of refractory canine pemphigus foliaceus NAVDV 2007, Kauai, Hawaii

Topical therapy

- Systemic drug sparing
- Risk of skin thinning and systemic absorption.
- Use lower potency during maintenance.

Colbetsol propionate 0.05% - 0.1%
Mometasone 0.1% (Econ) , Betamethasone dipropionate (Opinone)
Betametasone valerate (Celestone, Betnovate)
Triamcinolone (Panalog, Aristocort)
Hydrocortisone
Other options

**Tetracycline / niacinamide** (see later):
- Mild cases or drug sparing maintenance

**Exotic therapies**
- Gold salts
- Anti-neoplastic drugs
- Intravenous globulins
- Antimalarials hydroxychloroquine (5–10 mg/kg once daily)
- High dose pulse prednisolone, 10mg/kg daily for the first 3 days, then every 5 days until controlled. Maintenance doses between pulses

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**Cutaneous (Discoid) Lupus Erythematosus**

**COMMON!**

There are gross differences in how the canine and human “discoid” lupus appears; hence, cutaneous lupus erythematosus (CLE) is a more appropriate name for the canine condition.

Collies and Shelties predisposed but may occur in a variety of breeds.

Severely exacerbated by UV radiation

Target = basement membrane area. Target antigens unclear.

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**Cutaneous (Discoid) Lupus**

Nasal planum is common target but may involve other mucocutaneous junctions, pinnae, scrotum and other sites

Depigmentation, erosions and ulceration are typical lesions.

Limited to skin only. ANA -ve
Cutaneous (Discoid) Lupus

Cutaneous (Discoid) Lupus

Cutaneous (Discoid) Lupus
Cutaneous "discoid" lupus.

Alternative sites

Cutaneous (Discoid) Lupus Diagnosis

DDX
- Mucocutaneous pyoderma
- Other immune-mediated diseases (pemphigus, SLE, dermatomyositis, vasculitis and the uveo-dermatologic syndrome).
- Nasal dermatophytosis
- Solar or physical dermatitis
- Neoplasia

*Diagnosis is confirmed by biopsy.* Histopathology can not reliably differentiate cutaneous lupus from mucocutaneous junctional pyoderma and therefore biopsy should be undertaken after two weeks of antibiotics.

Mucocutaneous pyoderma pre and post antibiotics
Areas showing depigmentation and erythema should be selected for biopsy, rather than areas of ulceration and/or crusts.

Balance the severity of cutaneous lupus against the risks of therapy.

Use the least toxic drugs and control sunlight exposure.

**Treatment of Cutaneous (Discoid) Lupus Overview**

Sun Avoidance essential

Short term immunosuppressive doses of prednisolone to induce remission. Long term immunosuppression, as per pemphigus foliaceus, is the last resort.

**Topical Corticosteroids**
Corticosteroids: skin thinning, calcinosis, cutis and infections

**Tetracyclines and niacinamide**
Ancillary therapy

- Vitamin E
- Omega 3/6 oils
- Antibiotics for secondary infection
**Topical Tacrolimus**

Similar action but different binding site to cyclosporine

Pimecrolimus: No studies and dubious absorption

10 cases, 0.1% tacrolimus, 80% responded. 75% of responding cases could be maintained on topical tacrolimus alone.

0.03% may be effective for maintenance

Unregistered and wear gloves

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**Oral Cyclosporine**

Many anecdotal reports that effective at atopic dermatitis protocol

- **Tetracycline and Niacinamide** (nicotinamide)
  - Multiple anti-inflammatory properties
  - Neither effective alone in dogs
  - 70% success rate in maintaining CLE
  - Dogs >10kg BW 500mg of each TID. Smaller dogs 250mg of each TID
  - Doxycycline (7.5-10mg/kg SID) may be substituted for tetracycline.

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**Vitamin E and Essential Fatty Acids**

- **Vitamin E**
  - Mild anti-inflammatory effects
  - 500-1000 IU/day
  - No benefit from megadoses
  - May take 2 months for effects

- **Omega 3/6 fatty acids**
  - Mild anti-inflammatory effects
  - No optimum dose rate or omega 3:6 ratio determined for immune mediated disease
  - Indicative dose = 1ml of cold water marine fish oil/3kg
  - May take 2 months for effects
Juvenile Cellulitis (Puppy Strangles)

Usually a disease of puppies but has been reported in adults.
No aetiological agent recognized.
Vaccination ?? Drugs ???
More than one sibling may be involved

Swelling of lips, eyelids, face +/- pinnae with pustules and cellulitis.
Fever and lymphadenopathy
May involve genitalia and anus
Reports of concurrent polyarthritis
Juvenile Cellulitis DDX

- Pustules with swelling of the face and lips
  - Bacterial pyoderma or deep mycosis
  - Demodicosis with/without secondary infection
  - Dermatophytosis with secondary infection
  - Immune mediated diseases
    - Pemphigus complex
    - Systemic lupus erythematosus
    - Drug reaction
    - Angioedema

- Fever and mandibular lymphadenopathy
  - Systemic bacterial or viral infection
  - Oropharyngeal infection
  - Immune mediated fever (SLE) or fever of unknown origin

Juvenile Cellulitis Work Up

- Juvenile cellulitis requires aggressive immunosuppressive treatment to prevent scarring.
- GET THE DIAGNOSIS RIGHT
### Juvenile Cellulitis Work Up

- **Scrape and hair pluck for demodicosis**
- **Woods light and hair pluck sample. There is not enough time for a fungal culture unless highly suspicious.**
- **Sample intact pustule for cytology and culture**
- **Biopsy with PAS and Gram stains**

### Typical cytology = Sterile pyogranulomatous inflammation (intact neutrophils and macrophages with no bacteria)

### Juvenile Cellulitis Treatment

- **Immunosuppressive doses of prednisolone (2mg+/kg SID).**
- **Every other day after 10-14 days**
- **Let the growth of the puppy taper the dose.**
- **6-8 weeks total therapy**
- **Antibiotics for 10-14 days to control surface infection**
Juvenile Cellulitis – rapid response to effective treatment expected

Case Study: Gapetto. 8yo Whippet

- Treated 10 days before with carprofen and cephaalexin for minor skin disease
- Rapidly developed to involve muzzle, lips, eyelids
- Mandibular lymphadenopathy

VASCULITIS

Haemorrhages
Infarcts
Vasculitis – causes and Dx

- Infections
- Drugs
- Vaccines
- Idiopathic
- Cold agglutinin

Burns
Clotting defects - diascopy
Other immune mediated
EM/TEN
Pemphigus complex
Other bullous diseases

BIOPSY

Treatment
Identify and remove cause
Acute immunosuppressive steroids – Risk vs benefit
Antimicrobials as per burns: make sure was not cause!
Long term immunosuppression if chronic

Pentoxifylline (Oxpentifylline - Trental),
- Xanthine derivative with properties similar to theophylline.
- Variety of actions including decreased cytokine production and response and reduces endothelial expression of adhesion molecules (integrins).
- A lag period of 4-12 weeks occurs before any benefits are seen.
- The initial dose = 20mg/kg BID
- Gastrointestinal irritant and must be taken with food. Major side effects are uncommon.
- Propentofylline (Vivitonin, Intervet) has many similar properties and may have similar benefits (unproven).