Autoimmune Disease in the Dog

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by Jo Tucker

The Importance of a Good Immune System

The immune system is very complex. It is designed to protect the body by identifying, and then destroying, foreign invaders such as bacteria or viruses. In order to do this the immune system develops a `memory', probably before birth, to distinguish between what is:

'itself' - the good cells - its own body

and

'non-self' - the bad cells - foreign to its body

The term `autoimmune' is used when the immune system begins destroying good cells for no apparent reason i.e. there are no underlying causes such as infectious or chronic inflammatory disease, or tumours.

A dog with an autoimmune disease ***does not*** have a weakened immune system, on the contrary it works extremely well - but what it does have, when triggered, is a confused one. The immune system of a genetically predisposed dog has the potential of being unable to distinguish between 'self' and 'foreign'. These dogs may develop an autoimmune disease if they encounter a 'trigger' that confuses their immune system into thinking that a part, or parts, of their own body is a foreign invader. The immune system will respond by mounting an attack to remove the invader from the body, and in doing so destroys 'itself' thereby creating a situation that causes a primary autoimmune disease. Unfortunately, we cannot see our genes and a 'genetically predisposed' dog looks like any other dog until an autoimmune disease develops.

What You Should Know About Autoimmune Disease in the Dog

Genetics

It is known that autoimmune disease in the dog occurs in animals that are genetically predisposed. This means that they have an inherited risk of developing autoimmune disease. It is thought to be a complicated mode of inheritance involving more than one gene; this is known as polygenic. Both parents carry the genes responsible and it does run in families, but this does not necessarily mean that if one dog in a litter gets an autoimmune disease the others will also follow. This is possibly due to the different mix of inherited

genes in individual pups in a litter, or environmental factors (potential triggers). Unfortunately, at the moment, there are no DNA tests for these diseases.

It is not known why dogs with a genetic predisposition develop a specific autoimmune disease or indeed develop more than one autoimmune disease. It may be due to the combination of inherited genes (or lack of them); different environmental influences; or a particular set of untimely circumstances that triggers specific diseases in a predisposed dog.

Age

It is more likely to occur in a young to middle aged dog, but occasionally dogs as old as 14, or more, have been known to develop an autoimmune disease.

Gender

Females seem to be more prone - and this probably due to hormonal influences. Also, it is known that hormones can be a major trigger factor for autoimmune disease in the dog, as in humans.

So, for a dog to develop an autoimmune disease it needs to have a genetic predisposition, but that's not all, as it would have to encounter a `trigger' that causes the immune system to malfunction.

So what are trigger factors?

Anything within your dog's environment that may challenge the immune system can be a potential `trigger'. A dog that develops an autoimmune disease may have encountered the same trigger factor before, with no detrimental effect, but for some reason `on this occasion' it has caused the immune system to malfunction resulting in the dog developing an autoimmune disease.

Possible trigger factors are:

1. Stress eg., fireworks, thunderstorms, separation anxiety, whelping, hormones etc.
2. Viral or bacterial infection.
3. Reaction to chemicals, drugs or vaccines.

To sum up:

A primary autoimmune disease may occur if a genetically predisposed dog encounters a trigger factor that causes the immune system to become confused and mounts an attack on its own body parts or systems.

How do you control the immune system and get it to behave normally again?

Drugs, predominately steroids, are used to significantly suppress the immune system in order to stop the destruction and allow the body to heal and work normally again. When clinical improvement is seen, the drugs are reduced over a period of time, slowly releasing the immune system back to normal function and, hopefully, achieving a state of remission. There is no cure for autoimmune disease but long-term remission can be achieved. Dogs may have an autoimmune disease only once and never get it again but there is always a possibility that a predisposed dog could relapse or get another autoimmune disease at a later date. Some dogs will stay in remission without any drugs and others will have to be controlled on a low, every other day maintenance dose.

Numerous Autoimmune Diseases

There are many different types of autoimmune disease affecting different parts of the body. A dog can develop an autoimmune disease that affects one part of the body only, or that affects several parts simultaneously. There are many autoimmune diseases that are not featured below.

ENDOCRINE GLANDS:

Immune Mediated Endocrine Disease includes:

Primary Hypothyroidism, Addison's Disease, Diabetes Mellitus and Poly-endocrine Disease (more than one endocrine gland involved). Hypothyroidism and Addison's disease are discussed below.

Hypothyroidism – An underactive thyroid gland

'More than 95% of cases of canine hypothyroidism are believed to be due to acquired primary hypothyroidism. Destruction of the thyroid gland can result from lymphocytic thyroiditis, idiopathic thyroid atrophy or rarely neoplastic invasion.' **Canine Medicine and Therapeutics by Neil Gorman.**

Hypothyroidism or under-active thyroid glands, is the most common autoimmune disease in the dog and is probably evident in most breeds, although the incidence appears to be higher in some breeds than others. This disease is usually a slow process resulting in the destruction of the thyroid glands by antibodies directed against the thyroid (lymphocytic thyroiditis). As the body only needs less than 20% thyroid production to function, clinical signs of this disease often develop over a lengthy period of time and are so gradual that the owner is not always aware that the dog is slowing down. The body will cope very well with diminishing thyroid glands, but when the glands have been more than 80% destroyed then clinical signs become more obvious.

The thyroid is essential to life; it circulates thyroid hormones to all parts of the body. If replacement therapy is not given to a hypothyroid dog it will die. Usually, the clinical signs show well before this time and a thyroid blood test should confirm a diagnosis. Thyroid disease is not always simple to diagnose but usually a low TT4 (total thyroid hormone) confirmed by a low FreeT4 (thyroid hormone measurement without protein) and a high TSH (Thyroid Stimulating Hormone) is considered to be

diagnostic of hypothyroidism. (In addition, tests to assess thyroid dysfunction may include: TT3, FT3, autoantibody, TSH and TRH response tests).

Measuring TT4 alone is not enough to make a definitive diagnosis as the dog could be suffering from a non-thyroidal illness (NTI), that is an illness affecting the amount of thyroid hormone within the circulation, rather than a primary autoimmune destruction of the glands. Non-thyroidal illness should be suspected if the dog has a low TT4 and a low TSH. Whippets and other sighthounds have a naturally lower TT4 than many other breeds but the FT4 is within normal limits.

Note: Several drugs, including prednisolone and diseases such as Cushing's syndrome, will lower the circulating TT4 levels and this should be taken into account when evaluating the results. Hypothyroidism is both over and under diagnosed.

Some clinical signs of hypothyroidism are:

Lethargy, mental dullness, unwillingness to exercise, stiffness in gait – limping, weight gain (obesity), dry scaly skin or greasy skin, excessive pigmentation (hyperpigmentation), skin lesions, on-going ear problems, coat texture and colour changes, loss of hair particularly on the tail and bilateral, symmetrical hair loss, signs of premature ageing, irregular seasons - poor infertility and libido, depression (tragic expression), irritability or aggression, intolerance to cold, seizures, voice change (pitch of bark), muscle weakness, megaoesophagus (weakness of muscles in the throat causing difficulty in swallowing).

On examination your vet may also find that a hypothyroid dog has a slow heart beat (bradycardia), eye abnormalities such as *corneal lipid deposits* or ulceration: dysfunction of the central nervous system (CNS), such as tilting of head, circling, unsteady gait (ataxia): Blood analysis may also reveal anaemia and high cholesterol.

The *prognosis* for dogs with hypothyroidism is excellent, although life-long daily treatment with hormone replacement, Levothyroxine, is required. Giving half the daily hormone replacement dose every twelve hours provides a more balanced level of thyroid hormone throughout a 24 hour period and avoids peaks and troughs. *(BSAVA Small Animal Endocrinology)* "**Levothyroxine is better absorbed on an empty stomach". Canine Medicine & Therapeutics by Neil Gorman**

Note: Sometimes dogs with hypothyroidism are prone to other autoimmune diseases.

Primary Addison's Disease (Hypoadrenocorticism)

The diagnosis of primary Addison's disease is not complicated but some vets seem to have a reluctance even considering it in their *differential diagnoses*. It is often misdiagnosed as CRF (chronic renal failure), heart failure, gastrointestinal disease and even autoimmune haemolytic anaemia (AIHA) . Many vets say "It won't be Addison's as we never see it". Unless your vet is looking for Addison's disease then it will not be diagnosed. Addison's disease is known as 'The Great Pretender'. Many dogs are presented to their vet at least three times in the six months prior to diagnosis, and many are in an Addisonian crisis before it is identified. **Dogs have died waiting for the results of an ACTH test through lack of supportive care.**

The biggest hurdle can be to convince your vet to consider that it's possible that your dog may have Addison's disease and not to dismiss the notion without proving it and carrying out a thorough investigation and possibly an ACTH test.

Even if your breed is known to be predisposed to Addison's disease, it is important not to become too obsessive and suspect that your dog has Addison's just because of a bout of diarrhoea or an episode of being a little off colour, but it is equally important to be aware of the tell-tale signs which could aid a diagnosis and maybe save your dog's life.

Points to Consider When Identifying Primary Addison's Disease:

Clinical signs: Lethargy, depression, nervousness, weight loss, anorexia (no appetite), vomiting, weakness (particularly of the back legs), shaking or muscle tremors, limping, diarrhoea (with or without traces of blood), abdominal pain, dehydration, excessive thirst and urination, weak pulse, slow heart rate and abnormal heart rhythm, anaemia (pale gums) and collapse

Is your dog young / middle aged?

Over a period of time, has your dog experienced several of the typical symptoms and has he/she responded well to *fluid therapy*?

Has your young to middle aged dog been diagnosed with kidney disease? Is he/she improving on the special treatment/diet provided by your vet? If the answer is no, then consider Addison's disease.

Do you have a dog whose breed is known to be genetically predisposed to Addison's disease?

Do you know of any relatives of your dog who may have been diagnosed with Addison's disease or kidney failure at a young age, or other autoimmune disease? Speak to your dog's breeder; they may be able to give you valuable information.

If You Suspect Addison's Disease

Have a *Full Serum Biochemistry panel* and a *Complete Blood Count* test done and ask your vet for a copy of the results for your own records. Study the results yourself and note any abnormalities. If symptoms persist, have a further blood test done to see if there are any changes, but don't leave it too long in between (a week or less) as deterioration seems to quicken in the last stages. Keep all laboratory reports for comparison in the future. Blood testing is never a waste of money (in the long term it can save you money), and it provides a 'bench mark' on which to compare further tests. Addison's disease is progressive so a blood test is only valid at the time it was taken. As the disease process progresses the values will change.

The Tell-tale Signs When Looking at Blood Test Results

Routine Laboratory Abnormalities - Haematology & Biochemistry

Sodium/Potassium Ratio

Greater than 90% of Primary Addisonian cases will have **low sodium (Na)** and **high potassium (K)** values, with a **ratio of less than 27**. **(Na:K)**

Prior to diagnosis, Addisonian dogs often show a ratio of less than 23. The low ratio alone is **very** suggestive, but not diagnostic, of Addison's disease. Individual electrolyte concentrations can be more reliable.

As the disease progresses, the ratio will drop even further and the dog may collapse and become critically ill especially if stressed or excited. Stress or excitement, to a dog with reduce adrenal function (even in one who has not exhibited typical, clinical signs of Addison's disease), can cause the dog to collapse or even die suddenly.

When comparing laboratory results look for the following as these will indicate Addison's disease.

INCREASED:

High Potassium (K)
High Creatinine,
High Urea, (BUN – blood urea nitrogen; or SUN - serum urea nitrogen)
High Urea/creatinine ratio (Azotaemia)
Increased Eosinophils
Increased Lymphocytes
High Bilirubin - in some cases
High Calcium (mild to moderate) – in some cases
ALT- ALP - AST (Mild to moderate increase of liver enzymes) – in some cases

DECREASED:

Low Sodium (Na)
Low Sodium/potassium ratio (K:Na ratio - less than 27)
Note: Addisonian dogs often have a ratio of <23
Low Chloride (80% of Addisonian dogs will have low chloride values)
Low Glucose – in some patients
Low Albumin (moderate to severe) – in some cases
Total white blood cell count (WBC) – in some cases
Red blood cell count (RBC or HCT)

Another possible difference between kidney disease and Addison's may be seen in the white blood cells (eg., neutrophils, eosinophils, lymphocytes). When a dog is ill (but does not have Addison's disease) he becomes stressed and this is often reflected in the white cells. The neutrophil numbers are expected to be high normal to increased, and the eosinophils and lymphocytes numbers are low normal to decreased. This is called 'stress leucogram' and is seen in both chronic and acute renal failure, **but not in Addison's disease.**

A dog with Addison's disease may show a different white cell reading than would be expected in such an ill dog. In fact there may even be reverse of what would normally be expected, known as 'reverse stress leucogram'.

Reverse Stress Leucogram – may be seen in Addisonian dogs

Low normal numbers of neutrophils

Increased numbers lymphocytes and eosinophils

Electrocardiogram

- Electrocardiogram (ECG) is a very useful tool to detect various abnormalities of the heart resulting from high potassium levels in the blood.

Another very awkward differential is autoimmune haemolytic anaemia (AIHA). I have known a few Beardies to be diagnosed with AIHA prior to being diagnosed with Addison's disease. The usual treatment for AIHA had been implemented but the dog's clinical signs did not improve, as expected, and clinical signs of Addison's disease, remained.

If this happens you should check for signs of Addison's on previous blood test results to see if there were any undetected tell-tale results such as high potassium, low sodium. These cases are further complicated because of the steroid treatment the dog will now be receiving for AIHA. A diagnostic ACTH test cannot be performed whilst a dog is on prednisolone, as it will interfere with the test results, so the dog's medication would have to be changed to dexamethasone for at least 2-3 days before an ACTH test is performed.

Prompt diagnosis and treatment, or supportive treatment, is crucial to the outcome of an Addisonian crisis and must be treated as a true emergency if the dog is to survive.

Life Saving Support

From BSAVA Manual of Small Animal Endocrinology, Chapter 19 – Endocrine Emergencies

"Whenever a diagnosis of Addisonian crisis is likely, treatment should be initiated without delay."

"A tentative diagnosis of acute *adrenocortical insufficiency* can be made on the basis of the history and results of physical examination."

"Since death from acute *adrenocortical insufficiency* is usually attributed to *vascular collapse* and shock, rapid correction of *hypovolaemia* is the first priority in treating this condition."

1. **Restoring blood volume and**
2. **Correcting imbalance of sodium and potassium levels and**
3. **Treatment of life-threatening *cardiac arrhythmias***

Within 1-2 hours, a <u>saline only</u> intravenous drip can restore correct hydration status, increase sodium levels and lower potassium levels which may be causing *hyperkalaemic myocardial toxicity.* In addition, other protocols may be used if myocardial toxicity is life threatening.

4. **Correct glucocorticoid deficiency**

Dexamethasone is usually given as this has little or no effect on the measurement of endogenous cortisol concentrations and therefore does not interfere with the ACTH test.

Treatment

Once a diagnosis is achieved, the prognosis for an Addisonian dog is excellent. The dog should feel much better in a few days but it may take up to 6-8 weeks after the start of treatment for the clinical signs and blood results to return to normal.

Since April 2016, the treatment for canine Addison's disease in the UK has changed from a daily mineralocorticoid tablet (with some glucocorticoid hormone included), to an injectable

mineralocorticoid called Zycortal Suspension (desoxycorticosterone pivalate), given approximately once every month, depending on clinical signs and the monitoring of sodium and potassium values.

The duration of time between Zycortal injections appears to vary from one individual to another. There are many reports suggesting that the initial recommended manufacturer's dose of 2.2mg/kg is much higher than necessary, and care must be taken not to overdose. Anecdotally, it seems more common now to start dosing at 1.8mg/kg or even 1.5mg/kg.

Ultimately, the dose of Zycortal must be tailored to the individual dog based on clinical signs and blood results until the optimal monthly dose of Zycortal is determined. This can be a long drawn out process taking many months to complete. Anecdotal evidence suggests that the optimum maintenance dose is likely to be far lower than originally expected.

Please see these links:

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2c9b766a-c36b-44aa-bbd8-24fab24ca97c

http://www.endocrinevet.info/2011/11/q-prolonged-action-of-percorten-in-dog.html

www.addisondogs.com/addisons/articles/julia_bates_interview_2012.pdf

http://www.ncbi.nlm.nih.gov/pubmed/23438457

A daily dose of prednisolone, to replace glucocorticoid deficiency, will also be necessary when a dog is being treated with Zycortal. Replacement dose for glucocorticoid deficiency in an Addisonian dog is prednisolone 0.2–0.3mg/kg once a day (BSAVA Small Animal Formulary 6th Edition). This dose may need to be increased at times of stress because an Addisonian dog no longer has the 'supply and demand' facility for the 'fight/flight' response at times of stress. It might be prudent for the owner to anticipate added stress such as a brewing thunderstorm or kennelling, or the unexpected incident when out for a walk etc. It might be prudent to carry extra prednisolone at these times.

Life-long, daily glucocorticoid hormone replacement therapy is essential alongside regular subcutaneous injections of Zycortal.

Zycortal is expected to suit approximately 80% of Addisonian dogs, but those who fail to stabilise on Zycortal will have to revert to treatment with Florinef. See information below.

Florinef is a daily replacement mineralocorticoid hormone tablet (with some glucocorticoid activity) called fludrocortisone (Florinef). Tablets should be given regularly, around the same time/times every day. Initially, Florinef will be given with the addition of another hormone tablet called prednisolone. Prednisolone is a glucocorticoid hormone.

Note: Although Addison's disease is easy to treat with Florinef, daily medication is essential. Missing one or two doses of Florinef is not an option and it could prove to be fatal.

Florinef Treatment

Drugs & Dosage:

Extract from BSAVA Small Animal Formulary, 6th Edition

For mineralocorticoid supplementation in chronic or subacute adrenal insufficiency:
Fludrocortisone (Florinef) Oral: 0.1mg tablet

Initial dose: Start at 0.01mg/kg 24 hrs depending on size of animal. Monitor sodium and potassium levels every 1-2 weeks and adjust dose by 0.05 – 0.1mg accordingly. Most patients once stabilised will require approx. 0.1mg/5kg 24hrs.

For glucocorticoid supplementation in chronic or subacute adrenal insufficiency:

Prednisolone: 0.2-0.3mg/kg given once daily with fludrocortisone. The use of prednisolone may be discontinued in most cases once the animal is stable.

Useful References:

"When the disease is first diagnosed, a higher dose of prednisolone is often necessary (up to 0.5mg/kg every 12 hours) but should be tapered rapidly to the lowest amount". Ref: Unmasking the Great Pretender': how to recognise and manage canine Addison's disease by Audrey Cook BVM&S MRCVS Dip ACVIM-SAIM Dip ECVIM-CA.

'Most dogs can be successfully treated on once daily therapy but some will require twice daily treatment to maintain electrolyte concentrations within reference ranges. Fludrocortisone possesses a small degree of glucocorticoid activity and therefore also assists in weaning affected dogs off prednisolone therapy. The dosage of Fludrocortisone increases with time for reasons that are yet unclear and many dogs subsequently require doses as high as 0.03 mg/kg/day'. Ref: FECAVA Lecture Addison's Disease (Hypoadrenocorticism) in Dogs – Carmel T Mooney

Note: Florinef should be kept cool and stored in a fridge.

A gastroprotectant may be given if gastrointestinal bleeding is present.

Following replacement hormone treatment with Florinef and prednisolone, the dog should feel much better in a few days, but it may take up to 6-8 weeks for the clinical signs and blood results to return to normal. The optimum dose of Florinef is established during this time and several blood tests, to check that the sodium and potassium ratio is back within normal range, are necessary and should be performed weekly from the start of treatment.
The oldest dog with Addison's that I have known was over 16 years old when she died, so getting that diagnosis is worth fighting for.

Once diagnosis is achieved, the *prognosis* for an Addisonian dog is excellent. The dog should feel much better in a few days but it may take up to 6-8 weeks for the clinical signs and blood results to return to normal. Once stabilised the dogs will be maintained on Florinef (a mineralocorticoid with some glucocorticoid) only needing low replacement dose of prednisolone at times of stress (the 'supply and demand' facility for the f*ight/flight' response* is no longer available to Addisonian dogs). It might be prudent for the owner to anticipate stress such as a brewing thunderstorm and give a low, one-off dose of prednisolone. Life-long, daily hormone replacement therapy is <u>essential</u>. The oldest dog with Addison's that I have known was over 16 years old when she died, so getting that diagnosis is worth fighting for.

<u>AUTOIMMUNE SKIN DISEASE</u>

There are numerous autoimmune skin diseases. Some are primary, and some are a part of a multisystemic disease such as SLE (systemic Lupus Erythematosus) or hypothyroidism etc.

Symmetrical Lupoid Onychodystrophy, Discoid Lupus Erythematosus and Pemphigus foliaceus are discussed.

Symmetrical Lupoid Onychodystrophy

The first thing you may notice if your dog has a nail problem is when he cries out in pain and limps, or licks his foot. It is natural to think that he has caught his nail on something that perhaps has broken it and made it bleed. It is probably not until the same happens to a second and maybe a third nail that you start to connect the two and wonder if there is more to this than just a couple of broken nails.

One lost nail may be due to trauma or even an infection but if the problem extends to nails, on other feet, then it is likely to be due to an autoimmune destruction of the nail bed and surrounding skin and tissue. Auto-antibodies infiltrate and damage the nail bed skin and surrounding area causing the nails to fall off or grow deformed. This is called Symmetrical Lupoid Onychodystrophy, otherwise known as SLO. Clinical signs of SLO can include: lameness, complete or partial loss of nails, licking of feet, swollen toes, bleeding and/or discharge from the nail or surrounding skin, deformity caused by abnormal growth, and secondary infections.

SLO can be a primary autoimmune disease or part of other autoimmune skin diseases such as one of the pemphigus skin diseases (where the foot pad and other areas of skin would be involved) or a multi systemic autoimmune disease SLE (Systemic Lupus Erythematosus) when the dog would show signs of feeling very unwell.

A dog with primary SLO is generally well in himself although some may be depressed due to pain involved in losing nails. A haematological and biological blood test will be unremarkable but a full blood test is essential to first rule out an underlying disease that may cause *sloughing* of the nails. To obtain a definitive diagnosis of SLO the amputation of the first digit of a toe is required. This is to enable the pathologist to identify infiltrating immune cells which confirms the diagnosis. Many owners consider this too drastic to be acceptable and would rather take the overwhelming clinical signs of SLO, and breed predisposition, into consideration and start a treatment regime. A *punch biopsy* can be taken but it rarely gives conclusive results. It is reasonable and not uncommon for a vet to assume an incorrect diagnosis of bacterial/fungal infection and treat accordingly. This treatment will not work if it is SLO and the condition will continue to get worse and more nails will fracture and fall off. This can go on for several months before vet and owner realise that the treatment is just not working.

Discoid Lupus Erythematosus – DLE (Cutaneous Lupus)

Discoid lupus is an autoimmune skin disease that causes depigmentation, and ulceration and crusting of the lips, nose and *nasal planum,* with loss of the 'cobblestone' appearance. It also affects areas around the eyes and sometimes the ears, often causing hair loss in these areas. Although the dog is not systemically ill, this condition is very painful, especially if the dog 'knocks' its nose and, as always with severe pain, this can make the dog very depressed.

Pemphigus Foliaceus

Pemphigus is a group of autoimmune skin diseases. Pemphigus foliaceus is the most common in this group. Autoantibodies are directed against the epidermis, the outer layers of the skin. You may notice *pustules* or crusting on the muzzle, face, lips and ears before the disease slowly progresses to the dog's trunk. The footpads may become thickened and sometimes the surface layer of the pad will lift off. Diagnosis is obtained by several skin biopsies and *immunoflourescent staining.* Many skin conditions take on a similar appearance so it is very important for other conditions such as *demodicosis*, *drug eruptions* etc., to be excluded before treating with *immunosuppressive* drugs. Secondary infection may be present and this should be treated with antibiotics.

Treatments for Autoimmune Skin Disease

Unlike systemic autoimmune diseases, there are several treatment options for autoimmune skin disease, these include:

Steroids (prednisolone, Medrone, Betamethasone etc). Immunosuppressive doses of steroids are the mainstay of treatment for AI skin disease in the pemphigus and bullous pemphigoid group such as Pemphigus Foliaceus, Pemphigus Vulgaris, Pemphigus Erythematosus, Pemphigus Vegetans and Bullous Pemphigoid. (See Prof. Michael J Day immunosuppressive drug protocol)

Cytotoxic drugs eg., Azathioprine or Atopica (cyclosporine). Often used alongside steroids. See this link to other immunosuppressive drugs.

https://www.dvm360.com/view/immunosuppressive-drugs-beyond-glucocorticoids-proceedings

Topical immunomodulating ointment *(Tacrolimus 0.1% - 2 or 3 times a day for 4-6 weeks to achieve remission, then the frequency can be reduced to lowest maintenance levels - Manual of Skin Diseases of the Dog and /Cat by Sue Paterson).* Tacrolimus does not have the same adverse effects on the internal organs of the body as a tablet/injectable immunomodulating steroid and cytotoxic drugs, and it is a good treatment option.

A combination of tetracycline or doxycycline and niacinamide (Vitamin B3), and 'steroid sparing' supplements such as essential fatty acids and natural Vitamin E in therapeutic doses. If the use of steroids is appropriate, then the regime is the same as systemic autoimmune diseases, with or without a 'combination' drug.

There is a group of five antibiotics that go under the heading of 'Tetracyclines'. From this group, there is a choice of using one of the following: Doxycycline, Tetracycline or Minocycline. These antibiotics are not used for their antimicrobial properties but for their anti-inflammatory and *immunomodulating* effects, and the ability to suppress antibody production. Any one of these can be used in combination with niacinamide (vitamin B3) for the treatment of immune mediated skin diseases. It is more commonly used, and seems to be especially successful, for the treatment of SLO. It should be noted that food or dairy products can reduce the amount of tetracycline absorbed by 50% or more. To maximise *bioavailability* it is recommended to administer the drug two hours before or after food. Unlike tetracycline, doxycycline is not affected by food or dairy products to the same extent (no more than 20% reduction) and this is thought to be insignificant. Doxycycline is also more convenient to administer because it is given only once a day.

It takes 1-3 months before positive results are seen and treatment is likely to be continued for 6 months or more. Doxycycline or tetracycline with niacinamide seems to be a good treatment choice as it avoids the use of steroids and other stronger drugs.

A more recently licensed drug for *atopic dermatitis* in the dog is Atopica (cyclosporine), an immune modulating antibiotic. Since being licensed it is becoming very widely used for a variety of autoimmune diseases. Atopica is effective for immune mediated skin disease, but it is a very expensive drug and the cost is often prohibitive. Administration of grapefruit juice two hours before cyclosporine, however, leads to a significant increase of its *bioavailability* and the dose, and consequently the cost, of cyclosporine can be significantly reduced. **(Reference: Effect of Grapefruit Juice on the Pharmacokinetics of cyclosporine in dogs. Veterinary Record Feb 7, 2004).** This drug should not be given to dogs with *hepatic or renal insufficiency* and it is advised to check these functions before treatment starts. Atopica should not be given within two hours of food. For further details see the reference to cyclosporine in treatments for inflammatory/systemic autoimmune disease.

Essential fatty acids and natural Vitamin E also play an active role in the treatment of skin diseases and should be included in any treatment regime. Chinese herbs are also thought to be beneficial, and biotin in the treatment of SLO. It is always worth trying other treatment options before using *immunosuppressive* doses of steroids and azathioprine, and very expensive drugs such as Atopica, however some skin disease, such as those in the pemphigus group may need more aggressive treatment.

Shampoos or ointments such as fuciderm and Protopic (tacrolimus) can be useful in the treatment of skin disease. Protopic has been used successfully in the treatment of *anal furunculosis.*

INFLAMMATORY/SYSTEMIC AUTOIMMUNE DISEASE

There are numerodisease in Dogsus, primary inflammatory autoimmune diseases that can affect any organ or system of the body. Non-regenerative Autoimmune Haemolytic Anaemia (AIHA), Immune Mediated Thrombocytopenia, Evans Syndrome and Immune Mediated Polyarthritis, Steroid Responsive Meningitis and Systemic Lupus Erythematosus (SLE) and Multisystemic Disease Syndromes are discussed.

(AIHA) Non-regenerative Autoimmune Haemolytic Anaemia

A dog can be anaemic from either blood loss (internal bleeding), or destruction of the red blood cells, or a decrease in their production in the bone marrow.

There are many reasons why anaemia might develop, eg. Immune mediated destruction of the red blood cells occurring within the **circulation of the blood** is known as **regenerative** immune mediated haemolytic anaemia. This can be secondary to: tick borne diseases such as *Lyme disease*, cancer, haemangiosarcoma, parasites, poisoning (zinc, onions etc.), a reaction to drug administration, hyperthermia, *systemic disease etc.*

or

Primary non-regenerative AIHA (an autoimmune destruction of the immature red blood cells, or the precursor cells, within the bone marrow) where there is no detectible underlying disease.

Primary non-regenerative immune mediated haemolytic anaemia (NRIMHA) may also be termed as acquired Pure Red Cell Aplasia (PRCA). It is thought that NRIMHA progresses to acquired PRCA and therefore the term PRCA is interchangeable.

The life of a red blood cell is approximately 110-120 days. After this time the old red blood cells naturally leave the body and are replaced by young red blood cells, (*reticulocytes*). *Reticulocytes* are formed in the bone marrow, and when they are mature enough, they migrate to the circulation where they fully mature and then exit the body when their life span is complete. It's a circle of life – as the old red blood cells die off new ones replace them. This is a normal daily occurrence.

If this normal process is prevented from happening, as in the case of a dog with non-regenerative AIHA, where the dog's own immune system is producing antibodies which are destroying these young red blood cells or the precursor cells in the bone marrow, eventually the dog will become anaemic. This is a chronic form of AHIA.

The destruction of the red blood cells in the bone marrow starts some weeks before clinical signs appear and initially, the dog will cope quite well, as their body adjusts to the gradual effects of this form of anaemia. However, eventually there will come a time when the lack of red blood cells in the circulation shows in various, external clinical signs.

Common, Initial 'Tell-tale' Signs of Chronic Anaemia:

Your dog may have a craving to eat the earth or compost, or chew on concrete or bricks. Another indicator could be bright, orange coloured faeces and dark coloured urine (this is the blood pigment leaving the body). Your dog may become weak or lethargic, or even collapse for a few minutes through lack of oxygen to the brain, especially when excited. Take a look into your dog's mouth and see if the gums appear pale. If the red blood cell count is extremely low, the tongue and whites of the eyes may have a blue tint to them. Occasionally the dog's gums, skin and possibly whites of the eyes, will look yellow with jaundice. Other signs to consider include loss of appetite, high temperature, inexplicable limping and depression. Consideration must be given to recent potential trigger factors such as hormone imbalance (recent season/whelping), vaccination, drugs, pesticides, flea treatments etc., also predisposing factors such as breed and age. The family history of your dog is very relevant to any investigation, and can contribute towards achieving a diagnosis of an autoimmune disease. Dogs with a primary autoimmune disease have a genetic predisposition to one or several autoimmune diseases. Autoimmune disease runs in families so it is possible if one dog in a litter, or a relative, develops autoimmune disease the others may follow.

Non-regenerative haemolytic anaemia is the most common form of primary AIHA but your vet should not assume this diagnosis. As stated previously, a dog can become anaemic for a variety of reasons and these will need to be investigated. However, it appears some vets don't consider that AIHA can be a primary disease occurring in the bone marrow and very often a grim, incorrect diagnosis of leukaemia is given. Blood testing and examination of a blood smear is vitally important to a diagnosis of AIHA. Your vet, however, may want to perform a bone marrow biopsy, but this is an intrusive procedure, especially in a very poorly dog, and is now considered a 'diagnostic overkill'. A diagnosis of non-regenerative AIHA is often achieved by elimination of other primary or secondary causes of anaemia and, on examination of a blood smear, the absence of immature red blood cells.

Autoimmune disease is often a 'fight against time'. If the red blood cells are below 12%, a blood transfusion is likely to be necessary to 'buy time' for the treatment to work. The dog needs to be sustained through this early period of the disease. It is not necessary to have 'typed' donor blood for the first transfusion but subsequent transfusions need to be compatible therefore the recipient's blood should be taken and sent away for blood typing before the first transfusion is given so that the type can be determined should another transfusion be necessary. An alternative to whole blood transfusion is intravenous human immunoglobulin (IVIG). For more information see this link: http://veterinarymedicine.dvm360.com/just-ask-expert-human-igg-viable-treatment-imha

Blood transfusions carry risks but they can also save lives. Early diagnosis and treatment may avoid this procedure.

Once treatment has started, an increase in red blood cells will hopefully be seen in approximately 5 days (the time it takes for the *reticulocytes* to develop and migrate to the circulation). The level of *reticulocytes* seen in a normal blood smear is very low. When a dog is recovering from AIHA the levels should be very high and this reflects the level of anaemia. Correct dosage and duration of treatment is absolutely crucial to a favourable outcome.

(IMTP) Immune Mediated Thrombocytopenia

IMTP is a result of an immune destruction and decreased bone marrow production of the blood platelets. Blood platelets are essential for blood clotting. A dog with very low platelets can bleed to death in a relatively short period of time. The life of a blood platelet in a normal dog is approximately one week. In a dog with IMTP the life of a platelet is no more than one day and may be only a few hours.

"Immune Mediated Thrombocytopenia (IMTP) is the most common cause of markedly decreased platelet count in the dog. A strong presumptive diagnosis can be based solely on the detection of severe thrombocytopenia if history, physical examination and laboratory testing reveal no evidence of other causes. Treatment should therefore not be withheld in dogs with suspected IMTP pending results of specific anti-platelet antibody testing, particularly as such tests tend to be unreliable. A presumptive diagnosis can usually be confirmed within 1-2 weeks by an appropriate response to *immunosuppressive* therapy". Andrew Mackin, Chapter 36, Bleeding Disorders, Canine Medicine and Therapeutics by Neil Gorman

There is a very good reason for including the above reference as I have known many young dogs showing signs of bruising, and sometimes bleeding, and a low platelet count that have not been treated appropriately and have died. If your breed is not known to suffer from a genetic bleeding disorder such as *Von Willebrand's disease or haemophilia A,* and is showing classic, clinical signs of IMTP and has a low platelet count, IMTP should be hastily considered and *immunosuppressive* treatment started without delay.

In addition to *immunosuppressive* doses of steroids, with or without an additional immunosuppressive drug, a single dose of the drug Vincristine can produce a dramatic rise in platelets and may be used in life threatening cases of IMTP.

Note: *Vincristine is on the list of drugs that is likely to cause an adverse reaction if the dog has MDR1 gene mutation. MDR1 is the multi-drug resistance gene that produces a protein called P-glycoprotein*

which prevents toxins from crossing the blood-brain-barrier. If this protein isn't present, because of a gene mutation, the body is unable to excrete the drug and toxins will build up within the brain resulting in neurological symptoms. A simple cheek swab or blood test will determine the dog's status for the MDR1 gene, and it might be prudent to consider this before using Vincristine. Collie breeds more likely to have a MDR1 deficiency but for a list of breeds known to have the MDR1 mutation please refer to: http://www.ashgi.org/home-page/genetics-info/faq/mdr1-faqs

Recent studies suggest that the addition of Melatonin to immunosuppressive treatment increases platelet count and is safe and effective in the treatment of refractory IMTP with little or no noticeable side effects.

If the platelet count is particularly low, it may be necessary to give a *whole blood* transfusion or a *platelet rich* transfusion to 'buy time' for the treatment to work. Of course, other secondary causes of platelet destruction have to be taken into account and these include poisoning, bacterial infection, such as leptospirosis or, usually in older animals, cancer.

IMTP is more common in younger animals (this is another clue to aid a diagnosis). You might see the first signs of bruising on the belly, chest or legs. Evidence of blood in the urine and black tarry faeces (melena) indicates internal bleeding. Your dog may vomit dark blood which looks like 'coffee grounds'. Blood shot eyes and spontaneous bleeding, from both nostrils, gums, in fact any orifice, may occur when the platelets are less than 40,000 (normal range 150,000-400,000). However, for unknown reasons, not all dogs with very low platelets will bleed excessively**. Note: reference ranges may differ from one laboratory to another.** Clinical signs can include weakness and lethargy, pale gums, enlarged lymph nodes, high temperature and anorexia. However, it is not unusual for the dog to appear perfectly normal apart from external signs of bruising or bleeding. The dog's apparent wellness belies this condition and owner or vet should not be lulled into a false sense of security because the dog is bright and eating well. *Regenerative anaemia* may be present due to bleeding.

Note: Platelet counts by an automated machine analyser should always be verified by examination of a blood smear.

Evans Syndrome

When both IMTP and AIHA occur concurrently, this is known as Evans syndrome. The treatment protocol for Evans Syndrome is the same as IMTP or AIHA, but often the survival rate is lower. The dog has not one, but two, separate life-threatening conditions to overcome. However, I have known many dogs with Evans syndrome achieve remission and do very well.

IMPA - Immune Mediated Polyarthritis

Primary Immune mediated polyarthritis is the most common *non-erosive polyarthritis* in the dog. IMPA can be primary, or secondary to other diseases such as SLE, myositis or meningitis. Symptoms of IMPA can closely resemble *Lyme disease* or multiple joint infection and this has to be considered in the differential diagnoses.

For a confirmed diagnosis of IMPA, *joint taps* need to be performed to obtain evidence of infiltrating immune cells within the *synovial fluid* in the joints. Clinical signs such as shifting lameness, soft

tissue swelling around the joints, difficulty in rising to a stand, stiffness in the neck and back, and very high temperatures etc., can be vague and evident for several months prior to diagnosis.

Clinical signs therefore can be intermittent and initially antibiotic and non-steroidal anti-inflammatory drugs are usually given, but little improvement is seen. The disease continues to progress until the dog becomes quite overcome by the inflammatory process. Also, it is not unusual for the dog to become depressed and anorexic and stand with its head held low, unwilling to move. This is a very painful condition.

MYOSITIS

Masticatory Myositis (MMM)

MMM is the most predominant form of myositis in dogs.

Clinical signs:

It involves three muscles of the head, presenting with symmetrical wasting of these muscles, pain when opening the mouth and restrictive jaw movement, causing difficulty in eating and barking. High temperature.

Diagnosis: Biopsy of affected muscle

Treatment: Immunosuppressive drugs/cytotoxic drugs

POLYMYOSITIS

Polymyositis involves the muscles of the head, limbs and trunk.

Clinical Signs

Muscle pain, swelling or atrophy and weakness, stiff gait, and unwillingness to exercise, difficulty in swallowing. High, inflammatory induced temperature.

Treatment: Immunosuppressive drugs/cytotoxic drugs

POLYARTHRITIS/POLYMYOSITIS SYNDROME

This form of non-erosive polyarthritis presents very similar to a multisystemic autoimmune disease SLE. In addition to the clinical symptoms of polyarthritis, affected dogs will also have muscle atrophy and pain involving the muscle of the limbs, spine and head. It can be difficult to differentiate between muscle and joint pain.

Treatment: Immunosuppressive drugs/cytotoxic drugs

Note: When muscles are involved, a lower dose of prednisolone is often used alongside a cytotoxic combination drug. This is to limit the muscle weakness side effects of prednisolone.

Steroid Responsive Meningitis Arteritis

Not to be confused with bacterial meningitis.

SRMA is inflammation of the meninges (membrane covering the brain) and peripheral nerve roots, caused by immune mediated infiltration via the spinal cord. The disease may acute or chronic and is cyclic in nature. Relapse is not uncommon.

Clinical signs:

High temperature (up to 42C – 107.6F)

Neck and joint pain with stiffness. Neck is often held in a low, stiff position and the dog shows a reluctance to move head.

Depression.

Diagnosis: Evidence of immune cells via spinal tap and clinical signs.

Treatment: Immunosuppressive doses of Steroids/cytotoxic drugs

SLE - Systemic Lupus Erythematosus

SLE is a *multisystemic* disease that can affect many parts and systems of the body. It is categorised into major and minor signs.

Major signs can be:

Shifting lameness (polyarthritis), anaemia and thrombocytopenia (blood abnormalities), skin lesions, kidney nephritis (inflammation)

Minor signs can be:

Inflammation of the heart, lungs & muscles, mouth ulcers, enlarged lymph nodes, gastrointestinal signs (vomiting and diarrhoea), central nervous system may be affected causing: Behavioural changes, seizures, and staggering (ataxia).

Clinical signs can be extremely varied and not all dogs with SLE will show the same symptoms. An antinuclear antibody blood test (ANA) can be useful in diagnosis but a negative result still does not rule out SLE.

The dog will normally demonstrate signs of pain and stiffness in the joints and this may be accompanied with anaemia, skin lesions and one or more of the minor signs. One would expect the dog to show other clinical signs such as high temperature, enlarged lymph nodes, thrombocytopenia, lethargy, depression, lack of appetite, muscle weakness (*myositis*) sometimes causing weakness of the throat muscles (megaoesophagus). Megaoesophagus is a serious complication and if this is present then the quicker correct treatment is started the more chance you have of limiting the effects. A dog will have difficulty in drinking and eating and this can cause recurring *aspirate pneumonia*. The primary autoimmune disease may have been brought under control but the effects of megaoesophagus may not resolve completely.

SLE can affect any body system/s. A definitive diagnosis may not be achieved, but it may be presumed, based on clinical evidence and response to treatment. Again, knowledge of *breed predisposition* and family history will be beneficial in obtaining a diagnosis. Dogs can have periods of remission and relapse. The *prognosis* for SLE is guarded.

Multisystemic Autoimmune Disease

In addition to Evans syndrome and SLE there are a number of multiple autoimmune disease syndromes such as: Polyarthritis/meningitis, polyarthritis/*myositis* and *polyglandular disease* such as hypothyroidism/Addison's disease/diabetes mellitus. It is not that uncommon for a dog with Addison's disease or another autoimmune disease to develop hypothyroidism at a later date.

Treatment for inflammatory/systemic Autoimmune Disease

Excluding autoimmune diseases where hormone replacement only is required, most of the diseases are treated by significantly suppressing the immune system in order to stop the destruction. There are only a few exceptions to this.

The drugs most commonly used for the treatment of autoimmune/immune mediated disease are steroids (corticosteroids), such as prednisolone. These may be used as the sole *immunosuppressive* agent or used in combination with *cytotoxic* drugs. *Cytotoxic* drugs are used in human medicine to prevent the body rejecting transplanted organs. Many vets can be reluctant to use a combination therapy to treat autoimmune disease, but there is certainly value in using a combined treatment, as an additional drug increases immunosuppression and generally allows the steroids to be weaned down in the shortest possible time whilst maintaining a good level of immunosuppression. It can make a huge difference to the outcome, and in some cases, it makes remission more achievable.

All drugs have the potential to cause side effects and the major concern for treating animals with high doses of steroids and other potent drugs are the unacceptable side effects that may occur. It is a fine balancing act between bringing the disease into remission and the side effects of the drugs. All drugs have the potential to cause a degree of liver toxicity but when the drugs are reduced the liver will recover. It has to be stated that without these life-saving drugs, in many cases, the dog would die, but the objective is to use the minimum dose to control the disease, for the minimum duration of time. However, the dose has to be '*immunosuppressive*' eg. Prednisolone 1-2mg/kg/every 12hrs usually starting at 1mg/kg/12hrs (Plumb's Veterinary Drug Handbook). If this dose does not produce the desired effect, it can be raised. The action of prednisolone is rapid and at times it works like a 'miracle drug'. **Note: It should be given with food to minimise stomach irritation.**

If the dose is too high the side effects may cause other major problems, if it is too low it will not control the disease or achieve remission. One of the most common accounts are when a dog has been on *immunosuppressive* doses of prednisolone for too long and they start to display overwhelming signs of iatrogenic Cushing's syndrome (see below) and very often the clinical progress they have made in combating the disease has reached a plateau and the dog now appears to be weak, off their food and quite depressed. Prolonged, high doses of prednisolone can also cause

bone marrow depression and the red blood cell count can decrease. These clinical signs can cause confusion for the vet and owner, and a relapse of the autoimmune disease is often suspected. It is not unusual for the steroids to be increased when in fact they should be decreased.

Azathioprine is just one 'combination' drug and it is usually tolerated well, but as with all drugs individual dogs can be affected in different ways. Side effects can include reduced bone marrow production, but this is rarely a problem unless the dog is kept on this drug for a long time. In contrast to prednisolone which has a rapid effect on the immune system, azathioprine takes at least 10 days to have some effect and approximately 4-6 weeks to reach its full potential.

Note: Azathioprine and all other cytotoxic drugs should be handled with extreme care. Cytotoxic drugs should not be handled by pregnant women. Rubber gloves should be worn and the tablets should never be split or broken.

Atopica (cyclosporine) is licensed for treatment of *atopic dermatitis* in the dog but it's increasingly being used as an immunosuppressant in 'combination' treatment with prednisolone and azathioprine for systemic autoimmune disease, despite the drug sheet stating 'It is not recommended to use other *immunosuppressive* agents concomitantly'. I have known many dogs on this triple combination treatment that have eventually become overwhelmed by the side effects of the drugs and the outcome has been poor. It may be worth initially, trying a more simple approach to treatment, using immunosuppressive doses of prednisolone, before embarking on a 'prescription overkill' that may prove to be a difficult, and an unnecessarily heavy drug regime for the dog.

In recent years, a more commonly used 'combination' immunosuppressive drug that has produced very favourable results, and without major side effects, is Mycophenolate Mofetil, often referred to as MMF. One major advantage of using MMF is, it only takes about 4 days to take effect. For a list of immunosuppressive drugs, the link below is an excellent resource:

https://www.dvm360.com/view/immunosuppressive-drugs-beyond-glucocorticoids-proceedings

It must be accepted that sometimes these 'heavy' drugs have to be used, especially if the dog is not responding to treatment; and sometimes an additional drug can make all the difference to the recovery of the dog. In these cases, the side effects have to be accepted as a 'trade off', in fact the dog may tolerate it very well. However, there may be no need to prescribe a combination drug when the correct immunosuppressive dose of steroids is used, and a good reducing protocol is followed, as this may be all that is required to bring the disease under control. The severity of the disease has to be taken into consideration when deciding on which combination drug regimen to use but more, isn't necessarily best, and introducing one combination drug at a time will limit the side effects for the dog.

In addition to drugs used to suppress the immune system, preventative measures such as administering antibiotics to prevent infection, *gastroprotectants* to avoid stomach ulcers, and low dose Aspirin or clopidogrel to minimise the risk of *thromboembolism* and *DIC (disseminated intravascular coagulation)* may be given.

WHAT TO EXPECT ONCE IMMUNOSUPPRESSIVE TREATMENT HAS STARTED

If a dog has a serious autoimmune disease, then the sooner treatment commences the better chance the dog has of survival. The main delay to starting treatment is obtaining a diagnosis or at least your vet being sure that he hasn't missed anything that could be made worse by giving high doses of steroids. Achieving a diagnosis can be a fight against time.

If your vet has decided that in all probabilities your dog has an autoimmune disease, then to a certain extent, which autoimmune disease your dog has, as far as treatment is concerned, is irrelevant because with the exception of a few diseases, they are all treated the same, that is, with *immunosuppressive* drugs. The main objective is to 'knock out' the immune system and virtually stop it from working (or near enough) so the destruction will cease and give the body a chance to recover. As previously stated, this treatment regime works in most cases, that is, if it has been given early enough and the dosage is correct. All dogs are different and some can tolerate the drugs better than others. In proportion to their size, small dogs seem more able to tolerate higher doses of steroids than large ones. Some diseases are more serious than others and carry a poorer *prognosis*. The initial crisis is a crucial time, however anecdotal evidence shows that many more dogs survive than die if correct treatment is administered in good time.

It is hoped that a positive response can be seen within 4-6 hours of starting treatment (depending on the disease), but in a serious, life-threatening situation, the first 2-7-14 days can be a very worrying time. Assuming the dog has stabilised he will quickly feel much better, and if he is in hospital may be allowed home within a week.

When he comes home, he will probably have a 'goody bag' full of drugs. He will be on a high dose of steroid, usually prednisolone, and he may also be on another 'combination' immunosuppressive drug. Your dog will be weaned off in a controlled manner according to his wellness and clinical observations.

Note: High doses of steroids must not be stopped abruptly. Your dog could go into an adrenal crisis if the medication is withdrawn too quickly.

In addition to *immunosuppressive* drugs, he should have something to protect his stomach from excess acid. The last thing your dog needs when he is feeling poorly is a bleeding stomach ulcer caused by the drugs. Sometimes, Antepsin, or similar, is given to coat and protect the stomach. Another common *gastroprotectant* used is Omeprazole.

Note: Gastroprotectants must not be given within two hours of other medication otherwise it will stop the drugs from being absorbed

To minimise irritation to the stomach it is usual for the daily dose of steroid to be split into two doses and given with food, one dose in the morning with breakfast and the other dose with his evening meal. I have known several dogs, who did not receive a gastroprotectant as a part of their treatment regime, and went on to develop anaemia. This is not autoimmune haemolytic anaemia but iron deficiency anaemia caused by bleeding stomach ulcers. Using a *gastroprotectant* is a good preventative measure. When the steroids have been significantly reduced to a low dose, a gastroprotectant may not be necessary.

Excess acid, produced because of the drugs, may make a dog prone to developing pancreatitis. A dog with pancreatitis will appear in pain and his back may be arched as if he can't straighten up. He may

be lethargic, seem bloated and have a tender abdomen. Dogs usually go off food and water, may vomit and look depressed. If you suspect that your dog has pancreatitis, don't try to feed him because it will make the condition worse. Take him to the vet as soon as possible as he may require treatment or need to go on an intravenous drip to stop him dehydrating. Again, the risk of pancreatitis should be minimal once the dog is on a lower dose of steroids. A low-fat diet is best when your dog is on high dose steroids or prone to pancreatitis.

As your dog's immune system is being significantly suppressed, he will be more likely to pick up infections, and will not have the ability to fight against them. As a precaution, a broad spectrum antibiotic is often prescribed. Also, it is sensible not to exercise him in areas where he is more likely to encounter infections, for example, a park or a popular dog walking area.

Whilst your dog is on high dose steroids he will want to eat and drink excessively. However, this also means that he will want to urinate more and this can sometimes cause temporary incontinence. You may have to get up to let him out during the night and if you leave the garden door open during the day, it may save some mopping up! He cannot help it and won't like it either, so don't be too hard on him, it's only temporary. You will notice as he is weaned off the drugs the unwanted side effects will subside and he should return to normal habits and behaviour. Urinary tract infections and/or bacterial skin *pustules* are not uncommon when a dog's immune system is suppressed, and this is often the reason for a dog to be off colour during this time. **Note: Always consider a urine infection if your dog seems under par. A course of antibiotics will usually sort this out quickly.**

Depending on what autoimmune disease your dog has, he will probably need to have regular blood tests. Biochemical blood tests will also keep an eye on other body functions, such as those of the liver and kidneys, which is important at this stage.

Assuming good progress is being made, the clinical signs of his illness are diminishing and positive signs of improvement are apparent, your vet will want to start weaning him down from the high doses of steroid. This process can take 3-6 months or more, and usually begins any time after 10 - 28 days from the start of treatment, depending on the results of his blood tests and his clinical signs.

Relapses are not uncommon, especially in diseases that are difficult to control, for example SLE. A relapse may mean that initially, your dog needed to be on a higher dose of *immunosuppressive* drugs for a longer period of time, or your dog may have been weaned off a little too quickly and then the dose withdrawn too soon.

If a relapse occurs, he will probably show similar clinical signs to his initial crisis. He will have to go back on an *immunosuppressive dose* of prednisolone, but it may not have to be quite as high as before. A combination drug may need to be added at this stage. The weaning process will then have to start all over again. Returning to an *immunosuppressive* dose will mean that he has to go back on a *gastroprotectant*.

Side Effects of the Drugs – Iatrogenic Cushing's Syndrome

Iatrogenic Cushing's syndrome is a side effect of high dose steroids and is caused by too much corticosteroid in the body. To a lesser extent, the immediate side effects observed when the dog initially goes on steroids eg., drinking, eating and urinating excessively is a mild example of Cushing's

syndrome. Personally, I like to see dogs responding to high doses of prednisolone in this way, as it means that they are responding to the drugs as they should.

Usually, Cushing's syndrome only becomes a real problem when exceptionally high doses, or prolonged high doses of steroids are administered, maybe due to a relapse, or in some cases where the vet is inexperienced in reducing steroid doses and keeps the dog on a high dose for longer than necessary; or when the dog is not responding to treatment and higher doses are necessary to control the disease. This is where the addition of a 'combination' therapy immunosuppressive drug is very useful.

All drugs carry side effects, but they do not carry the same side effects as prednisolone, therefore by using a secondary drug, in combination with prednisolone, the symptoms of iatrogenic Cushing's syndrome can be minimised. Some 'combination' immunosuppressant drugs as Azathioprine or cyclosporine, take at least 10 days to take effect, so starting the 'combination' therapy at the beginning of treatment may enable the prednisolone to be lowered within the 10-28 day band and still maintain a good level of immunosuppression. The advantage of using a secondary drug like Mycophenolate Mofetil alongside prednisolone, is that it starts to take effect within 4 days and this can make all the difference. If your dog is not responding to treatment then your vet may consider changing his treatment to other *immunosuppressive* drugs.

How Can I Tell if My Dog Develops Iatrogenic Cushing's Syndrome?

Iatrogenic means 'drug induced'. Clinical signs of Iatrogenic Cushing's syndrome are the same as primary Cushing's syndrome but can present with acute clinical signs. It reflects the level of corticosteroid in the body.

The most notable side effects are, heavy panting, some hair loss, and an increase in drinking and urinating, excessive pigmentation. This is something everyone seems to be aware of and accepts as normal when a dog is on high dose steroids. Very often the dog will be weaned down to a low dose before any major problems arise.

Acute Cushing's syndrome due to overdosing of corticoid steroids can be very serious. Blood results will reflect this, especially the liver enzymes which may be extremely high. Red blood cells and blood platelets may also be high and blood clotting may be a risk.

So when should you alert your vet to suspected, unacceptable level of corticosteroid? The owner should take note when other clinical signs occur, such as: Depression, anorexia, muscle wasting and extreme weakness, continuous panting, lethargy - unwillingness to exercise, skin lesions and thinning of the skin, excessive hair loss, pot-bellied appearance and sagging back, behavioural changes (aggression).

If your dog is showing these signs, it will probably mean that the dose of steroids needs to be lowered. It is important that it is not confused with a relapse of the dog's condition or an infection. The dilemma is that steroids must not be withdrawn too quickly otherwise the dog may go into an *adrenal insufficiency crisis*. If the clinical signs of iatrogenic Cushing's syndrome is intolerable, it is hoped that the high dose of steroids that he has been on will have already done their job and that his autoimmune disease will be stable. As long as the steroids are lowered in a controlled manner

and in time, all the symptoms of Cushing's will subside and your dog will return to normal, but extreme signs must not be ignored.

The Importance of Correct Treatment and Dosage

Iatrogenic Cushing's syndrome may also occur if the vet has initially prescribed a dose too high for the size of dog being treated. For example: I received an email from the owner of an Irish Setter, with AIHA. The dog was prescribed 200mg of prednisolone each day. I called the owner, only to hear that the dog had to be put to sleep that day. I was not surprised. The poor dog was on nearly twice the highest, recommended dose of prednisolone. She was 9 years old and had never had a day's illness in her life. What a terrible shock for the owners and what a lot of unnecessary suffering. I know what it feels like because I too, have lost a dog due to prescribed overdosing of prednisolone. The feelings of responsibility are enormous.

In contrast, some dogs are not treated with enough prednisolone. Here's another story:

A greyhound diagnosed with immune mediated thrombocytopenia (IMTP). Her vet gave her an initial shot of dexamethasone (a steroid which is 6 times stronger in terms of glucocorticoid activity than prednisolone). Some vets choose to give a shot of 'Dex' as an initial therapy in autoimmune disease, especially if the patient is acutely ill. Its effects can sometimes be seen within 6 hours and lasts for 36-72 hours.

The vet did really well and a marked improvement in her clinical signs was seen. It is usual, 24 to 48 hours after the shot of Dexamethasone for the treatment to change to an *immunosuppressive* dose of prednisolone tablets and for the owner to continue treatment in the usual way. However, the vet only prescribed 5mg of prednisolone a day. The owner said they were very concerned that after a few days of improvement, she seemed to be very poorly again. The vet couldn't understand why she was not continuing to improve. He gave her another shot of Dexamethasone and the same improvement was seen. I suggested to the owner that she either spoke to her vet about putting her dog on an *immunosuppressive* dose of prednisolone or change her vet. They saw another vet in the practice, who was more experienced in treating autoimmune disease, and the dog was put on the correct, *immunosuppressive* dose of prednisolone and the treatment was successful.

These case histories demonstrate how important it is to treat promptly and correctly.

Reducing the Tablets

When significant improvement in the dog's condition is seen, usually between 10-28 days, the initial steroid dose is usually reduced by 25%. The dose is generally given for another 10 - 28 days and depending on the dog's progress and clinical signs the dose is significantly reduced once more for a further 10-28 days; and again, in another 10-28 days. Anecdotal evidence has shown that if at this stage the dose is lowered more slowly, or reduced to an every other day dose over a period of months rather than weeks, relapse are less likely to occur. It is always tempting to get your dog off steroids as soon as possible, but when treating autoimmune disease, as long as the dog is on a low, every other day dose then taking the last stage slowly seems to work best, depending, of course, on the severity of the disease and allowing for the difference in individual response - no two dogs reactions are exactly the same. With some autoimmune diseases such as SLE, the dog is likely to be

on steroids for the rest of his life. Usually, an every other day dose can be achieved, but you risk a relapse if you take the dose too low. Below is the best example of a reducing immunosuppressive protocol I have come across. It is an excellent guide and can be adjusted to the individual.

Example: Reduction Protocol for prednisolone:

Clinical Immunology of the Dog & Cat , 2nd Edition, by Michael J Day

Professor Michael DayBSc, BVMS(Hons), PhD, DSc, DiplECVP, FASM, FRCPath, FRCVS

Professor of Veterinary Pathology, University of Bristol, UK and WSAVA - Chairman of Scientific Advisory Committee.

This example is based on a dog receiving an induction dose of 1.0mg/kg/q 12hrs *(q = every)*

Dose	Duration (based on clinical effect)
1.0mg/kg/q 12h	10-28 days
0.75mg/kg/q 12h	10-28 days
0.5mg/kg/q 12h	10-28 days
0.25mg/kg/q 12h	10-28 days
0.25mg/kg/q 24h	10-28 days
0.25-0.5mg/kg EOD	at least 21 days
0.25-0.5 mg/kg every third day	at least 21 days

Every reduction is made after consideration to improvement of clinical signs, blood results and side effects of the drugs.

Prednisolone: "Doses above 2.2mg/kg/day do not give more immunosuppression but do cause more side effects. Many internists believe that prednisolone doses should not exceed 80mg per day, regardless of the dog's weight." Plumb's Veterinary Drug Handbook Eight Edition.

The dose of azathioprine 2mg/kg/24 or 48 hrs, can be reduced initially by giving a lower dose tablet per day, or gradually reducing from daily dosing to every 2nd day, every 3rd day, every 4th day etc..... **Remember, azathioprine tablets should not be broken or handled without gloves.**

How Do I Know if My Dog Will Relapse?

Until you have attempted to wean your dog off of the tablets for the first time you will not know if he is likely to relapse or not. Sometimes during the weaning off process, before you even get down to an every other day dose, he may relapse. If this happens then the drug dosage has to be raised, probably up to the last dose before the relapse (maybe a little higher, depending on the severity of the relapse) and then start the weaning process again. If this happens again, then you and your vet

may have to settle for keeping him on a low maintenance dose to achieve a good quality of life. A low, every other day maintenance dose of prednisolone is preferred to enable the dog's liver to rest in between doses. There are many autoimmune diseases that carry a good, drug free *prognosis*. The more common, serious autoimmune diseases that may not need long term steroid therapy are: primary immune-mediated polyarthritis, autoimmune haemolytic anaemia and thrombocytopenia. However, as previously stated, all dogs are different and it very much depends on the individual dog, the severity of the disease, the experience of the vet and the vigilance and compliance of its owner.

If a relapse occurs whilst the dog is still being treated then true remission has not been achieved. If the dog has achieved remission and has enjoyed a period without drugs or is on EOD maintenance drugs, when a relapse occurs or he develops another autoimmune disease, he has encountered a 'trigger factor' which has induced this change.

After All This, Is It Worth It?

YES, absolutely worth it! Just ask all the people who have nursed a dog with autoimmune disease and still have the pleasure of seeing them enjoying a normal life, running and playing just like all the other dogs - even if they are on steroids! These dogs are usually young and very healthy and once the immune system is controlled, they are to all intents and purposes, normal dogs again. They may have a few ups and downs along the way, but on the whole they live life to the full and in some ways they are very extra special dogs because the relationship and dependency that builds up between the two of you is quite unique and fulfilling.

They did not ask to be born, or to have a genetic abnormality, or a hereditary disease which may have caused them to be seriously ill. They have a right to be treated appropriately and given the chance to live into old age, the same as any other illness. Learning about autoimmune disease before you need to will give you the awareness necessary to monitor your dog throughout its life and give him the best possible chance of survival and a good quality of life.

Finally, it may falsely appear that an alarming number of vets are not familiar with the symptoms of autoimmune diseases or how to treat them. Owners, who take their dog to, the vet and get a correct diagnosis, appropriate treatment, and their dog recovers, would probably have no need to contact CIMDA.

You and your vet are your dog's best friends and if your dog is showing signs of illness, the vet is the first place to go. If the symptoms are not improving, don't leave it too long before you ask for a referral, or if you feel your vet isn't dealing with your dog satisfactorily, go to another vet. Your vet could be the nicest person on earth, but if your dog does have an autoimmune disease and a diagnosis can't be reached, or your vet doesn't know how to treat your dog, then his/her condition will deteriorate unnecessarily.

Ultimately, your dog is your responsibility and he needs you to act on his behalf. Dog owners need vets, especially those whom we can work with, but do not expect them to be infallible. Your increased knowledge and awareness may help you to recognise the early signs of a possible autoimmune disease which will assist the vet and save valuable time and unnecessary suffering.

References:

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