MANAGEMENT OF IMMUNE-MEDIATED CYTOPAENIAS

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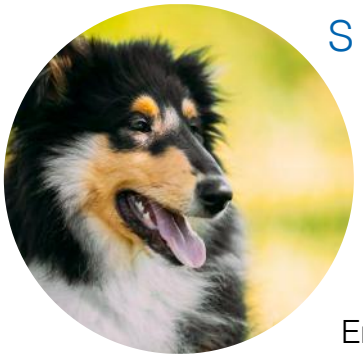
INTRODUCTION

Immune-mediated attacks on circulating blood components are a not uncommon cause of life-threatening acute and chronic disease in small animals. They tend to subdivide into immune-mediated thrombocytopaenia (IMT), immune-mediated haemolytic anaemia (IMHA) and immune-mediated neutropaenia (IMN), or combinations thereof such as Evan's syndrome (IMT plus IMHA).

The majority of disease is the result of true auto-immune (AI) disease involving antibodies against cell membrane antigen and activation of autoreactive T-lymphocytes. Secondary immune-mediated (IM) disease can be the result of neoplasia, infection, inflammatory disease, vaccination, drugs etc, causing an immune reaction to components bound to, or similar to components in, cell membranes.

This discussion will focus on management more, but will touch the other aspects briefly.



SIGNALMENT

There is an increasing incidence with age, and a slight disposition to entire females (related to progesterone). There are also certain breeds that are highly predisposed, such as Cocker Spaniels, Poodles, Old English Sheepdogs.

HISTORY AND PHYSICAL EXAMINATION – IMT

Clinical signs develop when the platelet count drops low enough to cause spontaneous haemorrhage (<30,000-40,000/µL). Rarely a clinical suspicion for IMT may arise in an asymptomatic patient with less severe thrombocytopaenia – dogs will often develop thrombocytopaenia over weeks or months. Bleeding in a patient with counts over 30,000-40,000 suggests another cause.

As platelets are involved with primary coagulation, the characteristic syndrome is small haemorrhages – petechiation, ecchymoses (these two being most consistent), haematuria, oral haemorrhage, haematochezia, epistaxis etc. Occasionally a chronic skin mass may start to bleed unexplainably.

Fever and systemic unwellness are uncommon with IMT, in fact patients are usually clinically well until they become anaemic later on, or unless they are unlucky enough to bleed somewhere clinically significant such as the lungs, eyes, brain (though this is very rare). If they have had time to develop anaemia then pallor, malaise and weakness, and maybe syncope if more severe, may be noted.

Large volume bleeding (body cavities, joints etc) is characteristic of disorders of secondary coagulation and is not expected with IMT.

Mild splenomegaly may be noted.

HISTORY AND PHYSICAL EXAMINATION – IMHA

These patients usually present with systemic unwellness. Weakness, lethargy, pallor and general malaise are usually directly related to the anaemia, however the systemic inflammatory response often results in systemic unwellness and fever. Haemolysis may be primarily extravascular, which is more likely to cause mild icterus. Intravascular haemolysis, which carries a worse prognosis, is more likely to result in haemoglobinuria and haemolysed serum.

Some patients will develop pulmonary thromboembolism resulting in dyspnoea, and the anaemia itself can cause dyspnoea or even syncope.

Mild splenomegaly is common.

HISTORY AND PHYSICAL EXAMINATION – IMN

This is usually suspected in a patient presented for signs of sepsis or severe focal bacterial infection, concurrent with a severe neutropaenia. Rarely it may be detected on routine laboratory screening.

The presentation is identical to any other similar case of severe infection, often with fever or hypothermia, and signs related to the source of infection.

LABORATORY FINDINGS

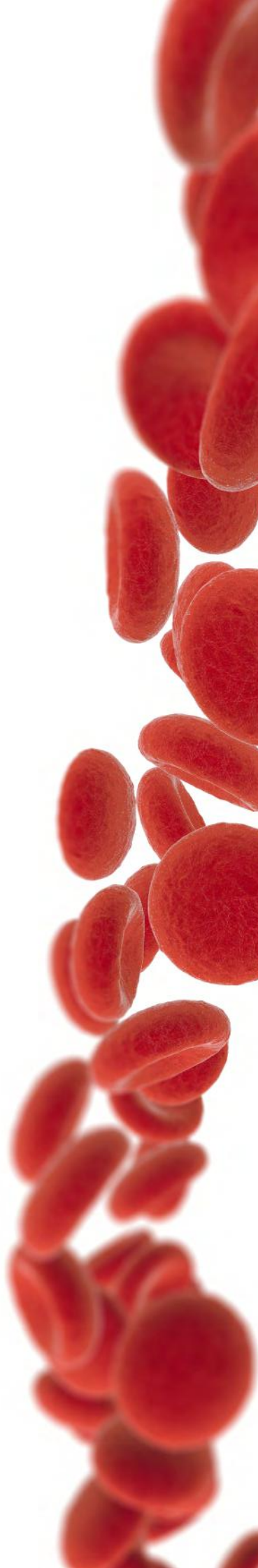
The hallmark finding in these diseases is a cytopaenia consistent with the affected cell line. Disease typically involves peripheral destruction, so one expects a regenerative response if enough time has elapsed for the marrow to respond. Rarely, the immune response may be directed at the precursors in the marrow, hence mimicking other disorders causing non-regenerative cytopaenias – these are more diagnostically challenging and sometimes necessitate bone marrow examination.

LABORATORY FINDINGS – IMT

CBC always shows a severe thrombocytopaenia by the time there is clinical haemorrhage. There is usually a predominance of megaplatelets, indicating a left shift or marrow response. With enough haemorrhage, an anaemia (pre-regenerative or regenerative) will develop. Usually there are minimal other changes in pure IMT.

LABORATORY FINDINGS – IMHA

CBC shows an anaemia, usually regenerative, sometimes pre-regenerative, and rarely non-regenerative as discussed above. This will become severe fairly rapidly, but sometimes dogs will present very early due to signs related more to the systemic inflammatory response, and the anaemia may still be quite mild.



Significant numbers of spherocytes have a high positive predictive value for IMHA.

Mild icterus and/or haemoglobinuria may be present, depending on the presence and severity of extravascular and intravascular disease respectively.

The generalised marrow response often results in a marked thrombocytosis and inflammatory leukogram. Hypoxia can result in liver enzyme elevations.

LABORATORY FINDINGS – IMN

The hallmark sign is a severe neutropaenia, that persists over days, and despite appropriate therapy for the infection. What neutrophils are seen are usually predominantly or exclusively immature (bands). Other laboratory changes are related to the presenting source and site of infection.

CONFIRMING DIAGNOSIS – IMT

As there is no reliable test for IMT – antiplatelet antibody tests proving clinically unhelpful - it is a diagnosis of exclusion. The combination of severe thrombocytopaenia with characteristic haemorrhagic signs and the absence of any evidence of other causes on initial bloodwork and urinalysis screening is enough to warrant a preliminary diagnosis and begin treatment. It should be noted that solid splenic masses do not usually cause immune-mediated thrombocytopaenia.

Imaging (sonography and radiography) and testing for relevant infectious diseases (in Hong Kong particularly Babesia and Ehrlichia, though these usually only cause a mild to moderate thrombocytopaenia) should be performed at the earliest opportunity but treatment should not be withheld pending these results.

CONFIRMING DIAGNOSIS – IMHA

In-saline agglutination tests (macroscopic and microscopic) and the Coomb's test can add support to the diagnosis, but neither are 100% specific or sensitive. Excluding other disease with imaging (sonography, radiography) and screening for relevant infectious diseases (in Hong Kong especially Babesia, also Ehrlichia, Dirofilariasis) is important.

The diagnosis is often made based on the presenting signs and clinical pathology described earlier, along with support from excluding other disease.

CONFIRMING DIAGNOSIS – IMN

Thorough history should allow exclusion of chemotherapeutics, oestrogens, parvovirus and other causes of severe neutropaenia.

Diagnosis can often be done by confirming the presence of anti-neutrophil antibodies, however given the moderate sensitivity of this test, a bone marrow examination may be needed to rule out primary marrow disease.

In some cases, a steroid trial may be performed, though this is not without risk, and as with any IM disease, sometimes the severity of disease may mean the response can be minimal.

TREATMENT FUNDAMENTALS

Because most IM cytopaenias are acute and life-threatening diseases, treatment should be aggressive and early. Using combinations of drugs at maximum doses early gives the best chance of success and saving lives. Two particular conditions stand out as genuine medical emergencies requiring rapid institution of definitive aggressive treatment – IMT with clinical haemorrhage, and IMHA with signs of intravascular haemolysis. It is important to not withhold treatment in a rapidly deteriorating animal with a strong clinical suspicion of

IM disease while waiting for lab results to come back. IMN is the exception due to the difficulty in distinguishing this condition early on and the far higher incidence of consumption neutropaenia.

Clinicians and owners need to be aware that the treatment itself carries some degree of risk. While a combination of drugs is more likely to induce remission, it also carries a greater degree of risk from immunosuppression, and once one moves past two immunosuppressives, the risks increase exponentially with each extra drug.

Tapering of drugs with time should be done slowly and ideally only when in remission, and one drug at a time. Choice of tapering can be challenging and varies largely case by case based on patient, client, disease, side-effects, costs etc.

Loss of control of the disease, or relapse, should warrant a return to full induction protocols.

PREDNISOLONE

This has for a long time been the cornerstone of treatment for IM disease. Doses should start at 2mg/kg/d for dogs or 3mg/kg/d for cats. Tapering traditionally has been done with reducing the maximum dose gradually before moving towards alternate day therapy, however for IM disease it is the author's strong opinion that better control is achieved with less side-effects if the maximum dose is maintained for longer while tapering an alternate day dose in between. Tapering should generally be done slowly and only when remission is achieved.

If oral dosing is impractical in the acute situation, dexamethasone can be substituted at one-seventh the dose, however there is a slightly higher risk of side-effects with this.

Side-effects of corticosteroids are well known and include immunosuppression and diabetes, particularly in cats.

Prednisone should not be used in cats as it may not be converted well to the biologically active form.

CYCLOSPORINE A (CSA)

This is becoming the new cornerstone therapy for IM disease, especially in dogs. Starting dose is 5mg/kg bid, however there is massive variation between individual patients in how well they absorb this drug, due to the intestine actively expelling it from enterocytes and it being reabsorbed and expelled repeatedly along the gut. Bioavailability is also affected by food (adversely, in dogs) and formulation (sandimmune vs atopica/neoral). It's not uncommon for dogs to need 30mg/kg bid.

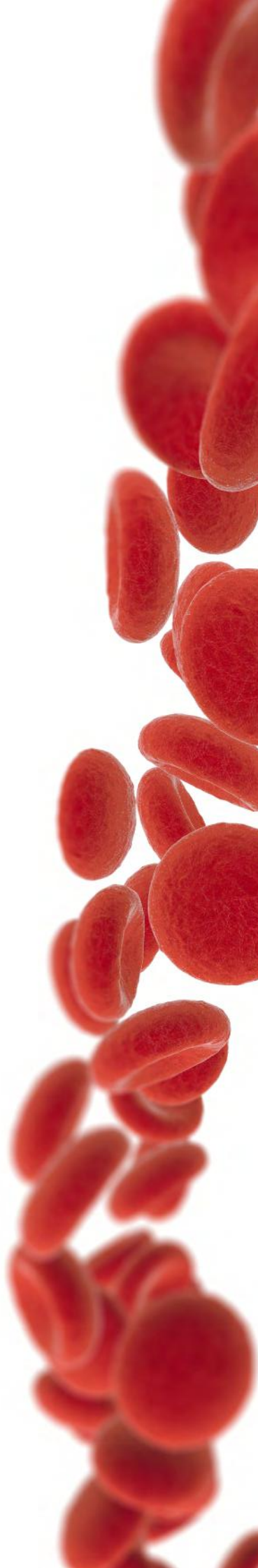
For IM cytopaenias where you are relying on the drug being in the blood, it is crucial to ensure you are achieving adequate levels there, unless you attain a rapid and complete remission (which is rare with IM cytopaenias). There are two ways this can be done.

The traditional method is by measuring trough (prepill, 11-12 hours postpill) whole blood levels. These can (and usually should) be done 2-3 days after starting or a dose change, and should achieve levels around 400-600ng/mL.

Blood levels occasionally correlate poorly with clinical efficacy however, so the more reliable method is to run a PCR to assess T-lymphocyte function. This needs to be collected 2-3 hours postpill and is only reliable 2 weeks after starting or changing dose. This is a particularly useful test for refractory cases.

Costs are usually an issue with this drug, and if becoming prohibitive and there seems to be no alternative drug, imidazole drugs such as fluconazole or itraconazole can be used to slow metabolism and raise drug levels.

Immunosuppressive side-effects can predispose to more unusual infections. There is a misconception that it is carcinogenic, however it merely affects immune surveillance of neoplasia, and the link in animals even with this is tenuous. Other side-effects include GI (minor), and rarely gingival hyperplasia.



VINCRISTINE

This is standard induction for haemorrhagic IMTs, using a slightly lower dose (0.02mg/kg) than oncological doses. As well as being immunosuppressive, it also stimulates marrow release of platelets. Administration technique is crucial as it is a potentially devastating vesicant. Side-effects otherwise are mostly GI and marrow related, though the latter is unusual at these lower doses.

It is usually given once at diagnosis, however rarely may be repeated a week later in refractory cases, or in re-induction protocols.

Public health precautions should be taken for all human in-contacts.

MELATONIN

This is standard long term therapy for IMT, and is the last drug, if ever, to be dropped out of the treatment. There are no side-effects of any great concern, and mechanism of action is still uncertain, however efficacy is mild to moderate only. Dose is 3-6mg per dog under 10kg bid, 6mg bid per dog over 10kg bid.

AZATHIOPRINE

This is usually used as the third drug, or where CsA is prohibitively expensive. Starting dose is 2mg/kg sid, however it takes one to four weeks to take real effect. Dosing should be tapered to q2d no later than two weeks after starting due to the unacceptable risk of side-effects with daily dosing. Cats often do not tolerate this drug well and it should not be used in this species as there are better alternatives.

Side-effects are hepatotoxicity, pancreatitis, and bone marrow related. The last one is to be particularly aware of, as some dogs with IMHA on azathioprine will develop a mild non-regenerative anaemia that may be misinterpreted as ongoing disease when in reality it is a side-effect of the drug.

Public health precautions should be taken.

CHLORAMBUCIL

This is mainly used in cats, as the second or third drug. It is usually very well tolerated, and side-effects are rare, though GI signs can rarely be significant. CBCs should be monitored for marrow suppression, which can be mistaken for ongoing disease. The drug should be discontinued or tapered if marrow disease is suspected to prevent more serious sequelae.

Dosing is usually 2mg per cat, either every 2-3 days (using around 3kg as the cutoff) or more commonly and conveniently, every Monday, Wednesday and Friday.

Public health precautions should be taken, and it must be refrigerated.

MYCOPHENOLATE

This is rarely used, and there is not much experience in veterinary medicine, however it may be superior to azathioprine in terms of efficacy and side-effects. The indications are similar, and the two should not be used together. The author generally uses this for refractory cases, starting at 10mg/kg bid. Side-effects are bone marrow and GI.

SURGERY

Splenectomy is a very useful treatment for refractory IMT, and the author will recommend this early in the course of disease if remission is difficult to obtain. Improvement can be as dramatic as a return to normal platelet counts within 24 hours, though most dogs slowly improve within a few days to a few weeks. Most dogs are either cured after a slow tapering of medication, or need much lower doses than presurgically to maintain the same level of control. It is unusual for a dog to have

no improvement at all with splenectomy. These surgeries are frequently done on markedly thrombocytopaenic patients, however with an appropriately experienced surgical and medical team they are considered fairly routine. The spleen should always be sent for histopathology and, rarely, an underlying disease may be found.

Ovariectomy is recommended for entire females as the progesterone surges during diestrus can exacerbate IM disease. Medical stabilization prior to surgery should be achieved.

SUPPORTIVE /ANCILLARY TREATMENT

There are various therapies that may be instituted apart from definitive treatment of the disease. Transfusions may be necessary for IMT or IMHA, and should be planned based on patient clinical situation and expected clinical course as much as current haematocrit and situation.

Antibiotics are usually used in the acute stages of suspected IMN while CBCs are monitored, given the majority of severe neutropaenias are consumptive (not IMN) and recover within a few days.

Anticoagulant therapy is used in IMHA due to the risk of pulmonary thromboembolism (PTE). Evidence for benefit is still not strong. There is more evidence to support the use of clopidogrel and aspirin, however the difficulty of microdosing aspirin (0.5mg/kg) for the average Hong Kong dog has meant clopidogrel (2-4mg/kg) is the author's preferred choice. Heparins are often used in the acute situation, however unfractionated heparin requires a great deal of monitoring and titration. Low molecular weight heparins require no monitoring but there are still large questions about their efficacy.

COMBINED DISEASE

Any combination of all three diseases has been recorded. In investigation and treatment, the clinician should be alert to the possibility, especially the more common Evan's syndrome (IMT plus IMHA). Therapy should be adjusted to suit both diseases, and the prognosis is correspondingly worse.

SUMMARY

Aggressive, early treatment is the key to successful treatment of most IM cytopaenias, however the clinician should be aware of the risk of side-effects of the treatment, which, like the disease, can be life-threatening. Diagnostic investigation should be thorough, however treatment should not be withheld and put a patient at risk in order to complete workup.

Tapering of medications should be done carefully and slowly. Long term management can be more of an art than a science, and the clinician should be watchful for sudden changes in condition or the appearance of new disease.

With aggressive and skilled management, most IM cytopaenias can be successfully treated, however the time, emotional and financial commitment involved can be enormous, and owners need to be aware of that.