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MANAGING IMHA IN PRACTICE

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Note: Doses here are taken from relevant consensus statements or formularies.[2,4] It is advised that doses are reassessed with another source prior to administering to patients

INTRODUCTION

A fantastic resource for the approach to immune-mediated haemolytic anaemia (IMHA) is the ACVIM Consensus on the diagnosis and treatment of IMHA. It has answers clinically relevant questions, alongside the strength of the evidence supporting the recommendations.[1, 2]

Often the most difficult parts of managing cases of immune-mediated haemolytic anaemia, is gaining enough evidence to make a diagnosis. 30% of cases will be non-regenerative on presentation despite IMHA classically being considered a regenerative anaemia, which can complicate matters.[1] Regeneration takes 3 – 5 days and reassessing as time progresses for evidence of regeneration is not always an option.

To classify the patient as regenerative or not, a reticulocyte count should be measured and quantified. The results should also be interpreted considering the patient's presentation and chronicity of the disease process. The following ranges can be used to semi-objectively quantify the degree of regeneration:

- < 60,000 Minimal regeneration
- 60,000 – 150,000 Mild regeneration
- 150,000 – 300,000 Moderate regeneration
- 300,000 Marked regeneration

Evaluating a blood smear for the degree of anisocytosis and polychromasia can be used as a surrogate marker of regeneration and is an inexpensive diagnostic. Interpretation of the automated haematology analyser results can also be useful. As the proportion of polychromatophils increases, the average mean cell volume (MCV) increases, and mean cell haemoglobin concentration (MCHC) decreases i.e. becomes macrocytic and hypochromic.

DIFFERENTIALS

The main differential diagnoses for a regenerative anaemia are blood loss, haemolysis and less commonly, haemophagocytic syndromes.

Blood loss can be suggested by several features:

- Hypovolaemia alongside the anaemia
  - Prolonged capillary refill time
  - Poor quality pulses
  - Cold extremities
- Lower serum albumin/total solid concentrations
- Hypotension
- Gastrointestinal bleeding particularly can be suspected when there is a thrombocytosis, raised urea and a microcytic hypochromic anaemia, with chronicity.

If it were to be solely an absence of red cells, then pulses tend to be hyperdynamic, the CRT within normal limits and extremities retain their temperature, reflected by an adequate blood volume and blood pressure.

For the blood loss to be significant enough to give rise to a clinically relevant anaemia, then the site of haemorrhage must have allowed substantial bleeding either acutely or chronically.

The sites to consider would include:

- Epistaxis – with possible ingestion of the blood rather than it being externally lost
- Thoracic or abdominal cavity bleed
- Gastrointestinal bleeding
- Urogenital loss
- Bleeding into mass lesions e.g. non-ruptured splenic tumours
- Parasitic infections, typically in small patients e.g. heavy flea/worm/tick burdens

Haemophagocytic syndromes, although often neoplastic in origin, are a set of conditions whereby there is inappropriate destruction of the red cells by activated macrophages. There can be breed predispositions, and often there will be more than one cell line affected.

Non-immune mediated haemolysis can also be a cause of a regenerative anaemia. These are less commonly encountered in comparison to the immune-mediated form, but given the difference in treatment, they are necessary to identify.

Some examples are listed below:

- Genetic defects in cellular metabolism such as phosphofructokinase and pyruvate kinase deficiencies
- Zinc toxicity
- Babesia
- Heinz bodies – Paracetamol, Onion/Garlic ingestion, Propofol additives
- Hypophosphataemia

DIAGNOSIS

To be confident with a diagnosis of IMHA, then at least two out of the following three findings should be identified:

- Positive in saline agglutination test
- Positive Coombs test
- Spherocytosis

In saline agglutination test (ISAT)

This can be a bit of a misnomer and may be better described as the saline dispersion test. The main differential for agglutination of EDTA treated blood is either true antibody-mediated agglutination or rouleaux. Rouleaux appears when there is a change in surface charge of the red cells, most often altered by the content of protein and fat in the blood, resulting in the red cells stacking like coins. When saline is added to the EDTA treated blood, this dilutes the protein/fat content of the blood and reduces the electrical charge on cell surfaces, allowing the cells to disperse. Current recommendations are to use a minimum of 4 drops of 0.9% saline to 1 drop of blood. It should then be evaluated both macroscopically and microscopically. No staining is necessary, a coverslip on top then directly into the microscope is appropriate. If there is a marked hyperproteinaemia, such as in cats with Feline Infectious Peritonitis or those with multiple myeloma, then additional saline drops may need to be added to result in dispersal.

Coombs (direct agglutination testing)

A Coombs test is a way in which it is documented that there are anti-erythrocyte antibodies on the surface of red cells. This involves washing the cells, then adding anti-dog (or cat) antibodies and evaluating for agglutination developing. This is performed at serial dilutions, and often at differing temperatures. This can result in positive results when ISAT was negative, potentially due to an overabundance of autoantibodies. From the evidence available, previous transfusions and immunosuppressives do not appear to give rise to false positives or negatives respectively in the short term, but this cannot be said conclusively, and therefore obtaining a pre-treatment blood sample from anaemic animals is ideal. Infectious diseases can result in

positives and should be included in the differential list for a positive result. A downside is that it will take time to receive the results, and a decision to treat is often required earlier.

Spherocytosis

Due to the redundant cell membrane of erythrocytes, they take on their classic shape of being biconcave. The result of looking at this three-dimensional structure in two dimensions with a microscope, is the presence of a central pallor. In IMHA, macrophages attempt to phagocytose antibody-labelled red blood cells. When this is incomplete, and only a section of the cell membrane is removed, the remaining membrane reseals, giving rise to a spherocyte. Without the excess of cell membrane, the biconcave shape is no longer possible, and instead a sphere is formed. Whilst a sphere in three dimensions, on two-dimensional microscopy this is instead evident as a smaller cell lacking a central pallor.

It is important to be strict when evaluating for spherocytes. They should be smaller than the other erythrocytes, lack a central pallor and be perfectly circular. When possible, they should be evaluated for at the in a section where there are cells with a central pallor for comparison.

Their presence is relatively specific but not sensitive, and the more we see in a high-powered field (100x) the more confident we are of their significance. There can be other causes aside from IMHA, such as fragmentation or storage lesions from blood products. Although rare, certain breeds, such as Golden Retrievers, can have a congenital form of spherocytosis due to a genetic defect accounting for the structural integrity of the red cells. With cats, it can be very difficult to discern spherocytes from normal cat red cells due to the less apparent central pallor, and clinical pathologist review is likely to be necessary.

Supportive findings

In cases where you are suspicious of IMHA, but testing is inconclusive or pending, then additional findings can support the foundations of a diagnosis.

These can include:

- Haemoglobinaemia
- Haemoglobinuria
- Icterus
- Ghost cell presence

SCREENING

Once a diagnosis of IMHA is made, then depending on your geographical area and disease prevalence, screening of the patient for underlying triggers giving rise to the autoimmune disease may be indicated. If no underlying cause is identified, which is most cases, then it is termed non-associative (or primary).

The evidence base for definitive triggers of IMHA are limited, but from the ACVIM consensus statement, then those which have some evidence for involvement are:

- *Babesia gibsoni* infections – important as treatment can cause resolution of the IMHA without the need for immunosuppression
- *Mycoplasma haemofelis*
- Medications e.g. certain antibiotics

Owners wishes, finances and clinical suspicion may dictate the degree of investigations that are undertaken. In our institution, investigations would typically include three view thoracic radiographs, abdominal radiograph to exclude zinc foreign bodies, abdominal ultrasound, urine analysis, and relevant infectious disease testing. Urine analysis is encouraged, to evaluate for co-morbidities which may alter the plan, such as the presence of a urinary tract infection.

PRECURSOR TARGETED (NON-REGENERATIVE) IMHA

A non-regenerative form of IMHA, also termed precursor targeted or PIMA, is also possible. In this form of the condition, the autoimmune target is the immature red cells within the bone marrow. The cells are

destroyed within the marrow before they make it into circulation, giving the appearance of a non-regenerative process on blood sampling. Some of these cases will be ISAT and Coombs positive, whilst others are not, and this cannot be relied upon. The diagnosis is made upon bone marrow sampling, often aspirates are enough, but a core may be necessary. Inappropriate phagocytosis of the red cell precursors may be evident, but the classic appearance is one of maturation arrest. This is when there are many immature precursors, but as they age there is a sudden loss of that precursor and all later stages. Additional diagnostics and treatment are the same as for regenerative IMHAs.

TREATMENT

TRANSFUSION

Emergency blood transfusions may be necessary to stabilise the patient to allow further management. In these cases, the red cells are needed rather than volume and the best blood product is likely to be packed red blood cells. These have the benefit of having a higher concentration of red cells, minimising the unnecessary plasma volume of whole blood. There was previously concern that administering blood was "fuelling the fire", but this is not of concern and the priority is ensuring that there is sufficient oxygen carrying capacity whilst providing time for a treatment response. There is some evidence that there is a benefit to using "fresher" packed red cells in dogs with IMHA, if the choice is available.[3] More details about transfusions can be found in the notes from the Transfusion talk.

IMMUNOSUPPRESSION

The first line of treatment is most often corticosteroids, unless there is a contraindication. At present, there is no evidence that a second line immunosuppressive medication improves the outcomes, but there is a place for them in a subset of cases. Large breed dogs that are susceptible to steroid side effects may benefit from an additional immunosuppressive medication being commenced, to allow a more rapid weaning of the steroid. The consensus statement suggests that a second agent may be added earlier n those with life threatening disease, a consistently decreasing PCV despite corticosteroids or a reliance upon consistent blood transfusions.[2] Further information on immunosuppressive options is covered in the "Immunosuppressives – Beyond pred" talk.

THROMBOPROPHYLAXIS

A major cause of mortality in patients with IMHA is thromboembolic events. This is due to a combination of factors leading to inappropriate activation of the coagulation system. In IMHA, they tend to be in the venous system, and termed red clots, rather than the platelet-rich white clots. Despite this, both anti-platelet and anti-coagulants can be used, and indeed combined. Thromboembolic events have been documented in dogs and cats with non-regenerative IMHA, and we would anticoagulate these patients as well.

Whilst hospitalised, **Dalteparin** may be a parenteral option that allows early treatment and has the benefit of a relatively short half-life if discontinuation becomes necessary. Dosing in dogs is 100 – 175 units/kg SC q 8 hours. For cats, a dosage of 75 units/kg SC q6 – 8 hours is advised.[4]

Rivaroxaban is alternative anticoagulant, acting as a factor Xa inhibitor. It has the benefit of being able to administer orally. Dosing is reported at 1 – 2 mg/kg/DAY for dogs, and 0.5 – 1 mg/kg/DAY for cats.[4]

Anti-platelet drugs can be used, as more recent understanding of coagulation demonstrates the importance of platelet and clotting cascade interplay.

In dogs, **Clopidogrel** can be given as a single loading dose of 4 – 10 mg/kg PO initially to gain therapeutic concentrations quicker, then reducing to 1.1 – 3 mg/kg PO q 24 hours as maintenance. [4]

In cats, a 37.5mg (total dose) can be given on day one as a loading dose, followed by 18.75 mg TOTAL PO q 24 hours then given as maintenance dosing.[4]

Aspirin (low dose) is an alternative but has been shown to be less effective in cats in comparison to Clopidogrel for preventing arterial thromboembolic disease.[5] Some dogs are also aspirin non-responders, and the medication is ineffective. Dosing of Aspirin is 1 – 2 mg/kg PO q 24 hours.[2]

The length of thromboprophylaxis treatment required is unknown and there are not currently prospective studies to guide this. There are other considerations to help guide this, such as the relative risk of thromboembolic disease, co-morbidities, medication side effects and previous history of thromboembolic events.

In general, within our hospital thromboprophylaxis is usually continued until:

- Packed cell volume has returned to normal, or at least stable at > 30%
- No evidence of ongoing red cell destruction (ISAT negative, no spherocytosis)
- Prednisolone dosing is below 1 mg/kg, and ideally below 0.5 mg/kg

OTHER CONSIDERATIONS

Therapeutic plasma exchange, where the patient's plasma is removed, and partially replaced with balanced crystalloids and donor plasma, to deplete circulating autoantibodies has been used with success. This is typically expensive and requires specialist equipment but can be an option and may be lifesaving in refractory cases.

Intravenous immunoglobulin (IVIG) can be considered in unresponsive cases, however there is a lack of evidence for its efficacy in IMHA. IVIG are pooled immunoglobulins obtained from healthy human donors. They are thought to work by saturating receptors and preventing phagocytosis of opsonised red cells. There can be several risks including the possibility of an immunologic reaction to the foreign proteins, worsening of the hypercoagulable state, and it can be expensive, particularly in larger breed dogs.

As the spleen is a store of macrophages, it acts as a major site for red cell destruction. There is recent evidence that splenectomy may assist in these patients.[6] There is a lack of randomised control trials, and the subsets of patients that would benefit from this procedure, and when, is currently unknown. Consideration could be given to those not responding in the acute setting, or those with a high immunosuppressive dependency chronically. The medications the patient is receiving, both immunosuppressive and anti-coagulants would need to be given attention, as well as the potential exposure to infectious diseases that could be worsened by splenectomy.

MONITORING AND WEANING

Most patients that respond require medications for 4 – 6 months, if not longer, with the potential for relapse possible at any time during weaning or afterwards. Relapse is reported at a rate of 8 – 10%.[7]

In our hospital, we have the patient remain on the dose of immunosuppressives that were successful in gaining control of the anaemia for 4 weeks. The patient then has the immunosuppressive dose decreased by 20 – 25% every 3 – 4 weeks, checking a packed cell volume (spun PCV, rather than an automated haematocrit), in saline agglutination and blood smear at every visit. Ideally a urine sample would also be assessed at each visit, as with the corticosteroids, these dogs and cats are producing dilute urine more frequently, increasing the risk of an ascending urinary tract infections. The immunosuppression may also prevent them displaying the classic signs of cystitis.

There can be a point where the PCV is stable, but not returning to normal, and if this is the case alongside evidence of disease remission, then we may try to dose reduce the prednisolone in case there is steroid-associated gastrointestinal bleeding. We'd like the PCV to be above 30% before considering this where possible.

If finances allow, with the corticosteroids often causing the most quality-of-life affecting side effects, then we will wean this medication first. Once we are left with the second line immunosuppressive e.g. Mycophenolate, Cyclosporine, Azathioprine or Leflunomide, then we typically reduce to once daily dosing for a month, before stopping.

Once the patient has been weaned from all medications, we aim to see them for a final recheck to ensure that the PCV has remained stable, ISA is negative and there is an absence of spherocytes – confirming continued remission of the disease.

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