IMHA: When Blood is thinner than water

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Disclosure

IDEXX Employee

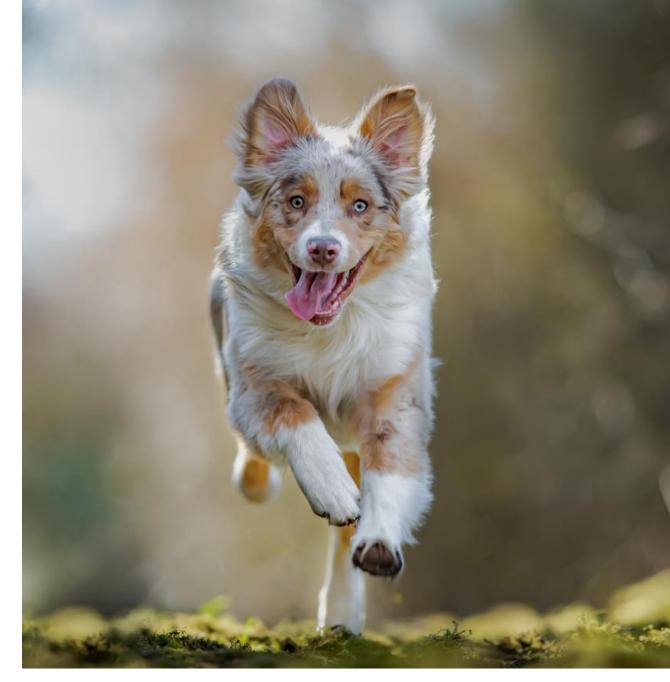
The information contained herein is intended to provide general guidance only. As with any diagnosis or treatment, you should use clinical discretion with each patient based on a complete evaluation of the patient, including history, physical presentation, and complete laboratory data. With respect to any drug therapy or monitoring program, you should refer to product inserts for a complete description of dosages, indications, interactions, and cautions. Diagnosis and treatment decisions are the ultimate responsibility of the primary care veterinarian.



Agenda

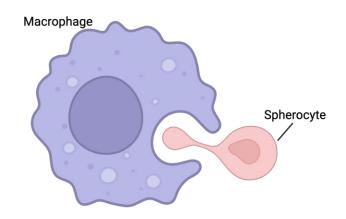
Objective

- 1. Pathophysiology
- 2. Diagnosis
- 3. Treatment
- 4. Case studies
- 5. Q&A



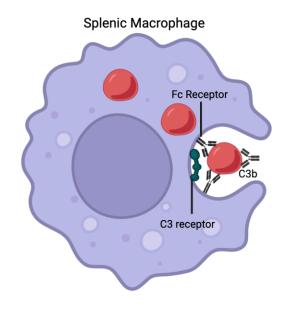
Pathophysiology

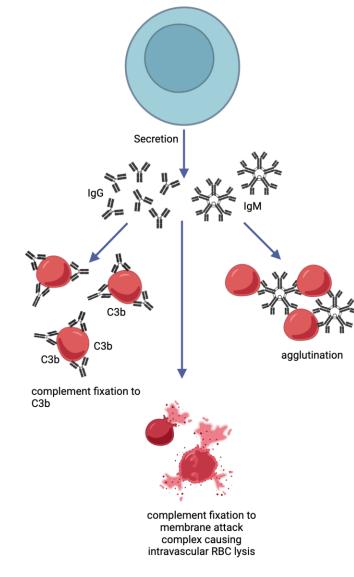
- Immune mediated haemolytic anaemia is due to antibody mediated destruction of red blood cells.
- Canine IMHA is most often primary, i.e, idiopathic.
 - Immune mediated dysregulation
 - Antibody production against unaltered red blood cells
 - No underlying disease identified
- Feline IMHA is most often secondary.



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Pathophysiology





Pathophysiology of IMHA

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Secondary causes for IMHA

Infectious

- + Haemobartonellosis
- + Salmonellosis
- + Anaplasma phagocytophilium
- + Babesia
- + Feline Infectious Peritonitis

Neoplastic

- + Lymphoma
- + Leukaemia
- + Bronchoalveloar carcinoma
- + Mast cell tumour
- + Splenic haemagiosarcoma

Inflammatory

- + Pancreatitis
- + Prostatitis
- + Systemic lupus erythematosus

Drugs/Toxins

- + Cephalosporins
- + Griseofulvin
- + Methimazole
- + Levamisole

Garden OA, Kidd L, Mexas AM, et al.ACVIM consensus statement on the diagnosis of immune-mediated hemolytic anemia in dogs and cats.J Vet Intern Med.2019;33:313–334.https://doi.org/10.1111/jvim.15441334GARDENET AL.

Diagnosis

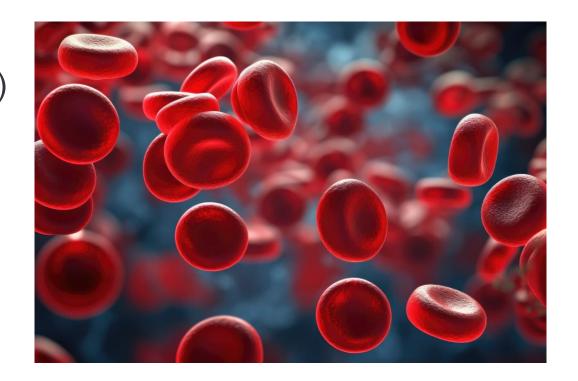
- Can be relatively straightforward
- Strong regenerative anaemia expected
- Positive In Saline Agglutination/Coombs expected

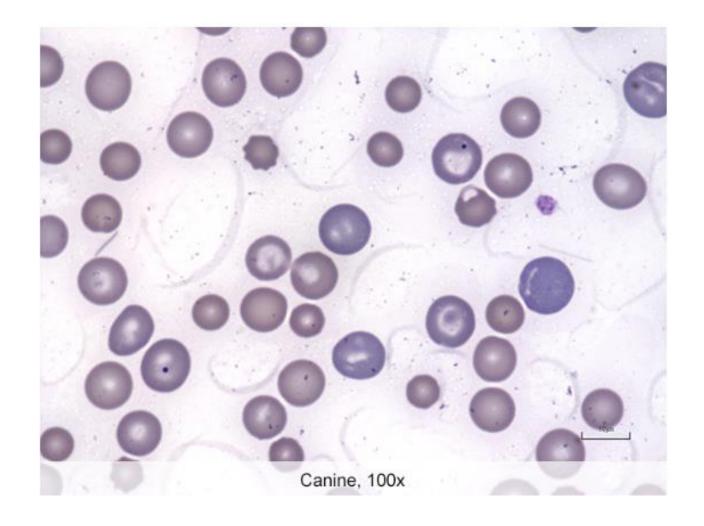
BUT 30% dogs present with non-regenerative anaemia

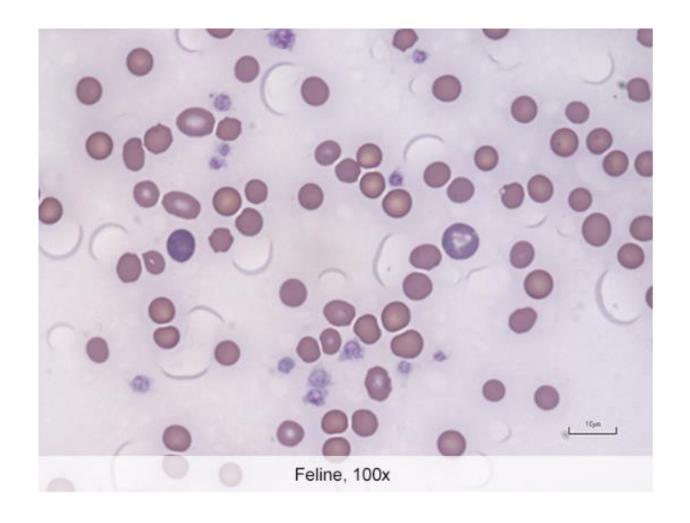
Takes 3-5 days for regenerative response to be seen so care with acute cases

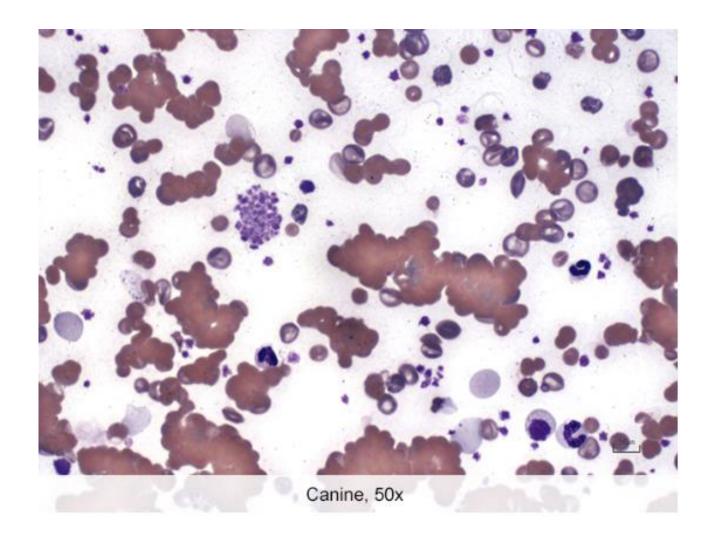


- + Signs of regeneration
 - + Anisocytosis
 - + Polychromasia
- + Spherocytes (not commonly seen in cats)
- + May see ghost cells
- + May see agglutination







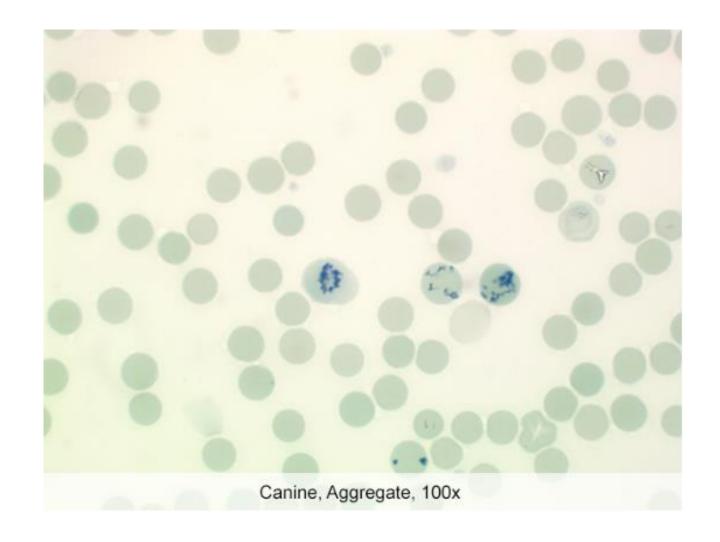


Assessing regeneration

- + Reticulocyte count assessed using new methylene blue stain
- Absolute reticulocyte count (x10⁹/L) = observed reticulocyte count (%) x total red blood cell count (x10¹²/L) x10
- + In dogs, an absolute reticulocyte count >60 x 10⁹/ L is consistent with a regenerative anaemia and in cats, and absolute reticulocyte count >50 x 10⁹/L is consistent with a regenerative anaemia.



Blood smear assessment - New Methylene Blue



Other testing

Serum biochemistry

- + Expect TP to be normal
- + May see hyperbilirubinaemia
- + May see haemoglobinaemia

Urinalysis

- + May see hyperbilirubinaemia
- + May see haemoglobinuria



Infectious disease testing and imaging

- + FIV/FeLV in cats
- + *Mycoplasma* testing in cats
- + 4Dx/Babesia PCR in dogs with travel history
- + Thoracic and abdominal imaging to rule out secondary causes.

Imaging

- Previous study documenting utility of thoracic radiographs and abdominal ultrasound in dogs with IMHA
 - + in 38 out of 50 dogs, the same clinical evaluation and assessment would have been performed without thoracic radiographs.
 - + In 32 out of 64 dogs, the same clinical evaluation and assessment would have been performed without abdominal ultrasound.
- + The results indicate that thoracic radiographs and abdominal ultrasound are of variable utility

Andres M, Hostnik E, Green E, Langston C, Parker VJ, Gilor C, Rudinsky AJ. Diagnostic utility of thoracic radiographs and abdominal ultrasound in canine immune-mediated hemolytic anemia. Can Vet J. 2019 Oct;60(10):1065-1071. PMID: 31597991; PMCID: PMC6741823.

Treatment for Primary IMHA

- + For severely affected patients, a blood transfusion can be lifesaving.
- + No specific PCV at which a transfusion should be considered
- + Pet Blood Bank can supply canine packed red blood cells, however whole blood from in clinic donor dogs can also be considered.
- + For cats there is no UK blood bank and as such we generally rely on in clinic donors.

Xenotransfusion

- + Previous study documenting outcome in forty-nine cats who underwent xenotransfusion
- + Six cats (12%) had febrile non-haemolytic transfusion reactions.
- + Ten cats (20%) died or were euthanased within 24 hours of xenotransfusion.
- + A delayed haemolytic transfusion reaction occurred in 25 of 39 (64%)
- + Of the 18 cats alive at 1 week after discharge, 15 (83%) were still alive at a median of 173 days after xenotransfusion.

Le Gal A, Thomas EK, Humm KR. Xenotransfusion of canine blood to cats: a review of 49 cases and their outcome. J Small Anim Pract. 2020 Mar;61(3):156-162. doi: 10.1111/jsap.13096. Epub 2019 Dec 22. PMID: 31867733.

Canine transfusion calculator

Dogs Weight (KG):		
Dogs PCV (%):		
Desired PCV (%):		
Desired PCV increase (%)		if PCV is unknown
Select the results you wou	uld like to see:	
☐ Packed Red Blood Cells		
☐ Plasma (Fresh Frozen Pla	asma or Frozen Plasma and Cry	o-Supernatant)
□ Cryo-Precipitate		
☐ Whole Blood		

https://www.petbloodbank uk.org/vet-professionals/ineed-advice/caninetransfusion-calculator/

Feline Formulae

- + Previous study investigate five formulae to predict post transfusion PCV in cats
- + PCV % increase = volume of blood transfused in ml/2 × bodyweight in kg performed best overall and is easy to calculate
- + However, no single formula was highly accurate at predicting the PCV increase after whole blood transfusion in cats

Reed N, Espadas I, Lalor SM, Kisielewicz C. Assessment of five formulae to predict post-transfusion packed cell volume in cats. J Feline Med Surg. 2014 Aug;16(8):651-6. doi: 10.1177/1098612X13517254. Epub 2014 Jan 6. PMID: 24393778.

Options for treatment

- + Steroid
- + Cyclosporin
- + Mycophenolate mofetil
- + Azathioprine NEVER IN CATS



Options for treatment

+ Steroid

+2-3mg/kg/day or 50-60mg/m2/day prednisolone PO in dogs >25Kg

+0.2-0.4mg/kg dexamethasone IV if PO not tolerated

+ Side effects include PU/PD/PP, iatrogenic hyperadrenocorticism, and

diabetes and immunosuppression



Cyclosporin

- + Cyclosporin
 - + 5mg/kg PO BID
- + Side effects
 - + Vomiting, diarrhoea, anorexia, gingival hyperplasia, increased risk of malignancy. Risk of toxoplasmosis in cats



Mycophenolate mofetil

- + Mycophenolate mofetil
 - + 10mg/kg PO BID
- + Side effects
 - + GI upsets, bone marrow suppression



Azathioprine

- + Azathioprine NEVER IN CATS
 - + 2mg/kg or 50mg/m2 PO SID
- + Side effects include bone marrow suppression, pancreatitis, hepatotoxicity.
- + Cats develop fatal leucopoenia and thrombocytopenia
 - + Deficient in the enzyme thiopurine methyltransferase (TPMT), which is important for azathioprine metabolism

Non responsive patients

- + Repeat transfusions to buy time
- + Add in additional immunosuppressant
- + Splenectomy?
- + IVIG?



Splenectomy

- + Previous study investigating splenectomy for the management of dogs with IMHA
- + Of the 7 dogs with IMHA, splenectomy was part of a successful management protocol in 4 dogs (2 complete and 2 partial responses)

Bestwick JP, Skelly BJ, Swann JW, Glanemann B, Bexfield N, Gkoka Z, Walker DJ, Silvestrini P, Adamantos S, Seth M, Warland J. Splenectomy in the management of primary immune-mediated hemolytic anemia and primary immune-mediated thrombocytopenia in dogs. J Vet Intern Med. 2022 Jul;36(4):1267-1280. doi: 10.1111/jvim.16469. Epub 2022 Jul 7. PMID: 35801263; PMCID: PMC9308443.

IVIG

- + Previous study investigating the IV use of the use of high-dose IgM-enriched hIVIG (Pentaglobin) in dogs with primary immune-mediated haemolytic anaemia
- + Ten of 11 dogs from the treatment group and 2 of 3 dogs from the control group achieved remission and survived until hospital discharge.
- + Survival and time to remission were not significantly different between groups.
- + The volume of packed red blood cells transfused, normalized for body weight, was not significantly different between groups.
- + Potential adverse reactions to Pentaglobin occurred in 2 dogs

Bestwick JP, Sharman M, Whitley NT, Kisielewicz C, Skelly BJ, Tappin S, Kellett-Gregory L, Seth M. The use of high-dose immunoglobulin M-enriched human immunoglobulin in dogs with immune-mediated hemolytic anemia. J Vet Intern Med. 2022 Jan;36(1):78-85. doi: 10.1111/jvim.16315. Epub 2021 Nov 15. PMID: 34779044; PMCID: PMC8783326.

Thromboembolism

- + Major cause of mortality in dogs
- + IMHA patients have evidence of hypercoagulability and platelet activation

Conway EA, Evans NP, Ridyard AE. Urinary 11-dehydrothromboxane B₂ concentrations in 20 dogs with primary immune-mediated hemolytic anemia. J Vet Intern Med. 2022 Jan;36(1):86-96. doi: 10.1111/jvim.16322. Epub 2021 Dec 3. PMID: 34859495; PMCID: PMC8783321.

Thromboprophylaxis

- + Aspirin (0.5mg/g/day) or clopidogrel (1.1-4mg/kg/day) most commonly used
- + Easily available and no need for intensive monitoring
- + Aspirin COX inhibitor. Thromboxane A2 is produced by platelet in COX1 dependant manner. Thromboxane is a potent platelet agonist.
- + Clopidogrel irreversibly inhibits platelet P2Y12 ADP receptor. ADP is potent activator of platelets.

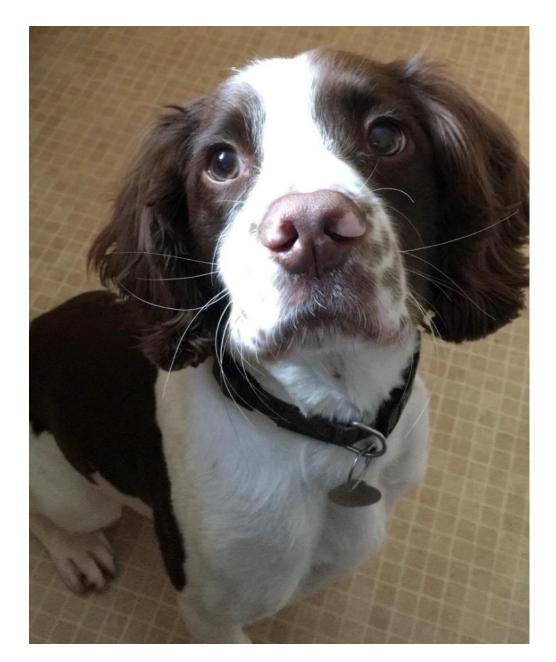
Clopidogrel use

- + Previous study investigating use of clopidogrel alone or in combination with ultra low dose aspirin in dogs with primary immune-mediated haemolytic anaemia
- + There was no identifiable adverse reaction, evidence of hemorrahage, or increase in transfusion requirements associated with CL therapy, either alone or combined with ULDA, compared with ULDA alone.
- + There was no significant difference between treatment groups with respect to survival to discharge and at 90 days.

Mellett AM, Nakamura RK, Bianco D. A prospective study of clopidogrel therapy in dogs with primary immune-mediated hemolytic anemia. J Vet Intern Med. 2011 Jan-Feb;25(1):71-5. doi: 10.1111/j.1939-1676.2010.0656.x. Epub 2010 Dec 13. PMID: 21155892.

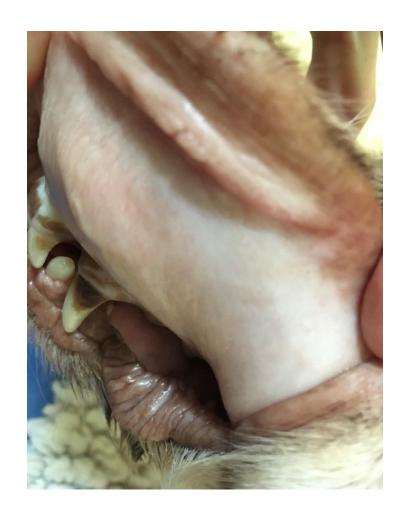
Poppy

- + 3yr FN English Springer Spaniel
- + Acute history of lethargy and pigmenturia
- + No known toxin exposure
- + No travel history
- + No current medications



Physical examination

- + Very lethargic
- + HR 180 with poor pulses
- + RR 50 with normal lung sounds
- + Pale mucous membranes
- + Abdominal palpation normal

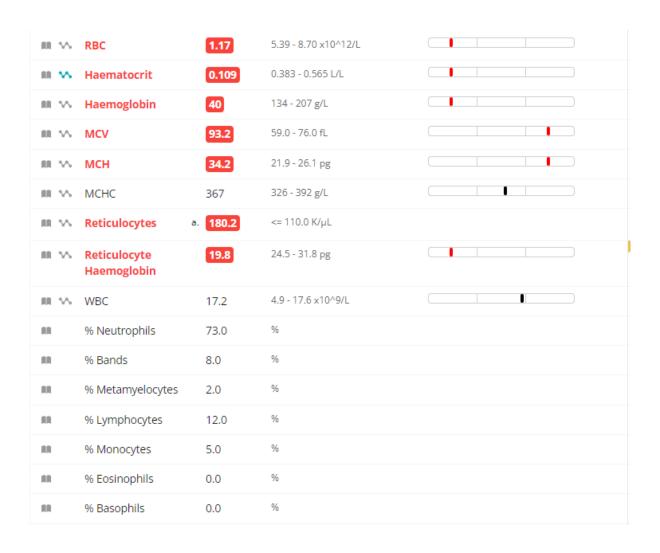


Stabilisation/Initial investigations

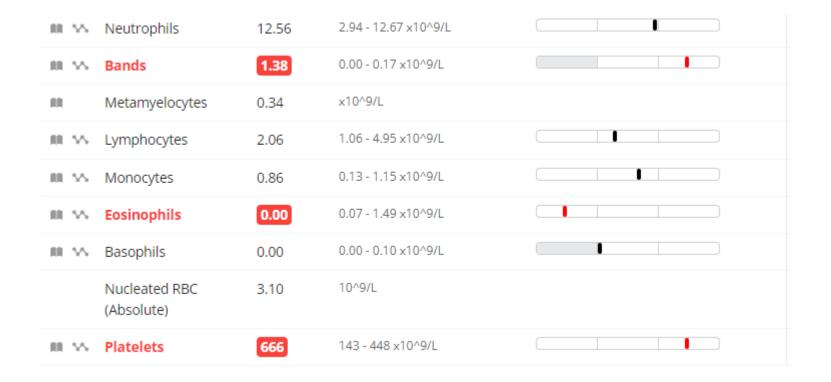
- + Supplemental oxygen
- + 10ml/kg bolus of Compound Sodium lactate
- + Haematology
- + Serum biochemistry
- + Urinalysis



Haematology results Day 1



Haematology results



Blood smear analysis

Blood Film Evaluation Red cells show marked anisocytosis and polychromasia.

Ghost cells, spherocytes and auto-agglutination present.

Metarubricytes noted.

Band cells present with few metamyelocytes. A few neutrophils show

Dohle bodies.

Platelet count falsely raised due to the presence of cell debris. Estimation of free platelets (>8 platelets seen per HPF) suggesting

platelet numbers are normal.

Manual Differential performed by a haematological technician to

replace or complete automated results.

Coombs' (37° C)

POSITIVE

Biochemistry results

■ S Glucose	6.08	3.89 - 7.95 mmol/L	
■ M IDEXX SDMA	a. 6	0 - 14 μg/dL	
⋒ ∨ Creatinine	61	44 - 159 μmol/L	
M ∿ Urea	5.3	2.5 - 9.6 mmol/L	
BUN: Creatinine Ratio	22		
■ M Phosphorus	0.92	0.81 - 2.20 mmol/L	
⋒ 	2.22	1.98 - 3.00 mmol/L	
■ M Total Protein	68	52 - 82 g/L	
■ M Albumin	30	22 - 39 g/L	
■ M Globulin	38	25 - 45 g/L	
Albumin: Globulin Ratio	0.8		
MM ∜∿ ALT	43	10 - 125 U/L	
MM VA ALP	95	23 - 212 U/L	

Biochemistry results

M ∜ GGT	0	0 - 11 U/L	
■ Silirubin - Total	15	0 - 15 μmol/L	
■ M Cholesterol	6.35	2.84 - 8.26 mmol/L	
■ M Amylase	544	500 - 1,500 U/L	
n 🐪 Lipase	424	200 - 1,800 U/L	

Urinalysis

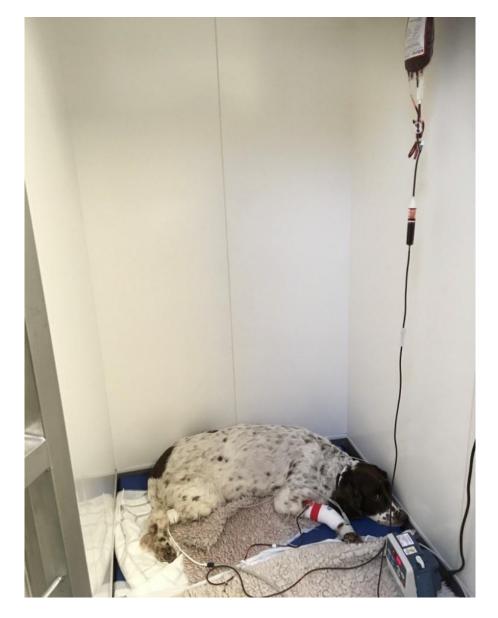
- + Port wine colour
- + Spun and no cell pelletsupernatant remained pigmented



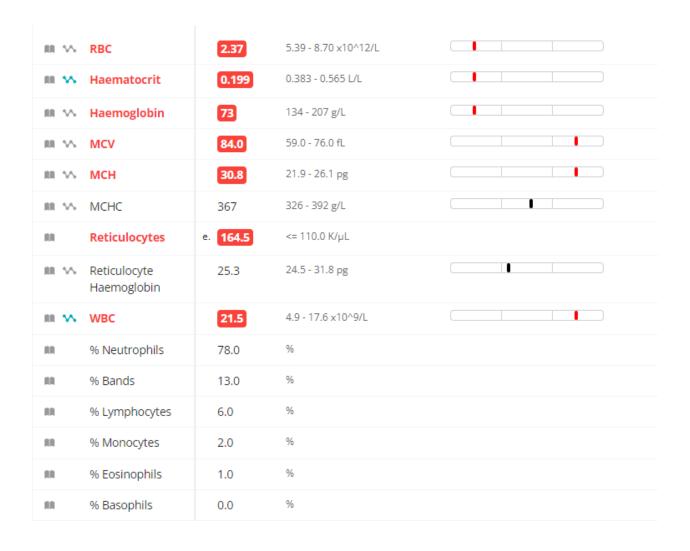
Initial Treatment

- + 0.3mg/kg dexamethasone IV
- + Clopidogrel 75mg PO SID
- + Blood type
- + DEA 1.1 negative
- + Packed red blood cell transfusion administered





Haematology results Day 2



Blood smear analysis

Blood Film Evaluation

Marked spherocytosis, mild polychromasia and moderate numbers of metarubricytes.

Moderate numbers of ghost cells and mild agglutination.

Band cells present.

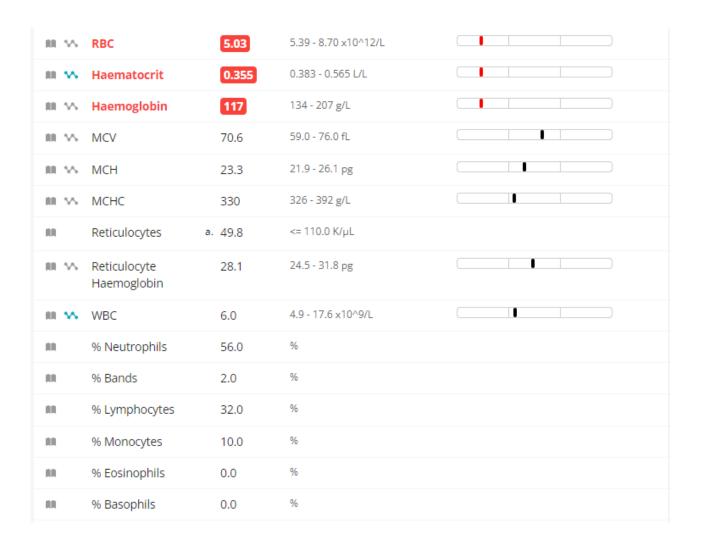
Manual Differential performed by a haematological technician to replace or complete automated results.

Treatment

- + Prednisolone 50mg PO SID (2mg/kg SID)
- + Mycophenolate 250mg PO BID (10mg/kg BID)
- + 75mg clopidogrel PO SID
- + Rest and TLC

+ Discharged Day 5 when PCV 25% and hemodynamically stable

Haematology results- day 10



Blood smear analysis

Blood Film Evaluation No morphological abnormalities detected in red blood cells.

No abnormal white cells seen.

Estimation of free platelets (>8 platelets seen per HPF) suggesting platelet numbers are normal.

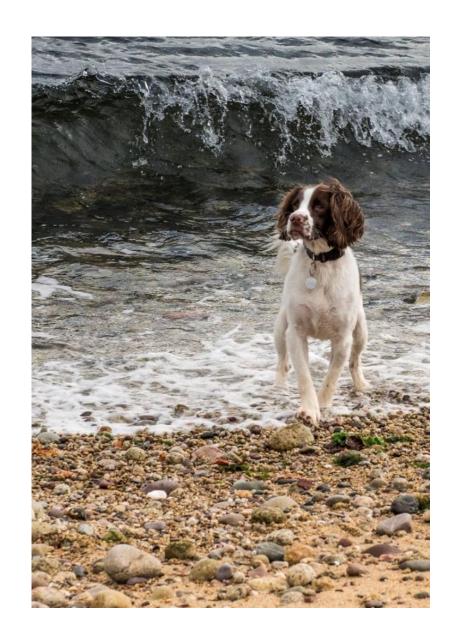
However, platelet clumps are seen. Platelet count and estimate should be considered the minimum value.

Manual differential performed by a haematological technician to replace or complete automated results.



Outcome

- + Responded well to treatment
- + Prednisolone tapered by 25% every 3 weeks, with haematology/smear performed prior to each tapering
- + Mycophenolate stopped after 2 months
- + No signs of recurrence



Maisie

- + 10m FN British Shorthair
- + Reduced appetite for past 2 weeks
- + Hiding under bed for last 3 days
- + Indoor only
- + Up to date with vaccinations
- + No current medications
- + No travel history

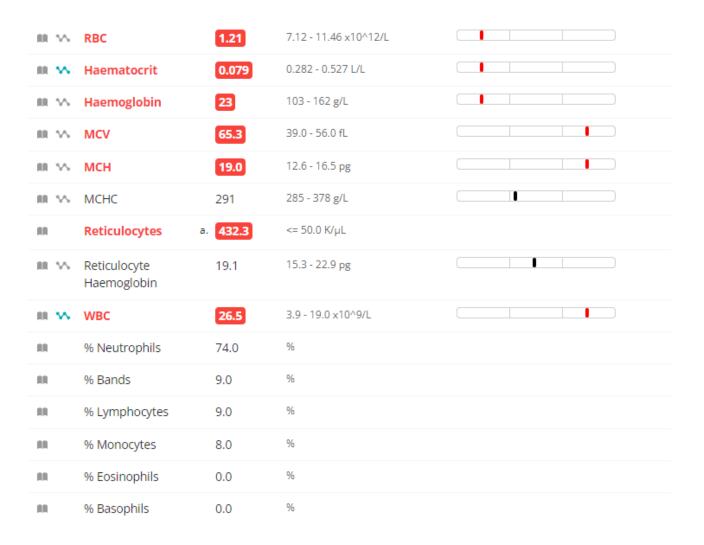


Physical examination

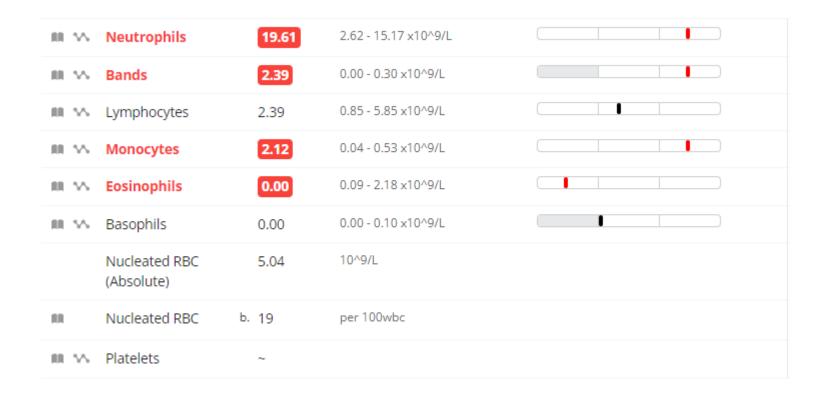
- + Very flat
- + Icteric skin and mucous membranes/conjunctiva
- + HR 240 with poor pulses
- + RR 24
- + Abdominal palpation fluid thrill



Haematology results



Haematology results



Blood smear analysis

Blood Film Evaluation

Red cells show marked anisocytosis and polychromasia.

Auto-agglutination present. Many ghost cells and metarubricytes noted.

Band cells seen.

Platelet count invalidated due to the presence of cell debris.

Estimation of free platelets (>8 platelets seen per HPF) suggesting platelet numbers are normal.

Manual Differential performed by a haematological technician to replace or complete automated results.

Biochemistry results

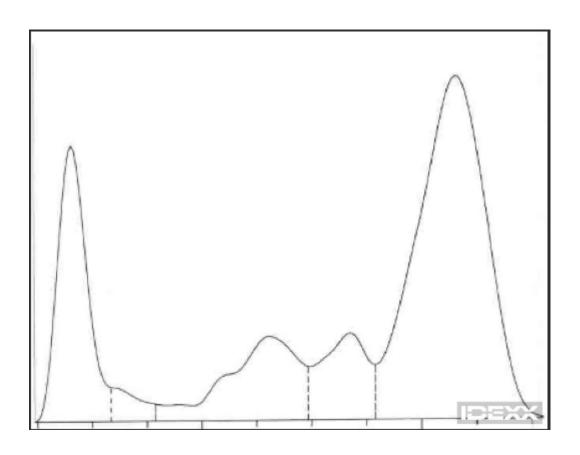
Glucose	7.64	3.95 - 8.84 mmol/L	
Creatinine	94	71 - 212 µmol/L	
Urea	20.3	5.7 - 12.9 mmol/L	
BUN: Creatinine Ratio	54		
Phosphorus	2.29	1.00 - 2.42 mmol/L	
Calcium	2.15	1.95 - 2.83 mmol/L	
Total Protein	96.2	60.0 - 80.0 g/L	
Albumin	19.4	25.0 - 45.0 g/L	
Globulin	76.8	25.0 - 45.0 g/L	
Albumin: Globulin Ratio	0.25	0.60 - 1.50	
ALT	226	12 - 130 U/L	
ALP	<10	14 - 111 U/L	
GGT	0	0 - 4 U/L	
Bilirubin - Total	39	0 - 15 μmol/L	
Cholesterol	2.53	1.68 - 5.81 mmol/L	

Stabilisation

- + Suspect secondary IMHA
- + 0.3mg/kg dexamethasone
- + Blood type A
- + Whole blood transfusion



Further investigations - Serum Protein Electrophoresis



FELINE PROTEIN ELECTROPHORESIS - AGAROSE GEL

Fraction	g/L	Interpretative guidelines
Albumin (spe)	18.29	(25.0 - 45.0)
Alpha 1	2.18	(2.0 - 5.0)
Alpha 2	13.50	(8.0 - 11.0)
Beta	8.83	(6.0 - 11.0)
Gamma	53.39	(12.0 - 32.0)

DESCRIPTION:

Albumin is similarly reduced on the trace. There is a mild increase in alpha 2 globulins and a marked polyclonal increase in gamma globulins. Other globulin fractions are normal.

Further testing

Coombs' (37° C)	a. Positive
Mycoplasma haemofelis RealPCR	NEGATIVE
Candidatus Mycoplasma haemominutum RealPCR	NEGATIVE
Candidatus Mycoplasma turicensis RealPCR	NEGATIVE

Further testing

FeLV Antigen by ELISA NEGATIVE

FIV Antibody by ELISA NEGATIVE

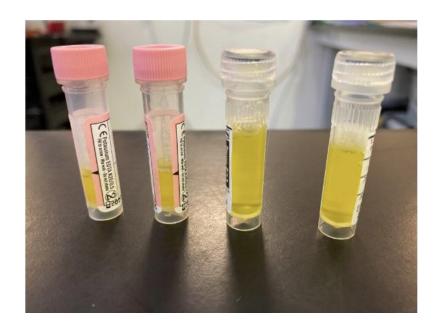
Alpha 1 Acid Glycoprotein 2.8

0.0 - 1.5 g/L



Abdominal ultrasound

- + Moderate ascites
 - + Abdominocentesis yellow, straw-coloured fluid obtained
- + Moderate mesenteric lymphadenopathy
- + Rest unremarkable

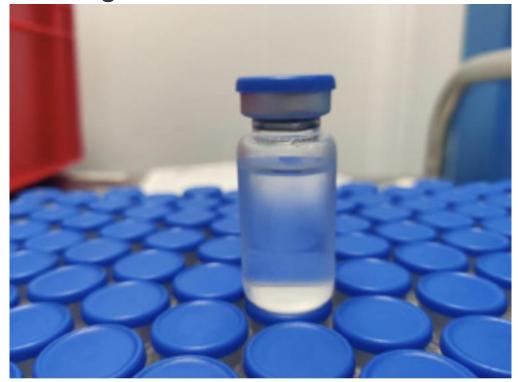


Analysis of abdominal effusion

Site:	ASC
Appearance	4ml, Viscous, Clear, Pale Yellow fluid, Containing Particles
Protein	80 g/L
Viscosity	¬DNR
RBC	less than 15,000
Nucleated Cells	17,090 /uL
Cell Count Method	Procyte
Clinical Pathologist's Report	INTERPRETATION: Exudate
Site:	ASCITIC FLUID & SWAB:
Aerobic Culture - Fluid	No bacterial growth.
Anaerobic Culture - Fluid	No anaerobes isolated
Feline Coronavirus RealPCR	a. POSITIVE

Investigations and treatment

- + Secondary IMHA due to FIP
- + Blood transfusion increased PCV to 13% and improved cardiovascular parameters
- + Remdesivir IV given alongside dexamethasone IV





JOURNAL OF VETERINARY INTERNAL MEDICINE



Thirty-two cats with effusive or non-effusive feline infectious peritonitis treated with a combination of remdesivir and GS-441524

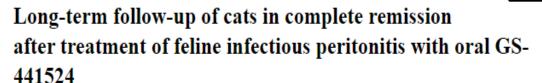
Jodie Green X. Harriet Syme, Sarah Tayler

First published: 04 July 2023 | https://doi.org/10.1111/jvim.16804

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Sage Journals

Original Article



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Sage Journals

Original Article

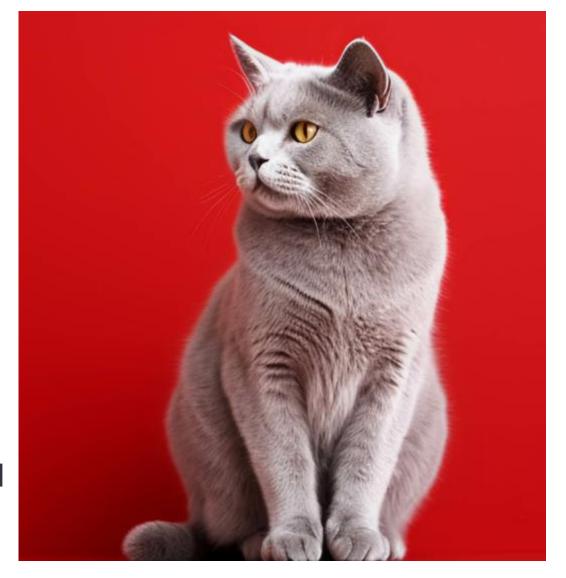


Retrospective study and outcome of 307 cats with feline infectious peritonitis treated with legally sourced veterinary compounded preparations of remdesivir and GS-441524 (2020–2022)

Samantha S Taylor (D 1,2,3, Sally Coggins 4, Emi N Barker (D 5,6, Danièlle Gunn-Moore 7, Kamalan Jeevaratnam 3, Jacqueline M Norris 4, David Hughes 8, Emily Stacey (D 9, Laura MacFarlane 10, Carolyn O'Brien 11, Rachel Korman 12, Gerard McLauchlan (D 13, Xavier Salord Torres 14, Aimee Taylor 5, Jos Bongers 15, Laura Espada Castro 15, Max Foreman (D 16, James McMurrough 17, Bethany Thomas (D 17, Emilie Royaux 18, Isabel Calvo Saiz 19, Guido Bertoldi 19, Caroline Harlos 20, Megan Work (D 21, Cameron Prior (D 21, Stephanie Sorrell (D 22, Richard Malik 4, and Séverine Tasker 2,6

Outcome

- + Hospitalised for 7 days. PCV increased to 18%.
- + Continued on 10mg/kg remdesivir IV for 4 days then 10mg/kg SQ for 3 days.
- + Continued IV dexamethasone in hospital
- + Transitioned to 12mg/kg GS-441524 for 84 days and oral prednisolone
- Prednisolone tapered and stopped over 3 weeks
- + Blood work normalised and ascites resolved
- + In remission



Summary

- + IMHA can be a life-threatening emergency.
- + Secondary IMHA is more common in cats.
- + Blood transfusions can be lifesaving.
- + Outcomes can be favourable and remission can be achieved.



Questions?

