Red Alert: diagnosis and management of IMHA

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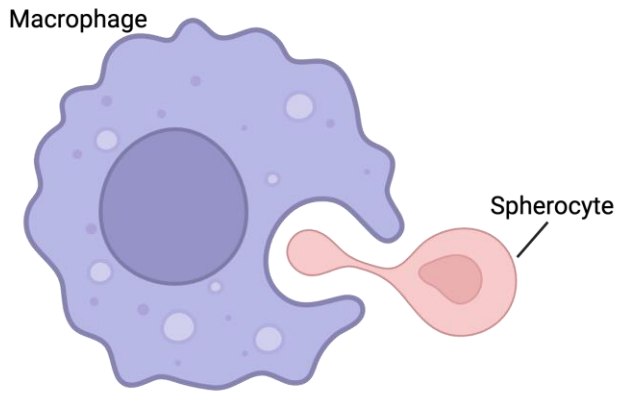
Agenda

Objective

1. Pathophysiology
2. Diagnosis
3. Treatment
4. Relapse
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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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

Diagnosis

- Haematology
- Blood smear
- In saline agglutination test
- Coombs test

Example of typical Haematology results in canine IMHA

RBC	1.17	5.39 - 8.70 x10^12/L	
Haematocrit	0.109	0.383 - 0.565 L/L	
Haemoglobin	40	134 - 207 g/L	
MCV	93.2	59.0 - 76.0 fL	
MCH	34.2	21.9 - 26.1 pg	
MCHC	367	326 - 392 g/L	
Reticulocytes a.	180.2	<= 110.0 K/µL	
Reticulocyte Haemoglobin	19.8	24.5 - 31.8 pg	
WBC	17.2	4.9 - 17.6 x10^9/L	
% Neutrophils	73.0	%	
% Bands	8.0	%	
% Metamyelocytes	2.0	%	
% Lymphocytes	12.0	%	
% Monocytes	5.0	%	
% Eosinophils	0.0	%	
% Basophils	0.0	%	

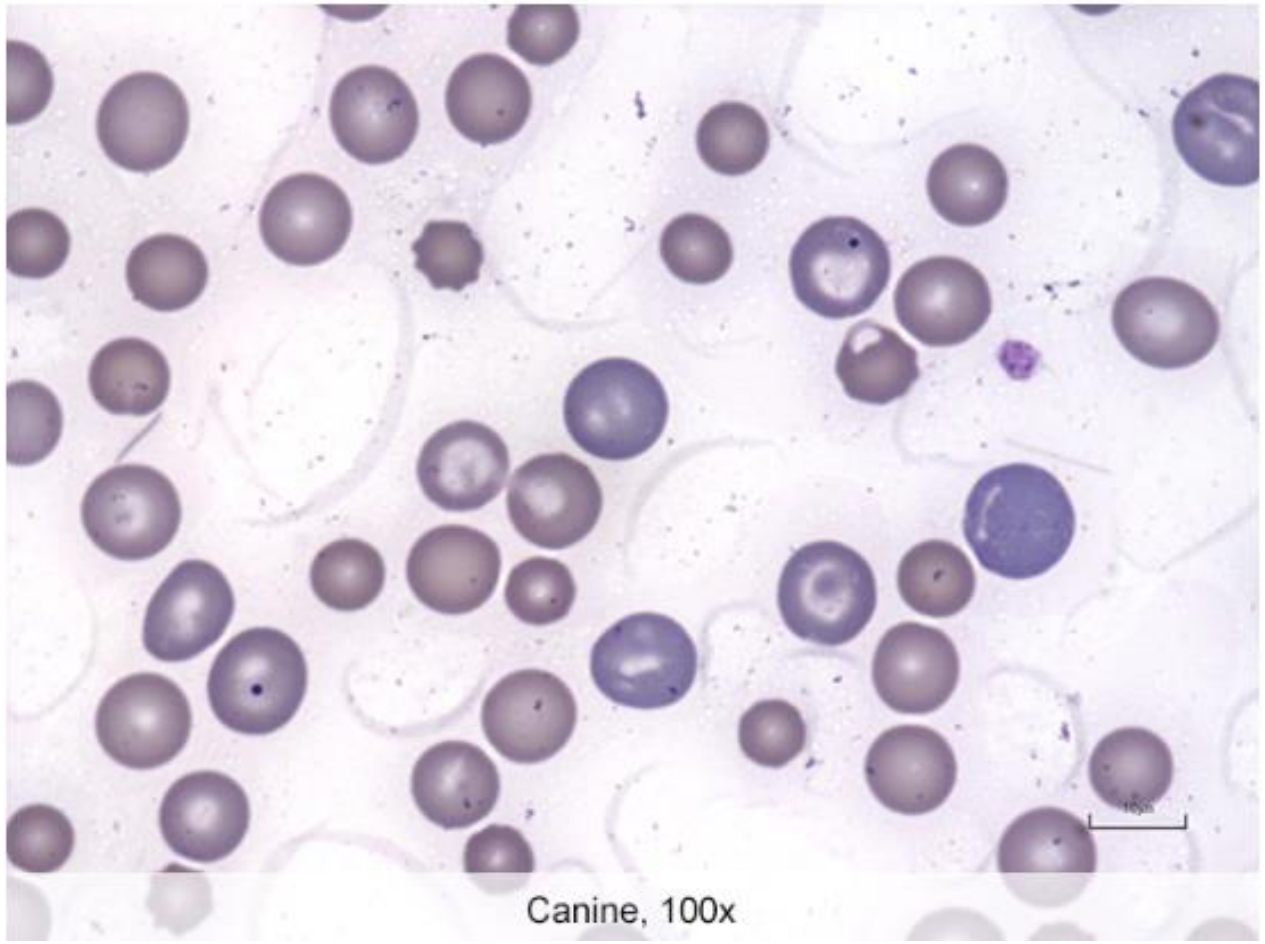
Haematology results

Neutrophils	12.56	2.94 - 12.67 x10^9/L	
Bands	**1.38**	0.00 - 0.17 x10^9/L	
Metamyelocytes	0.34	x10^9/L	
Lymphocytes	2.06	1.06 - 4.95 x10^9/L	
Monocytes	0.86	0.13 - 1.15 x10^9/L	
Eosinophils	**0.00**	0.07 - 1.49 x10^9/L	
Basophils	0.00	0.00 - 0.10 x10^9/L	
Nucleated RBC (Absolute)	3.10	10^9/L	
Platelets	**666**	143 - 448 x10^9/L	

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

Blood smear assessment



Canine, 100x

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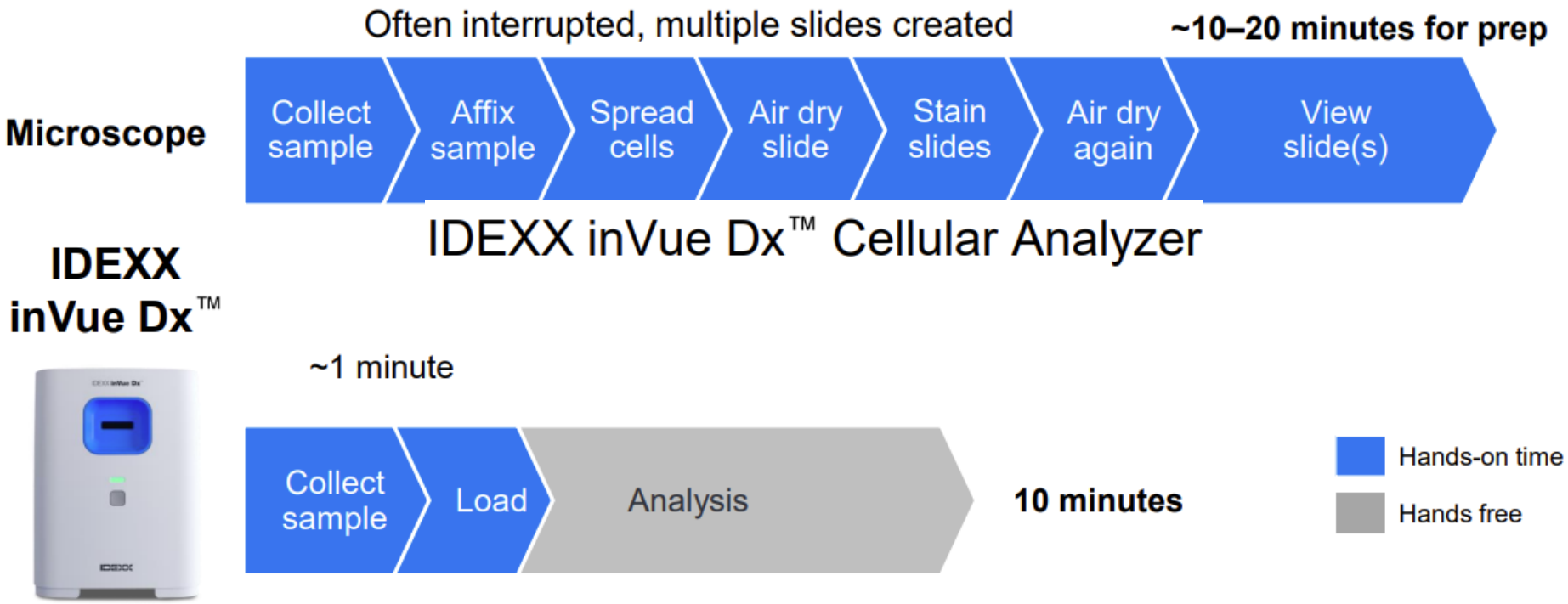
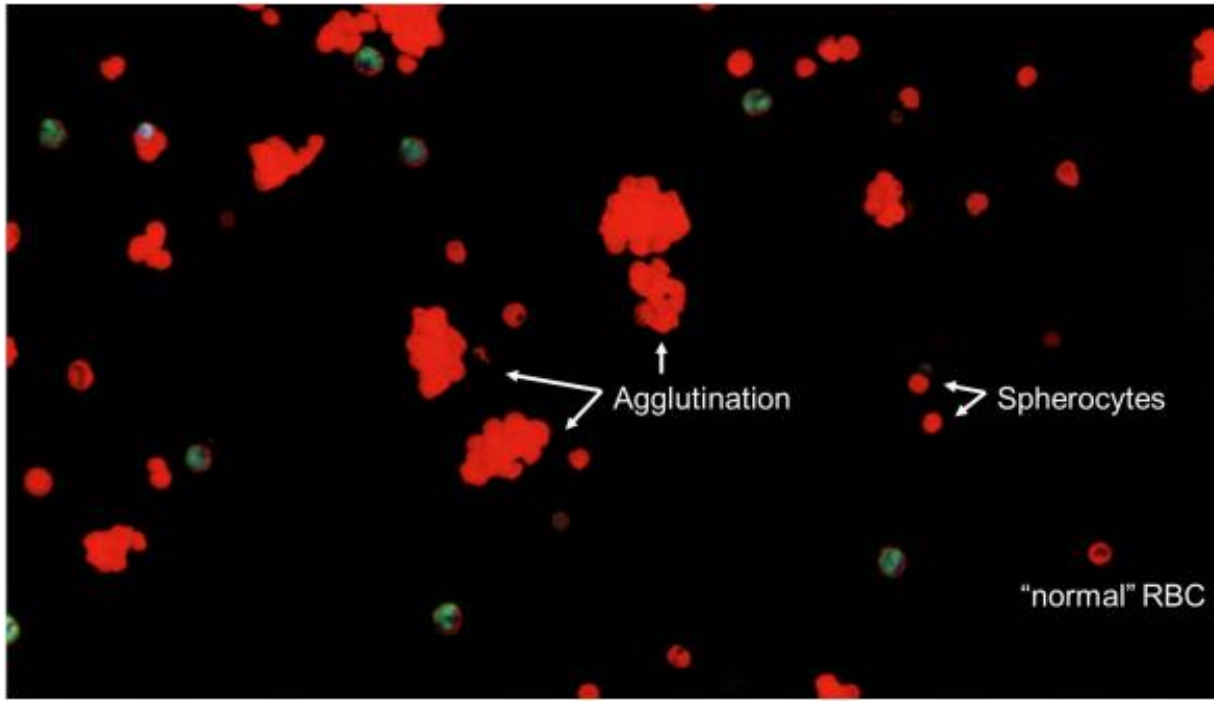


IDEXX inVue Dx™ Cellular Analyzer

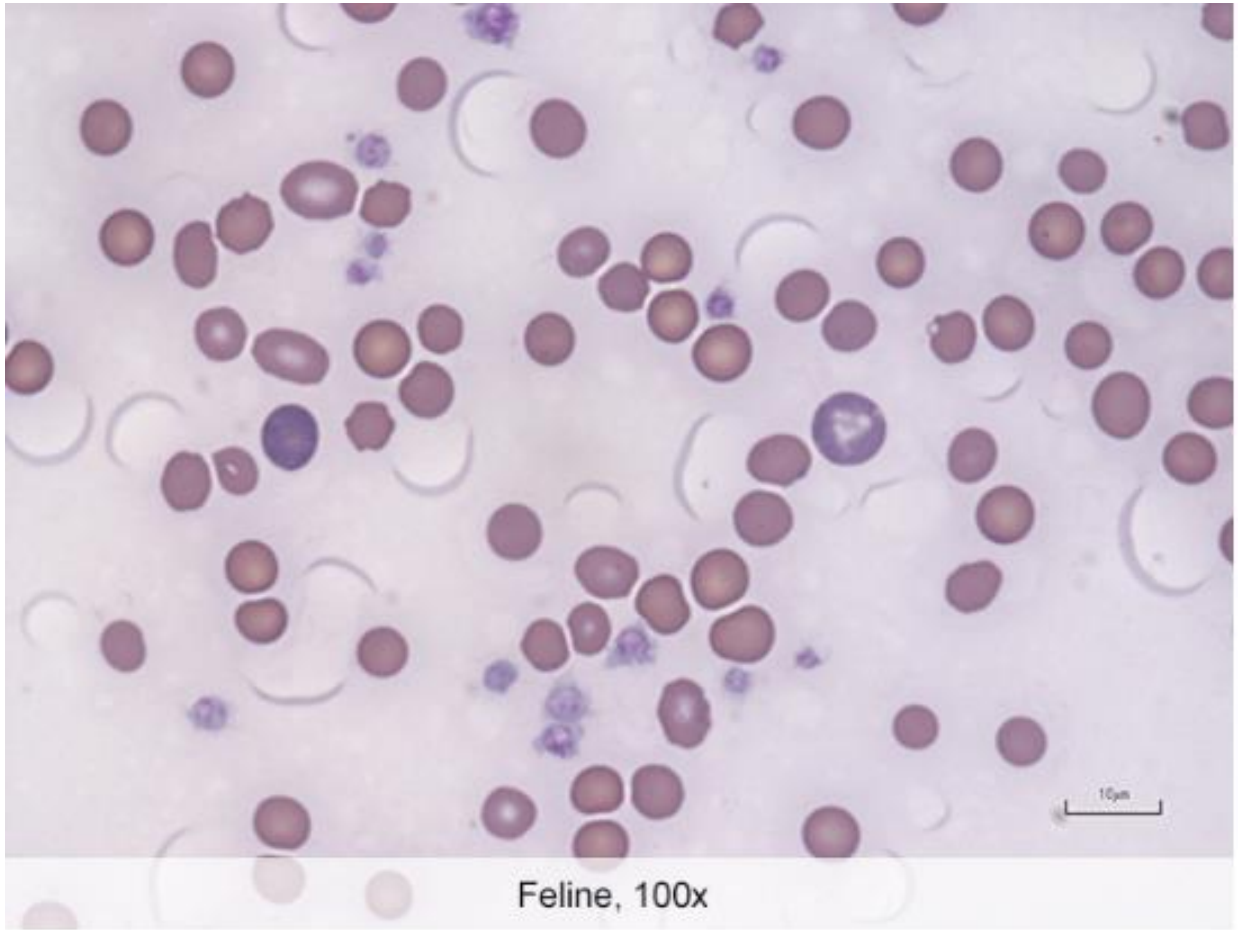


Spherocytosis

+ SPHEROCYTOSIS  IMHA

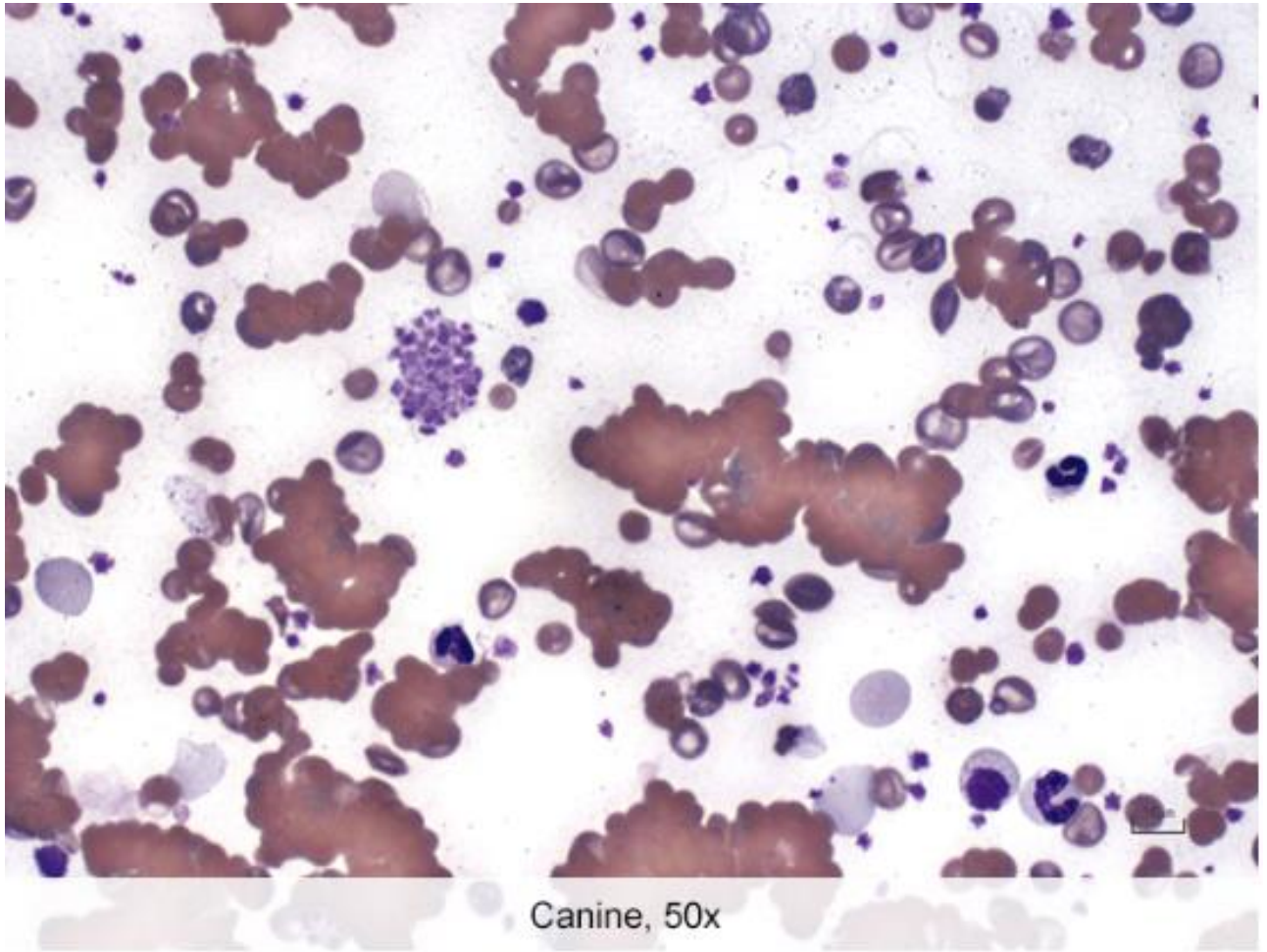
+ Need rule out causes of nonimmune mediated spherocytosis
  + Oxidative damage (e.g., zinc and acetaminophen)
  + Envenomation
  + Hypersplenism (e.g.,hepatosplenic lymphoma)
  + Pyruvate kinase deficiency
  + Disorders associated with erythrocyte fragmentation (e.g., endocarditis, microangiopathic haemolytic disorders including hemangiosarcoma or haemolytic uremic syndrome)
  + Dyserythropoiesis.

Blood smear assessment



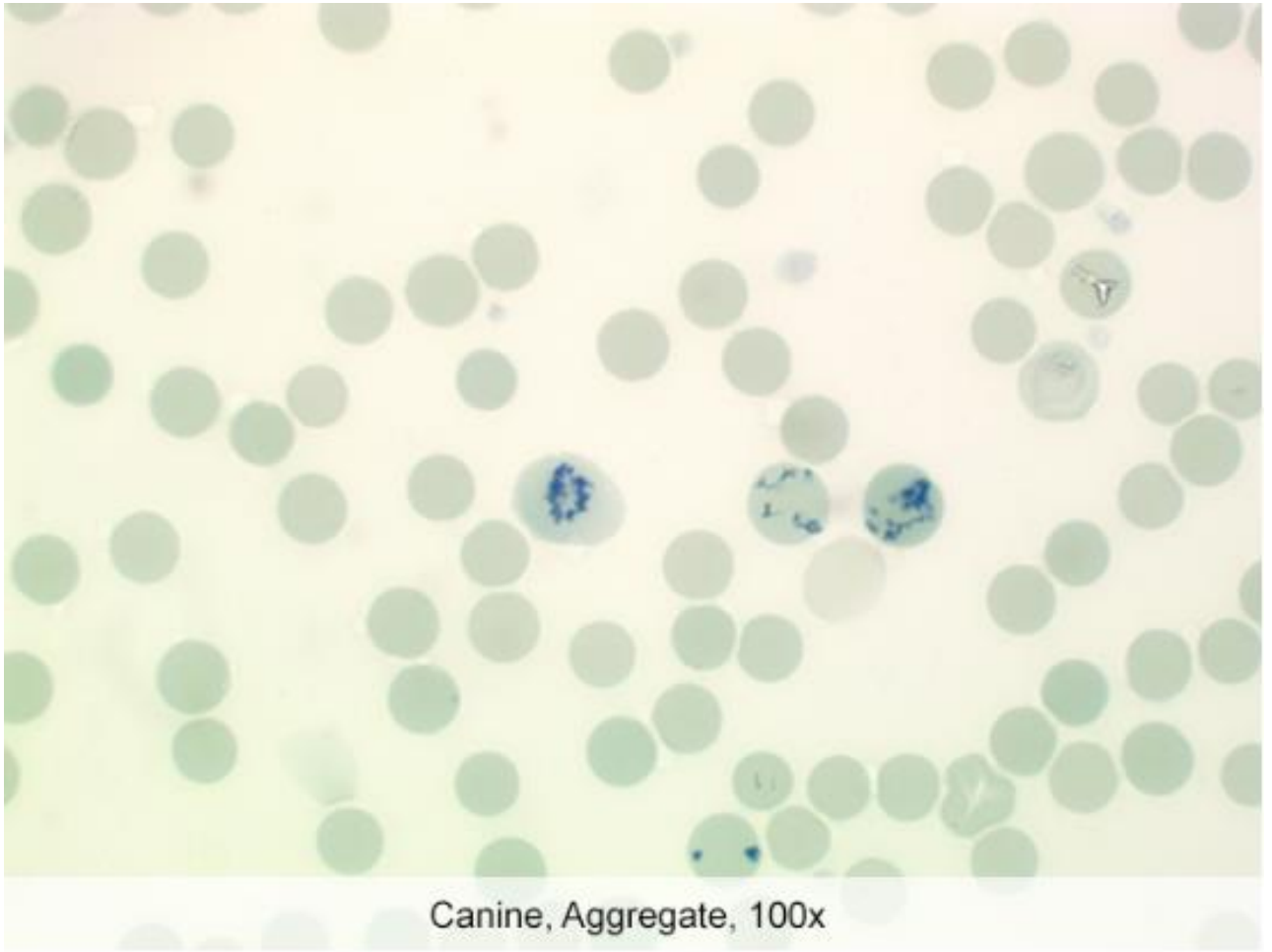
Feline, 100x

Blood smear assessment



Canine, 50x

Blood smear assessment – New Methylene Blue



Canine, Aggregate, 100x

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.

Treatment for Primary IMHA

- In severely affected cases a blood transfusion can be lifesaving.
- Pet Blood Bank can supply canine packed red blood cells, however whole blood from in clinic donor dogs can also be considered.
- In cats there is no UK blood bank and as such we generally rely on in clinic donor cats.

Blood Transfusion

+ Fresh pRBC, ideally no older than 7-10 days
+ No specific PCV at which a transfusion should be considered
+ Must type +/- cross match
+ Need to assess each individual patient
+ Formulae available to determine how much to transfuse

Cross matching

- Major cross match detects the presence of antibodies in the recipient against the red blood cells of the donor
- In dogs and cats essential to perform cross match 4-7 days after first transfusion
- Weak evidence that is required in cats in UK
  - Possible geographical differences
  - All reports of non-AB transfusion reactions in transfusion naïve cats originate in the United States

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.

First line treatment

- Immunosuppressive therapy
- Quickest acting are steroids
- Need adjust dose for larger breed dogs >25kg
- Can add in second line at diagnosis to try to reduce steroid side effects and/or in severe cases
  - No consensus as the “best” second line treatment

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
- Close monitoring essential
  - Haematology q2 weeks for first month then every 2-3months

Azathioprine

- Azathioprine NEVER IN CATS
  - 2mg/kg or 50mg/m2 PO SID
  - After 2-3 weeks, increase dosing interval may be increased to every other day until treatment is discontinued
- 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?
+ Add in additional immunosuppressant?
+ Splenectomy?
+ IVIG?

IVIG

- Not recommended for routine treatment

- Considered salvage measure in dogs not responding to treatment with 2 immunosuppressive drugs

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.

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 B_2 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 – antiplatelet action

+ Aspirin (0.5mg/g/day) or clopidogrel (1.1-4mg/kg/day) antiplatelet action
+ 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.

Thromboprophylaxis – anticoagulant drugs

- Rivaroxaban – most commonly used
  - direct factor Xa antagonist
  - Well tolerated
  - Main downside is expense
- Heparain and warfarin rarely used
  - Not recommended for IMHA thromboprophylaxis

When to reduce immunosuppression

- When PCV/HCT stable and >30% in dogs and >25% in cats for 2 weeks and improvement in laboratory parameters (spherocytosis, agglutination, serum bilirubin, reticulocyte count) can reduce prednisolone by 25%
- Non regen anaemia is common – can be due to immunosuppressive drugs
- If second immunosuppressive agent being used then can reduce prednisolone further by 25-50%
  - Keep second IM dose same unless azathioprine used

Typical follow up haematology in canine IMHA

RBC	5.03	5.39 - 8.70 x10^12/L	
Haematocrit	0.355	0.383 - 0.565 L/L	
Haemoglobin	117	134 - 207 g/L	
MCV	70.6	59.0 - 76.0 fL	
MCH	23.3	21.9 - 26.1 pg	
MCHC	330	326 - 392 g/L	
Reticulocytes	a. 49.8	<= 110.0 K/µL	
Reticulocyte Haemoglobin	28.1	24.5 - 31.8 pg	
WBC	6.0	4.9 - 17.6 x10^9/L	
% Neutrophils	56.0	%	
% Bands	2.0	%	
% Lymphocytes	32.0	%	
% Monocytes	10.0	%	
% Eosinophils	0.0	%	
% Basophils	0.0	%	

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.

Relapsing cases

- Recent UK study
  - Relapse rates at 12 months was 11% for primary IMHA
  - Relapse rate at 24 months was 18% for IMHA
  - 56% of IMHA relapses occurred in the first 12 months after diagnosis
    - NB can be delayed for years
  - 2 dogs developed a new immune mediated disease >12 months after diagnosis of IMHA
  - Vaccine administration after diagnosis was not associated with relapse

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

RBC	1.21	7.12 - 11.46 x10^12/L	
Haematocrit	0.079	0.282 - 0.527 L/L	
Haemoglobin	23	103 - 162 g/L	
MCV	65.3	39.0 - 56.0 fL	
MCH	19.0	12.6 - 16.5 pg	
MCHC	291	285 - 378 g/L	
Reticulocytes	a. 432.3	<= 50.0 K/µL	
Reticulocyte Haemoglobin	19.1	15.3 - 22.9 pg	
WBC	26.5	3.9 - 19.0 x10^9/L	
% Neutrophils	74.0	%	
% Bands	9.0	%	
% Lymphocytes	9.0	%	
% Monocytes	8.0	%	
% Eosinophils	0.0	%	
% Basophils	0.0	%	

Haematology results

Neutrophils	19.61	2.62 - 15.17 x10^9/L	
Bands	2.39	0.00 - 0.30 x10^9/L	
Lymphocytes	2.39	0.85 - 5.85 x10^9/L	
Monocytes	2.12	0.04 - 0.53 x10^9/L	
Eosinophils	0.00	0.09 - 2.18 x10^9/L	
Basophils	0.00	0.00 - 0.10 x10^9/L	
Nucleated RBC (Absolute)	5.04	10^9/L	
Nucleated RBC	b. 19	per 100wbc	
Platelets	~		

Blood smear analysis

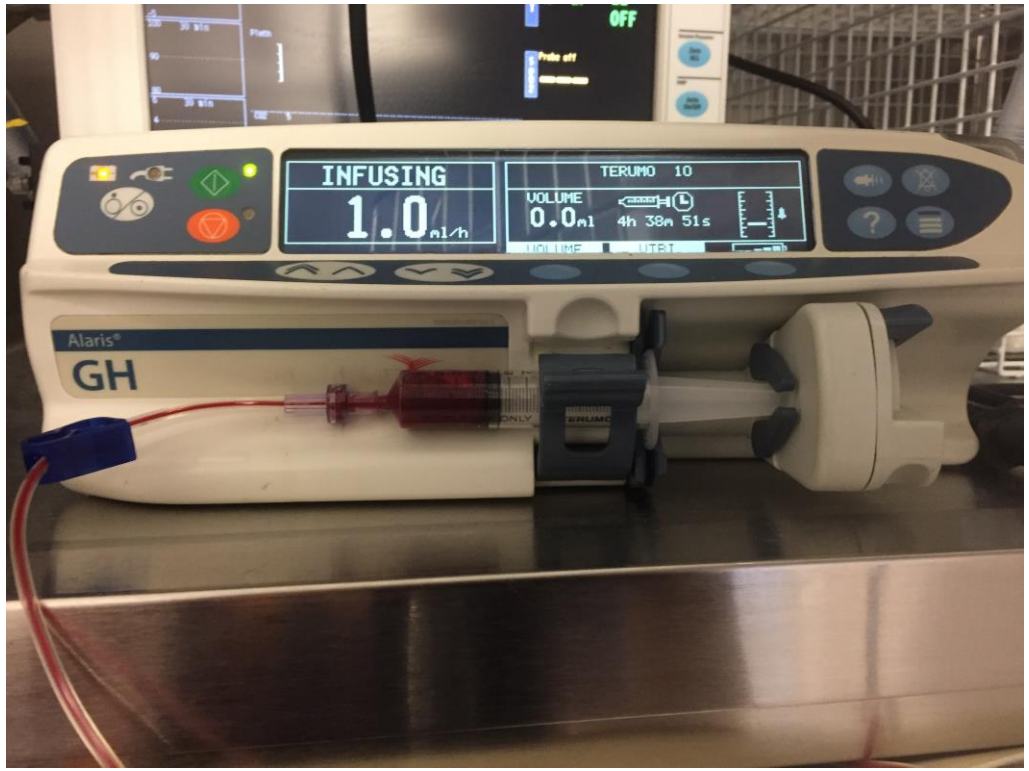
Blood Film Evaluation	Red cells show marked anisocytosis and polychromasia. Auto-agglutination present. Many ghost cells and metarubricytes noted. Band cells seen. Platelet count invalidated due to the presence of cell debris. Estimation of free platelets (>8 platelets seen per HPF) suggesting platelet numbers are normal. Manual Differential performed by a haematological technician to replace or complete automated results.

Biochemistry results

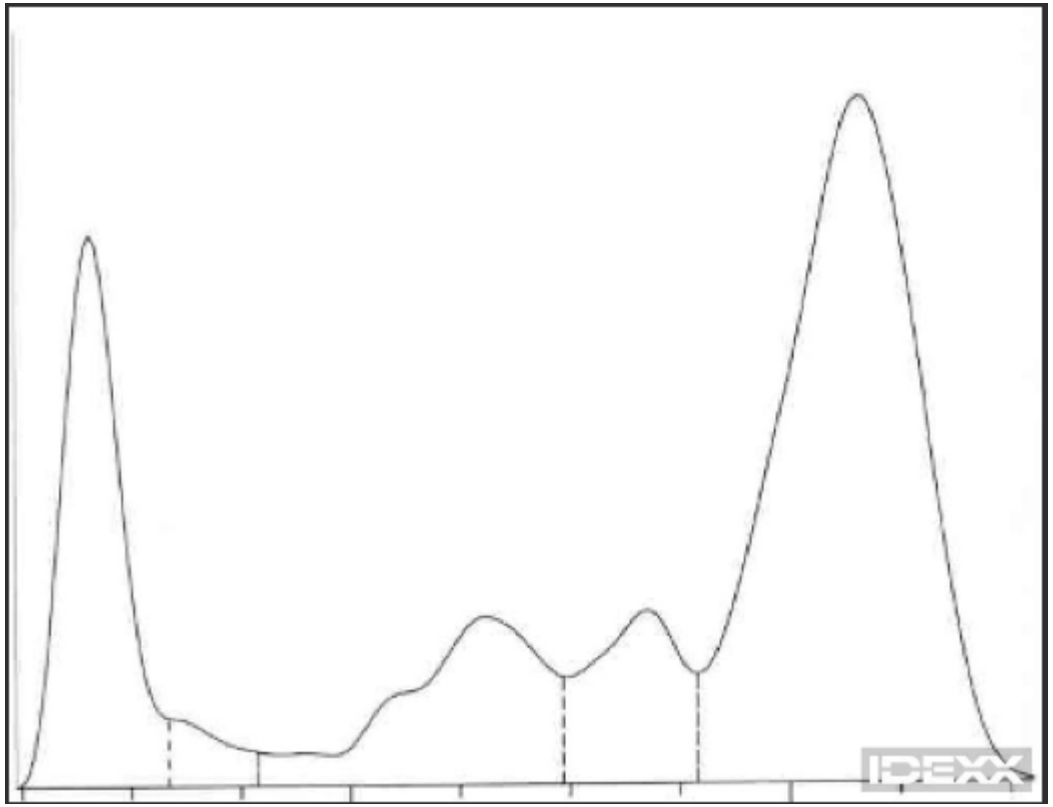
Glucose	7.64	3.95 - 8.84 mmol/L
Creatinine	94	71 - 212 µmol/L
Urea	**20.3**	5.7 - 12.9 mmol/L
BUN: Creatinine Ratio	54	
Phosphorus	2.29	1.00 - 2.42 mmol/L
Calcium	2.15	1.95 - 2.83 mmol/L
Total Protein	**96.2**	60.0 - 80.0 g/L
Albumin	**19.4**	25.0 - 45.0 g/L
Globulin	**76.8**	25.0 - 45.0 g/L
Albumin: 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

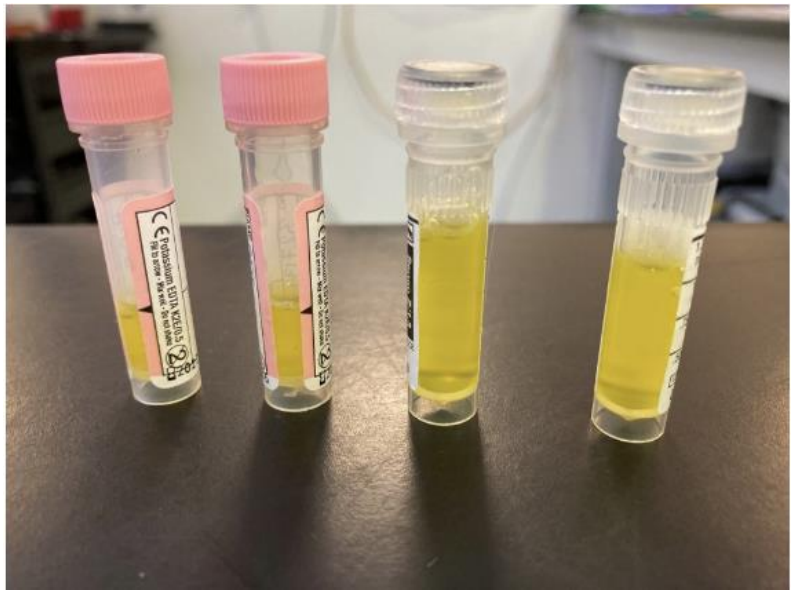
Coombs' (37° C)	a. Positive

Mycoplasma haemofelis RealPCR	NEGATIVE
Candidatus Mycoplasma haemominutum RealPCR	NEGATIVE
Candidatus Mycoplasma turicensis RealPCR	NEGATIVE

FeLV Antigen by ELISA	NEGATIVE
FIV Antibody by ELISA	NEGATIVE

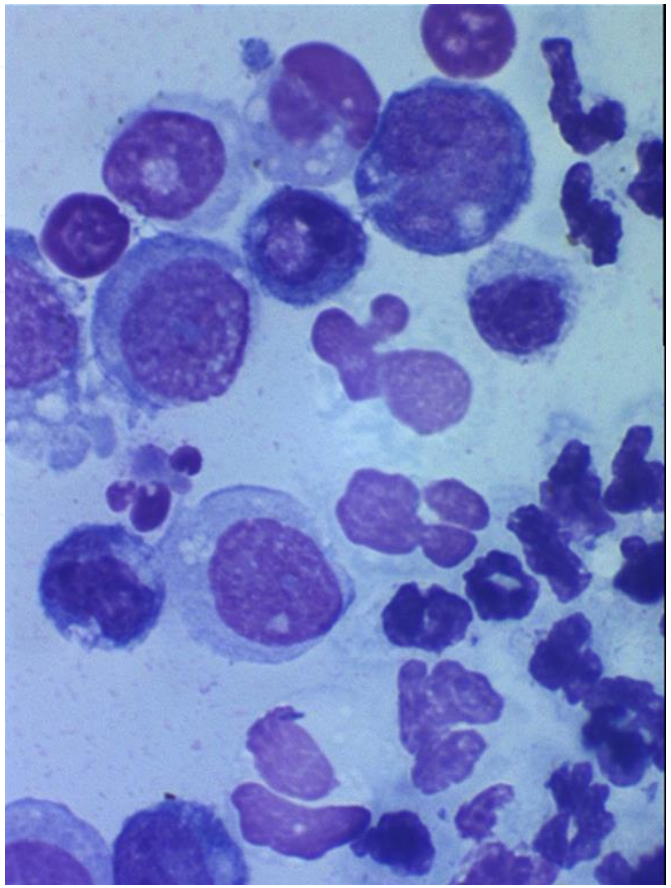
Abdominal ultrasound

- Moderate ascites
  - Abdominocentesis – yellow, straw coloured fluid obtained
- Moderate mesenteric lymphandenopathy
- 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	



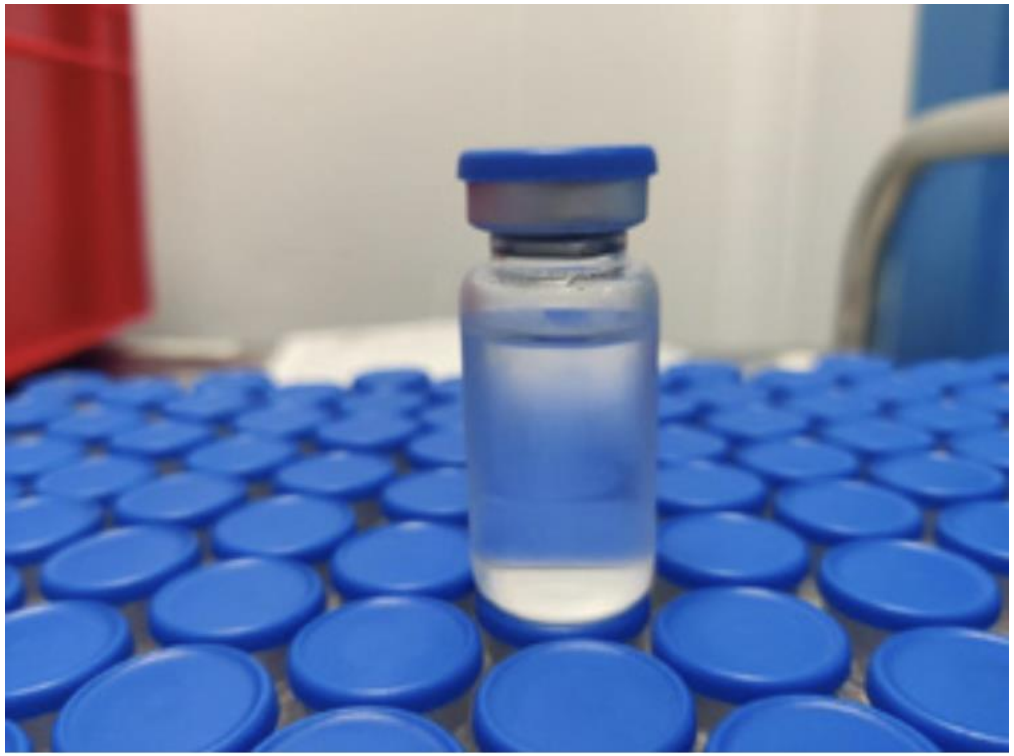
Further testing

FeLV Antigen by ELISA	NEGATIVE	
FIV Antibody by ELISA	NEGATIVE	

Alpha 1 Acid Glycoprotein	**2.8**	0.0 - 1.5 g/L	

Investigations and treatment

+ Secondary IMHA due to FIP
+ Blood transfusion increased PCV to 13% and improved cardiovascular parameters
+ GS-441524 PO given alongside dexamethasone IV



Outcome

- Hospitalised for 7 days. PCV increased to 18%.
- Continued15/kg GS-441524 for 84 days and oral prednisolone (1mg/kg SID)
- Prednisolone tapered and stopped over 8 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 life saving
- Outcomes can be favourable, and remission can be achieved