Red Alert: Diagnosis and Management of IMHA

Nancy A. Sanders, DVM
DACVIM(SAIM), DACVECC
IDEXX Medical Education Specialist

Financial Disclosure

I am a full-time IDEXX; the relationship does not affect the medicine; it will affect a few images.

The information contained herein is intended to provide general guidance only. Diagnosis, treatment, and monitoring should be patient specific and is the responsibility of the veterinarian providing primary care.

Learning objectives

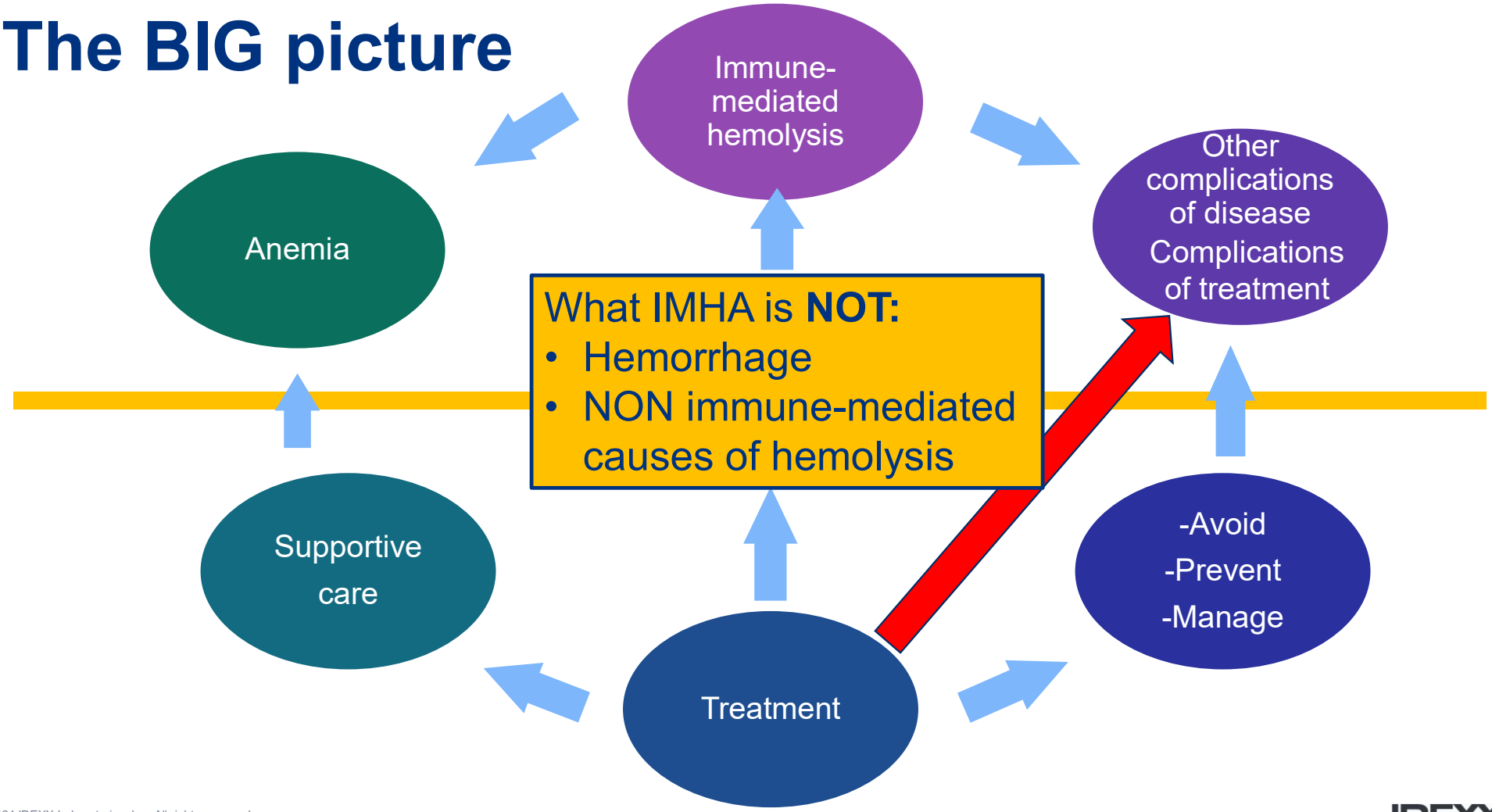
1. Review red blood cell physiology and pathophysiology in relation to IMHA
2. Define diagnostic criteria for IMHA and review important resources
3. Discuss treatment options for IMHA
4. Review common complications of boh IMHA and disease treatment
5. Enhance learning with case examples

The impact of immune-mediated hemolytic anemia in the veterinary industry

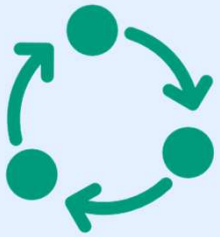
- Frequent cause of canine anemia
  - Most commonly idiopathic
  - Often severe
  - Mortality between 20-80% depending on the study
  - Most common immune-mediated disease of the dog
- Infrequent cause of anemia in cats
  - Most commonly secondary/triggered
  - Mortality 23-27%

1. McCullough S. Immune-mediated hemolytic anemia: understanding the nemesis. *Vet Clin North Am Small Anim Pract.* 2003 Nov;33(6):1295-315. doi: 10.1016/j.cvsm.2003.08.003
2. Swann JW, Szladovits B, Glanemann B. Demographic Characteristics, Survival and Prognostic Factors for Mortality in Cats with Primary Immune-Mediated Hemolytic Anemia. J Vet Intern Med. 2016 Jan-Feb;30(1):147-56. doi: 10.1111/jvim.13658. Epub 2015 Dec 9. PMID: 26645865; PMCID: PMC4913623.

The BIG picture



Etiopathogenesis



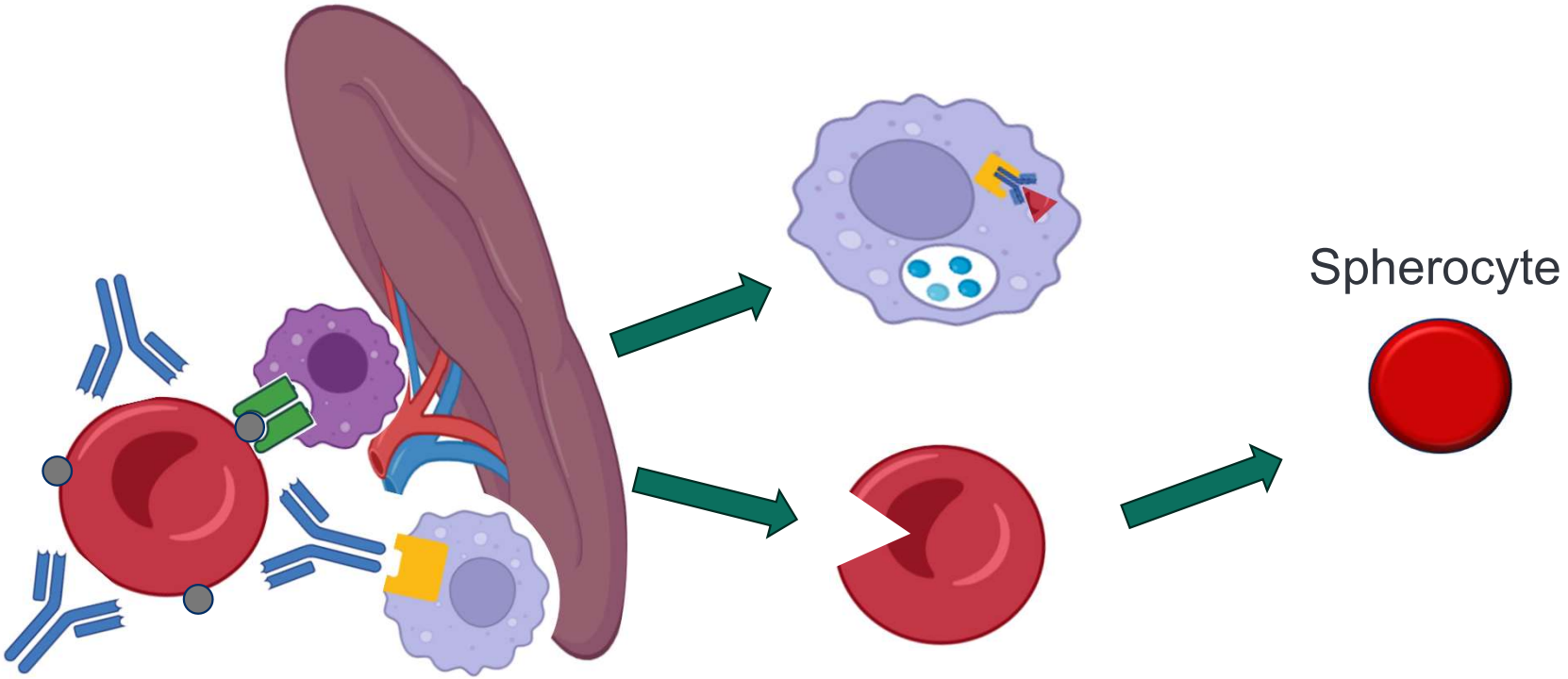
IMHA pathophysiology

- Normal RBC lifespan: 100-120 days
  - Aged cells destroyed by the spleen and the liver (phagocytes recognize antibodies directed against senescent surface antigens)

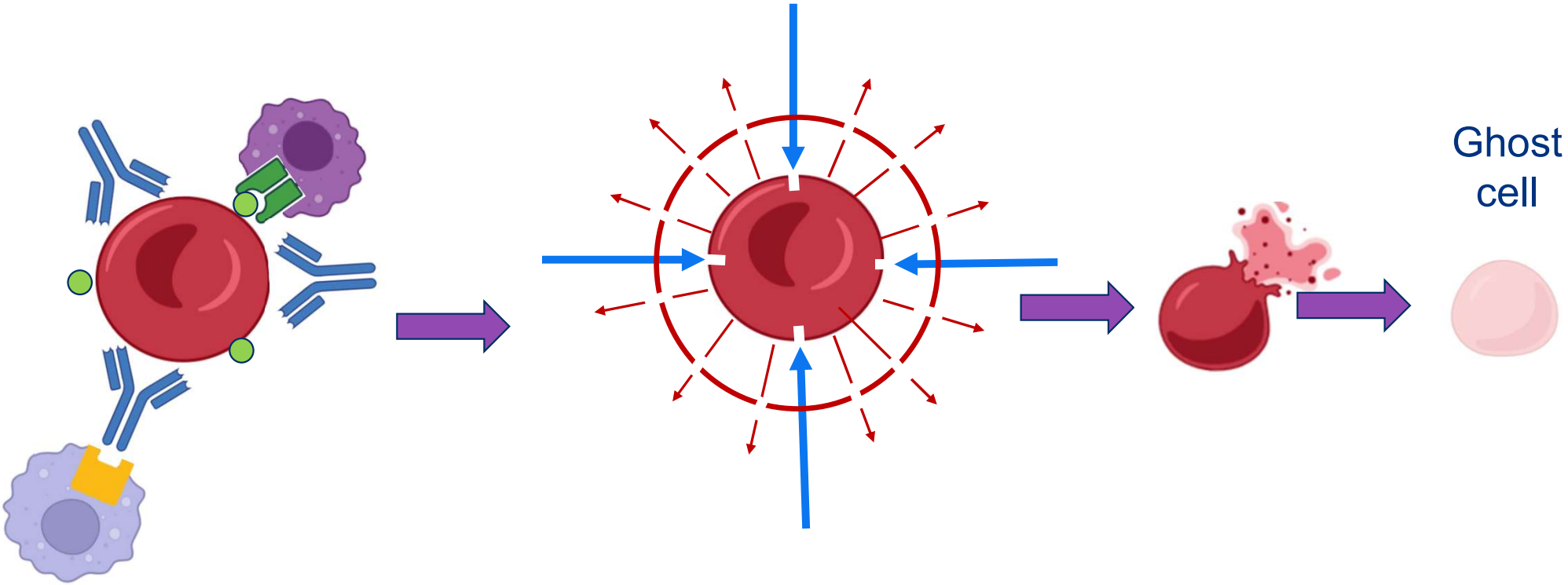
- IMHA = premature RBC destruction
  - Antibodies attach to either directly to RBC membrane (primary) or something foreign on RBC membrane (secondary)
    - Extravascular destruction
      - Less severe, RBC are removed by macrophages in the liver and the spleen
      - No hemoglobinemia
    - Intravascular destruction
      - Usually severe, occurs when a large quantity of antibodies attach to the surface of the RBC
      - Intravascular lysis leads to hemoglobinemia and hemoglobinuria

Balch A, Mackin A. Canine immune-mediated hemolytic anemia: pathophysiology, clinical signs, and diagnosis. *Compend Contin Educ Vet.* 2007 Apr;29(4):217-25.

Immune-mediated extravascular hemolysis



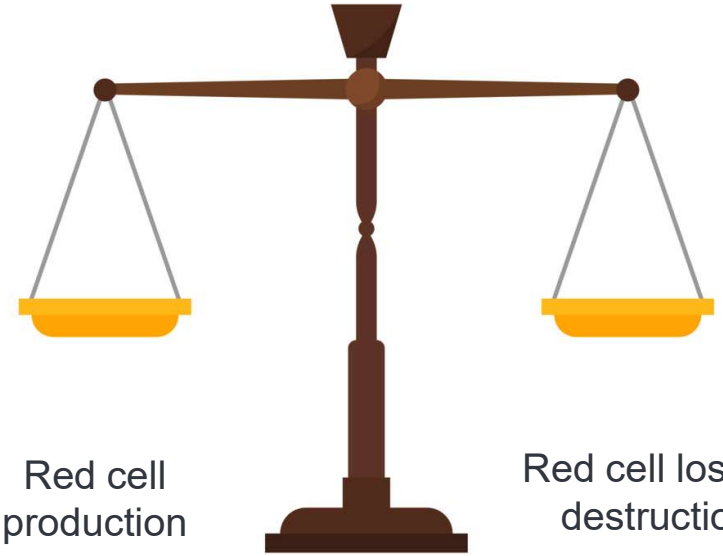
Immune-mediated intravascular hemolysis



Red cell mass reflects the balance between production and loss.

Absolute reticulocyte count within reference range

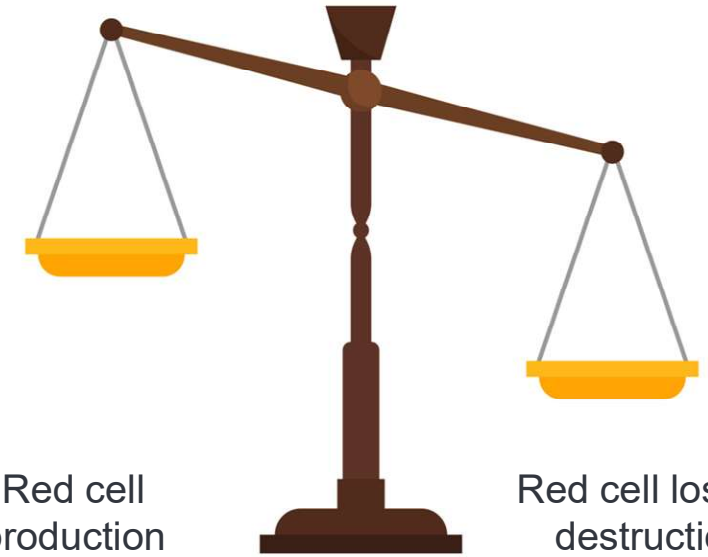
Absolute reticulocyte count above reference range



Rate of RBC loss outweighs rate of production ➡ anemic

Absolute reticulocyte count within reference range

Absolute reticulocyte count above reference range

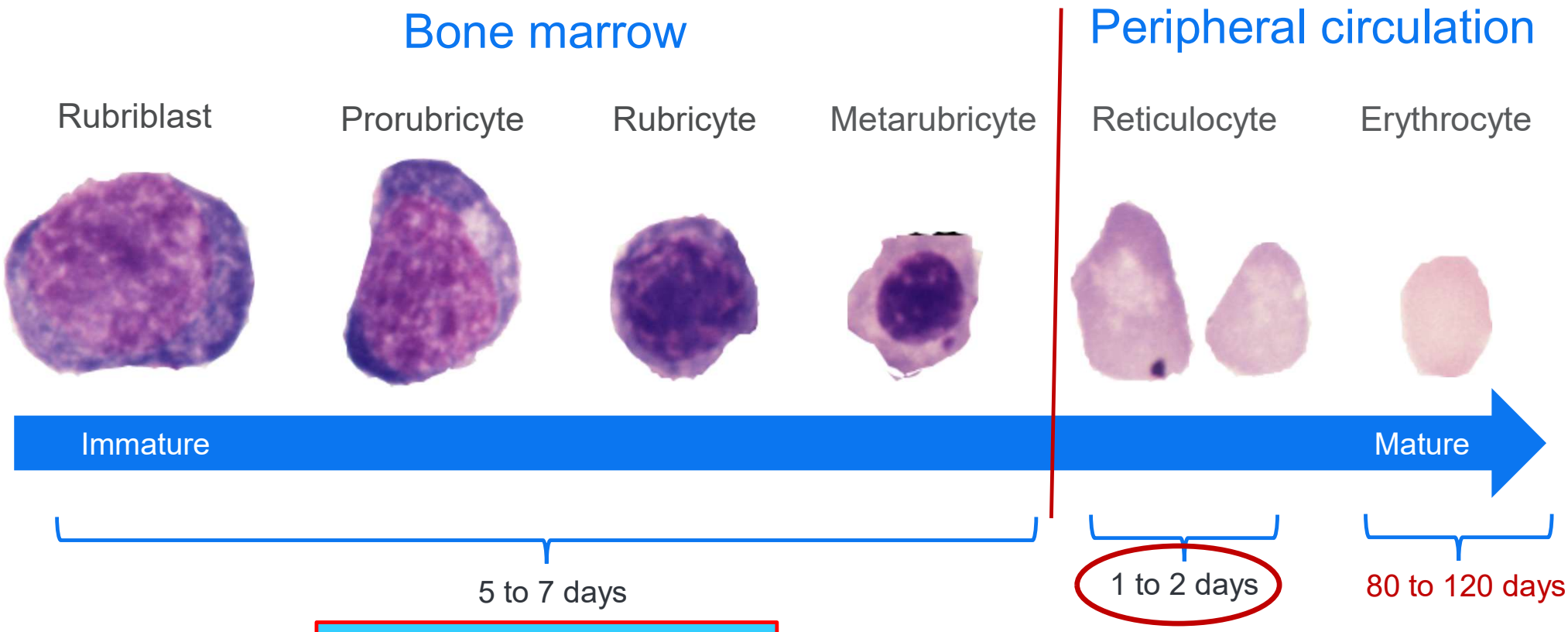


Red cell production

Red cell loss or destruction

IDEXX

Red blood cell maturation



IDEXX

"My patient is anemic"
Next question...

Regenerative?

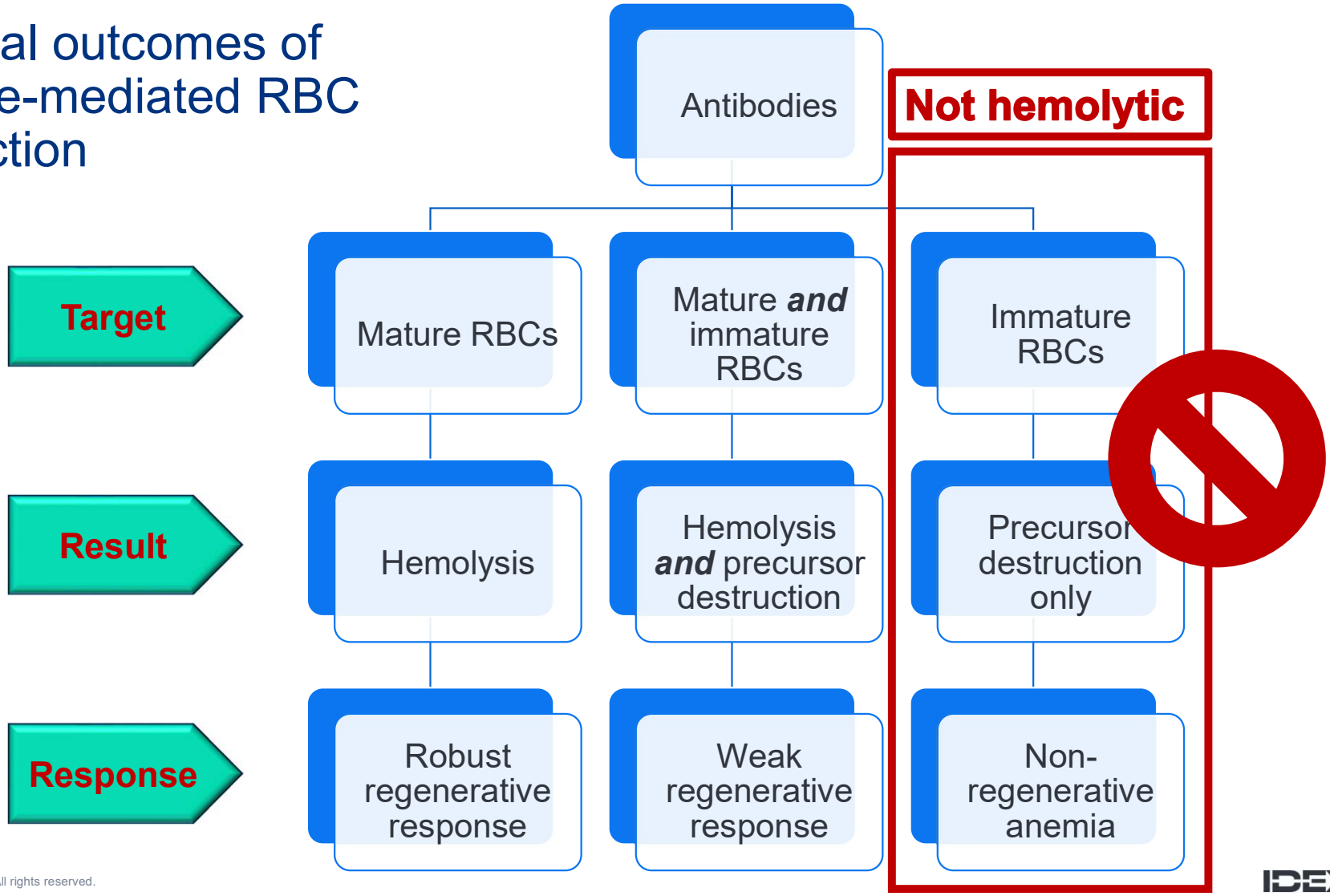
Hemorrhage
Hemolysis

Non-regenerative?

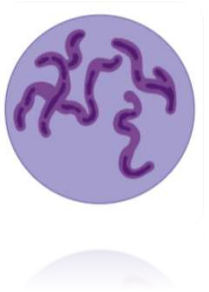
Chronic disease, e.g., CKD
Cancer, chemotherapy
Bone marrow disease
Pre-regenerative (acute disease)
PIMA, PRCA

IDEXX

Potential outcomes of immune-mediated RBC destruction



Indicators of RBC regeneration

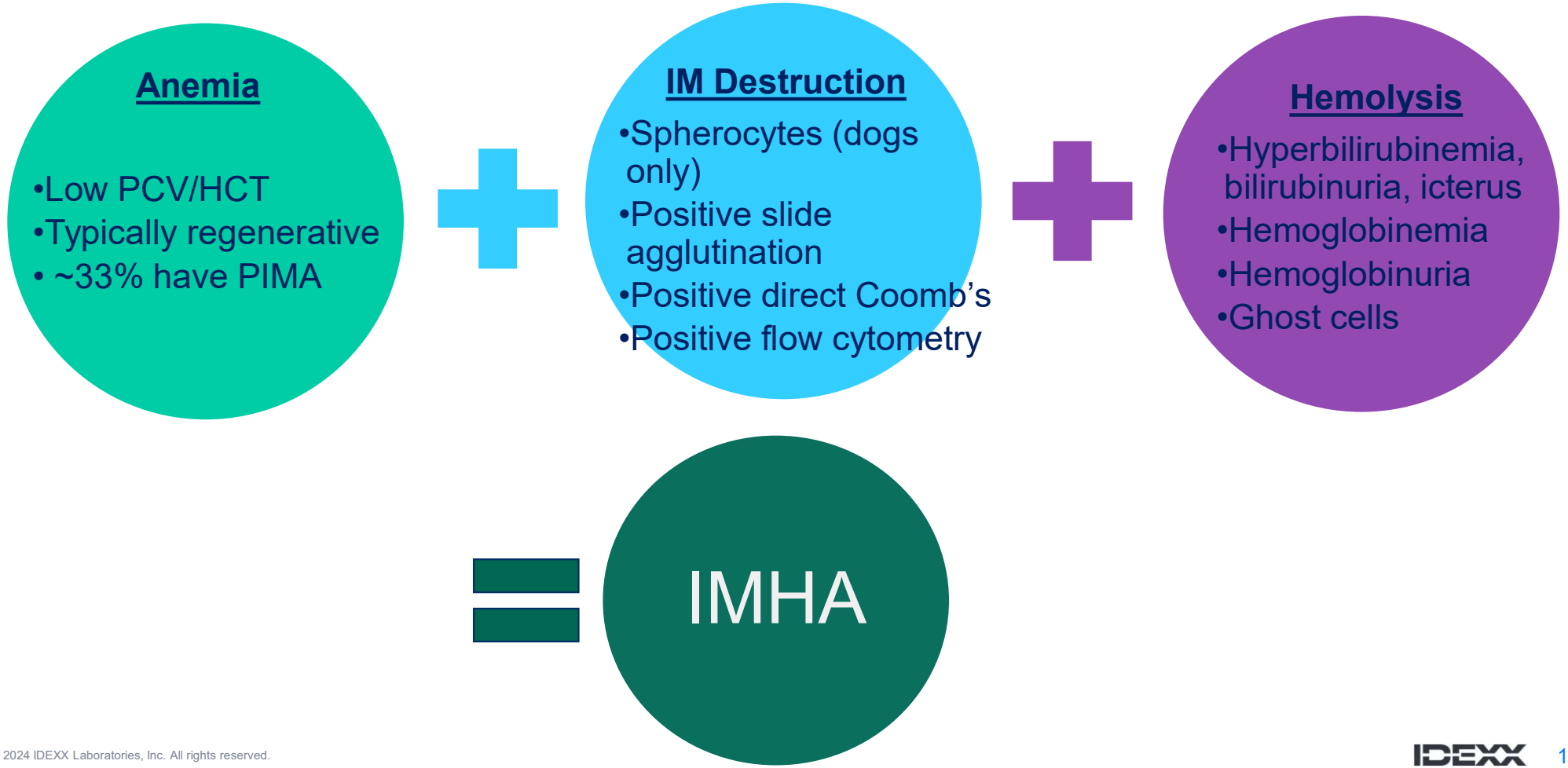


- Reticulocytosis
  - #1, most consistent indicator of regeneration
  - Very sensitive, fairly specific

- Only 8-11% patients with regenerative anemias have the classic changes:
  - RBC stippling
  - Macrocytosis
  - Anisocytosis
  - Circulating nucleated or younger RBCs

Diagnosis

Defining IMHA



If regenerative anemia, is it hemorrhage or hemolysis?

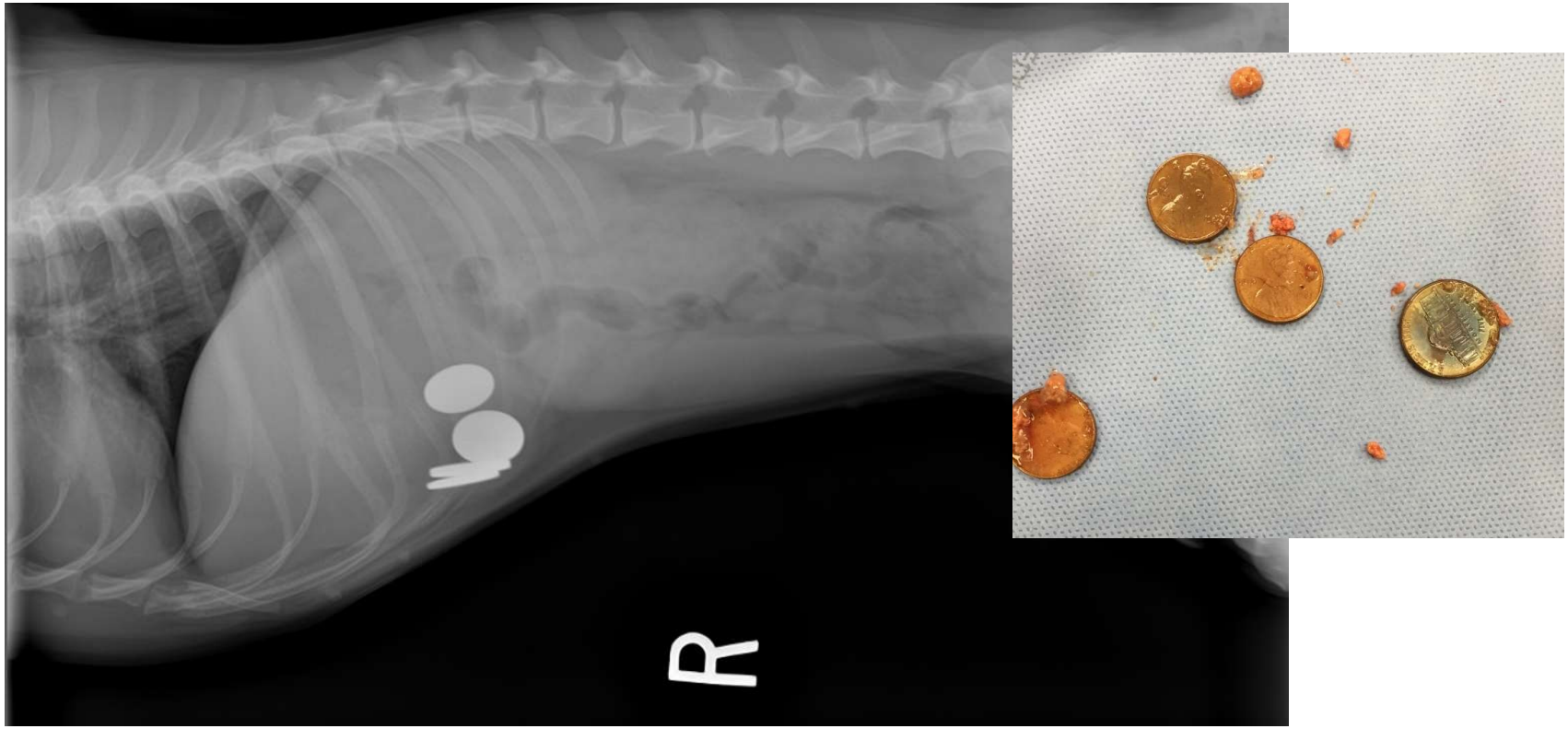
Finding	Hemorrhage	Hemolysis
Evidence of bleeding (internal or external)	Usually yes, not always	No
Pulse quality	Weak, snappy	Bounding
Spherocytes	No	Often, not always
RBC changes other than spherocytosis	Maybe (microangiopathy/ schistocytes etc.)	Maybe (ghost cells)
Autoagglutination	No	Often, not always
Hemoglobinuria	No	Yes, if intravascular
Bilirubinuria	Usually not, occasionally yes (chronic cavity bleed)	Usually yes
Serum bilirubin	Normal, occasionally slightly elevated (cavity bleed)	Normal to markedly increased
Total protein	Usually low, may be normal	Normal to high
Coomb's	Negative, false positives occur	Often positive, not always

IDEXX

Don’t forget NON immune-mediated causes of hemolysis

- Toxins/foods
  - Onions
  - Medications
  - Heavy metals
- Blood parasites
- Microangiopathy
- Heinz-body anemias
- Hypophosphatemia
- Congenital
  - PFK/PK deficiency
- Neonatal isoerythrolysis
- Thermal injury
- Massive envenomation
- Marked hypoosmolality
  - e.g., water intoxication, iatrogenic (hypotonic IV fluids)

Not all hemolytic anemias are immune-mediated



ACVIM American College of Veterinary Internal Medicine

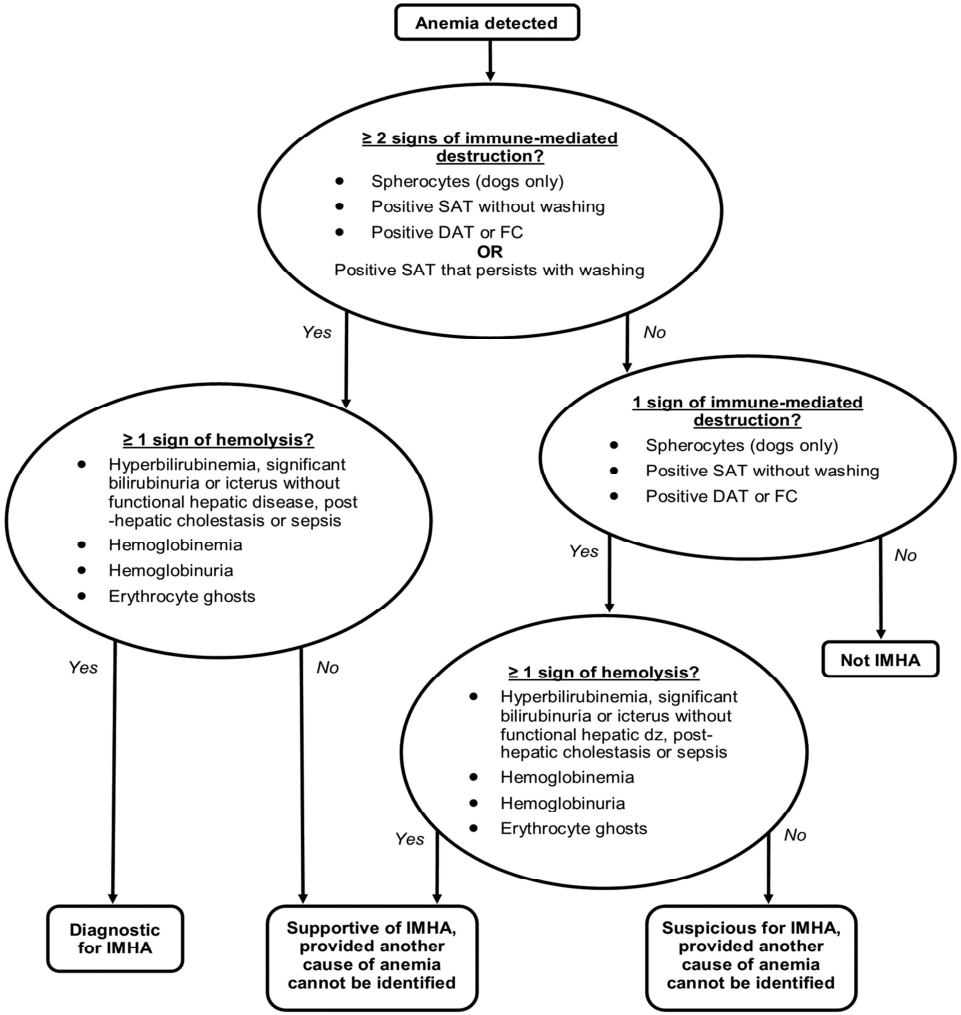
JOURNAL OF VETERINARY INTERNAL MEDICINE Open Access

CONSENSUS STATEMENT | Open Access

ACVIM consensus statement on the diagnosis of immune-mediated hemolytic anemia in dogs and cats

Oliver A. Garden, Linda Kidd, Angela M. Mexas, Yu-Mei Chang, Unity Jeffery, Shauna L. Blois, Jonathan E. Fogle, Amy L. MacNeill, George Lubas, Adam Birkenheuer ... See all authors

First published: 26 February 2019 | https://doi.org/10.1111/jvim.15441 | VIEW METRICS



Immune-mediated hemolytic anemia

Primary (auto-immune, non-associative)

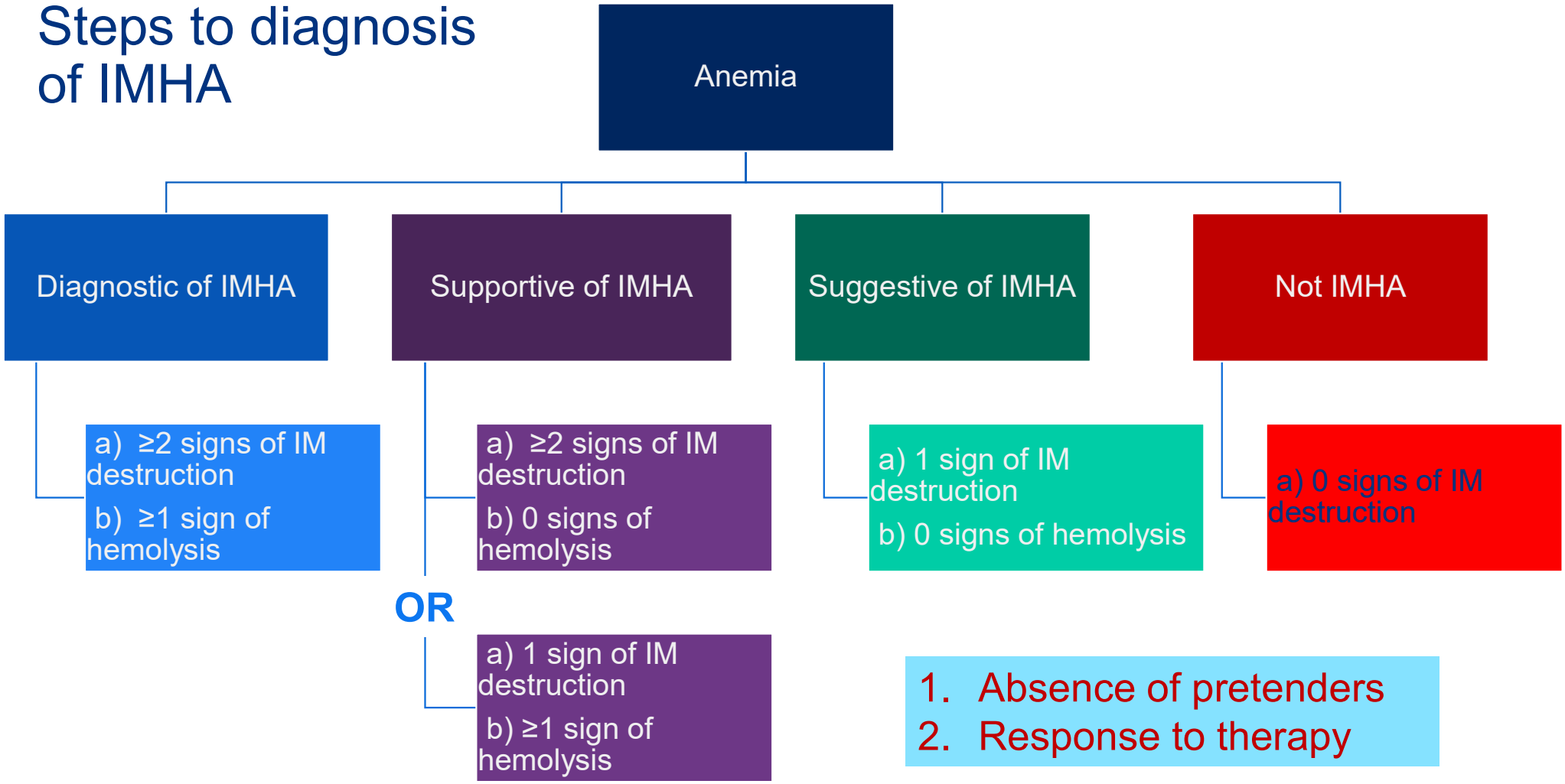
- Idiopathic
- 60-75% of cases
- Immune problem (T suppressor cell dysfunction)

Secondary (triggered, associative)

- The immune system is triggered to make a mistake by another process
  - Red blood cells become covered in non-self antigens
- Causes may include
  - SLE
  - Certain medications
    - TMS, penicillins, cephalosporins, levamisole, phenylbutazone, dipyrone, chlorpromazine
  - Infections
  - Ehrlichia, babesia, anaplasma, haemotropic mycoplasma, leptospirosis, heartworm, histoplasmosis Neoplasia
    - Lymphoma, HSA, leukemia, pulmonary and gastric carcinoma, diffuse sarcoma
  - Recent vaccination (?)

Balch A, Mackin A. Canine immune-mediated hemolytic anemia: pathophysiology, clinical signs, and diagnosis. *Compend Contin Educ Vet.* 2007 Apr;29(4):217-25.

Steps to diagnosis of IMHA



General work-up

Screening labs

- CBC
- Chemistry
- Urinalysis

Second tier diagnostics

- Confirm suspicions
  - Signs of hemolysis
  - Signs of immune-mediated component
- Look for triggers
  - Infectious disease testing
  - Cancer hunt
  - (Rule out drugs/toxins)
- Look for complications
  - Coagulation panel
  - Blood pressure

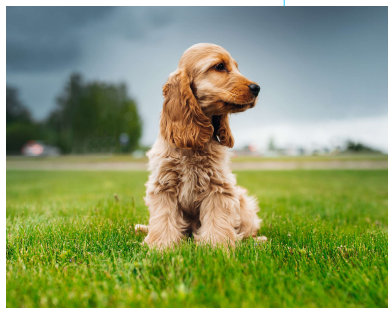
Third tier diagnostics

- More advanced diagnostics, if indicated
  - MRI/CT
  - Coomb's
  - Flow cytometry
  - Bone marrow sampling
  - Cytology
  - Histopathology

Classic IMHA case

Signalment
Clinical signs

- Middle aged female (spayed) dogs
- Cocker spaniels +/- other breeds over-represented
- Seasonal?
- Weak/lethargic
- Collapse
- GI signs
- Tachypnea



Physical

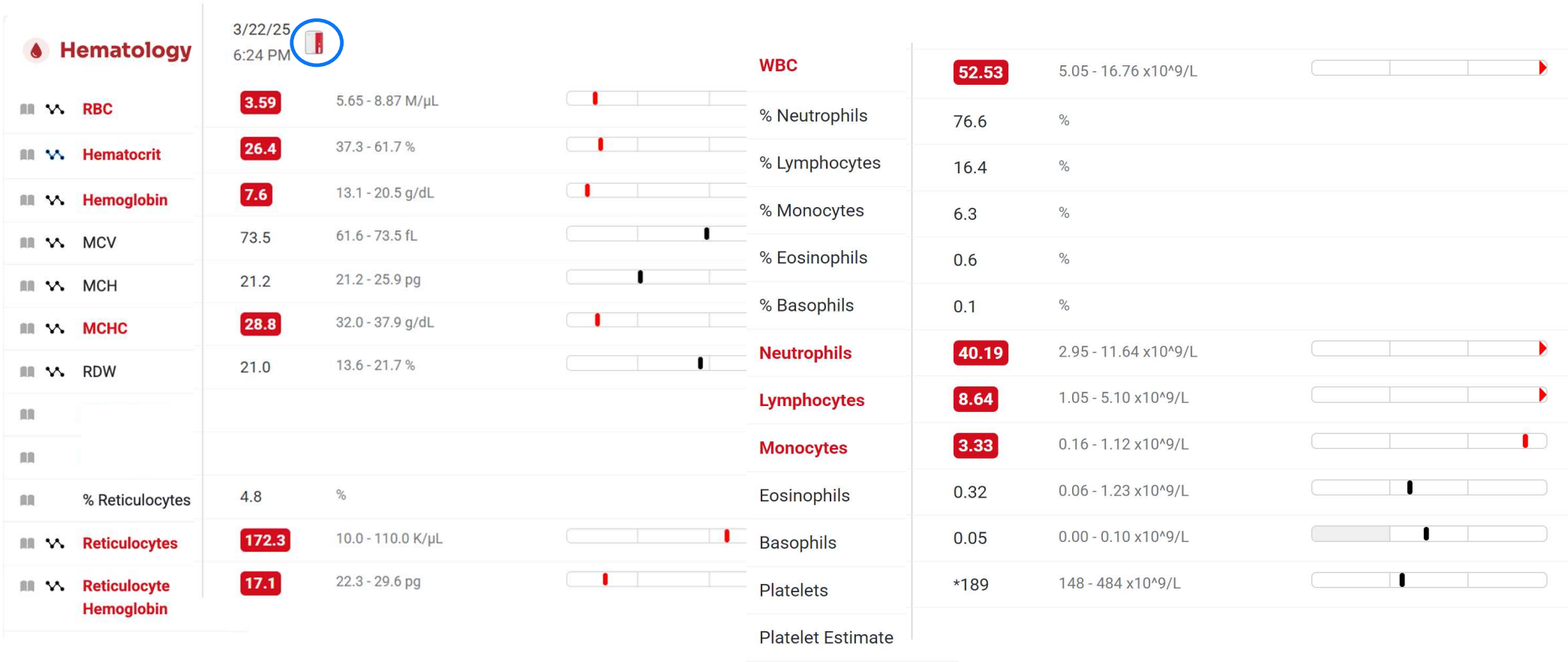
- Pale mucus membranes
- Jaundiced
- Generalized weakness
- Tachypnea
- Tachycardia
- Heart murmur (15-20% cases)
- Febrile
- Hepatosplenomegaly

Labs

- Anemia (usually regenerative)
- Autoagglutination
- Spherocytosis
- Mild to moderate thrombocytopenia (50-70% cases)
- Neutrophilia
- Elevated liver enzymes (ALT>>ALKP)
- Hyperbilirubinemia, bilirubinuria
- + Coomb's
- + Saline agglutination
- Hepatosplenomegaly


“Jimmy”
2-year-old MC doodle

Jimmy’s hemogram, leukogram, and thrombogram



Hematology

3/22/25
6:24 PM

RBC	3.59	5.65 - 8.87 M/µL	
Hematocrit	26.4	37.3 - 61.7 %	
Hemoglobin	7.6	13.1 - 20.5 g/dL	
MCV	73.5	61.6 - 73.5 fL	
MCH	21.2	21.2 - 25.9 pg	
MCHC	28.8	32.0 - 37.9 g/dL	
RDW	21.0	13.6 - 21.7 %	
% Reticulocytes	4.8	%	
Reticulocytes	172.3	10.0 - 110.0 K/µL	
Reticulocyte Hemoglobin	17.1	22.3 - 29.6 pg	

WBC	52.53	5.05 - 16.76 x10^9/L	
% Neutrophils	76.6	%	
% Lymphocytes	16.4	%	
% Monocytes	6.3	%	
% Eosinophils	0.6	%	
% Basophils	0.1	%	
Neutrophils	40.19	2.95 - 11.64 x10^9/L	
Lymphocytes	8.64	1.05 - 5.10 x10^9/L	
Monocytes	3.33	0.16 - 1.12 x10^9/L	
Eosinophils	0.32	0.06 - 1.23 x10^9/L	
Basophils	0.05	0.00 - 0.10 x10^9/L	
Platelets	*189	148 - 484 x10^9/L	
Platelet Estimate			

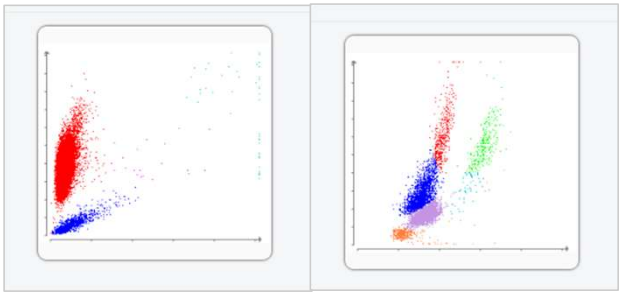
IDEXX

Complete hematology consists of *3* parts

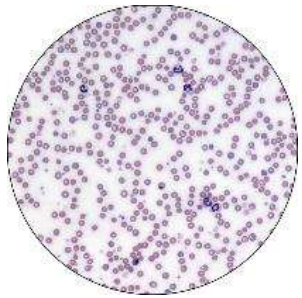
CBC

Hematology	5/13/20 11:25 AM	
Click to view Differentials		
RBC	6.33	6.54 - 12.20 M/µL
Hematocrit	29.2	30.3 - 52.3 %
Hemoglobin	9.7	9.8 - 16.2 g/dL
MCV	46.1	35.9 - 53.1 fL
MCH	15.3	11.8 - 17.3 pg
MCHC	33.2	28.1 - 35.8 g/dL
RDW	20.9	15.0 - 27.0 %
% Reticulocyte	0.1	%
Reticulocytes	5.7	3.0 - 50.0 K/µL
Reticulocyte Hemoglobin	15.2	13.2 - 20.8 pg
WBC	8.91	2.87 - 17.02 K/µL
% Neutrophils	56.9	%
% Lymphocytes	33.4	%
% Monocytes	5.6	%
% Eosinophils	3.4	%
% Basophils	0.7	%
Neutrophils	5.07	2.30 - 10.29 K/µL
Lymphocytes	2.98	0.92 - 6.88 K/µL
Monocytes	0.50	0.05 - 0.67 K/µL
Eosinophils	0.30	0.17 - 1.57 K/µL
Basophils	0.06	0.01 - 0.26 K/µL
Platelets	368	151 - 600 K/µL
MPV	16.7	11.4 - 21.6 fL
Plateletcrit	0.61	0.17 - 0.86 %

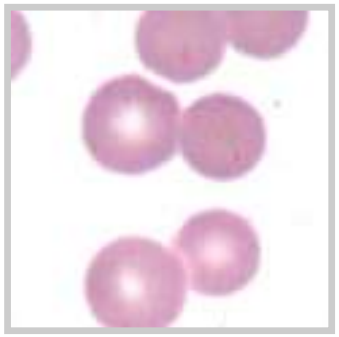
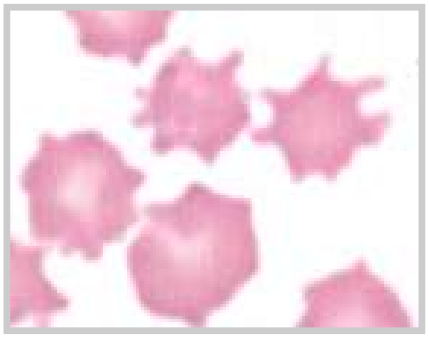
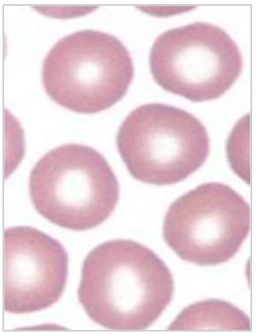
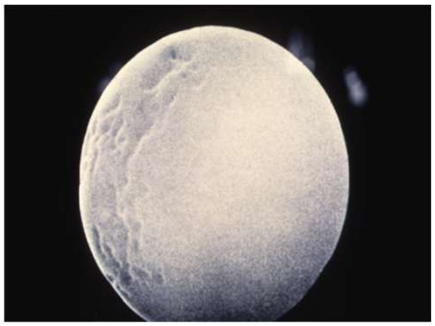
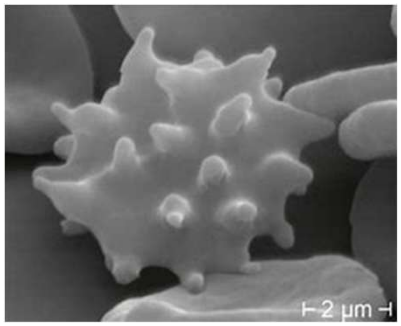
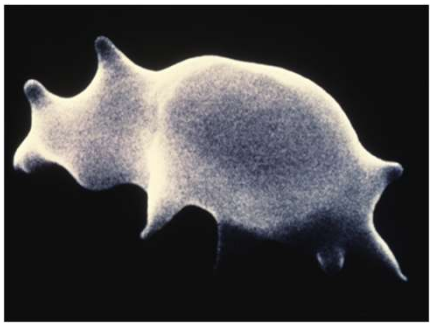
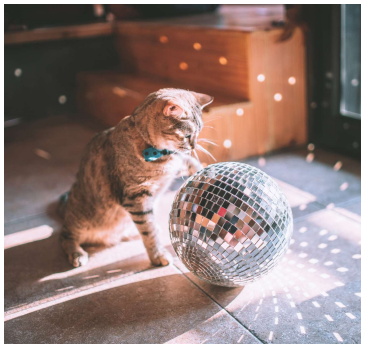
Dot plots/graphics



Blood morphology



Common red blood cell morphology

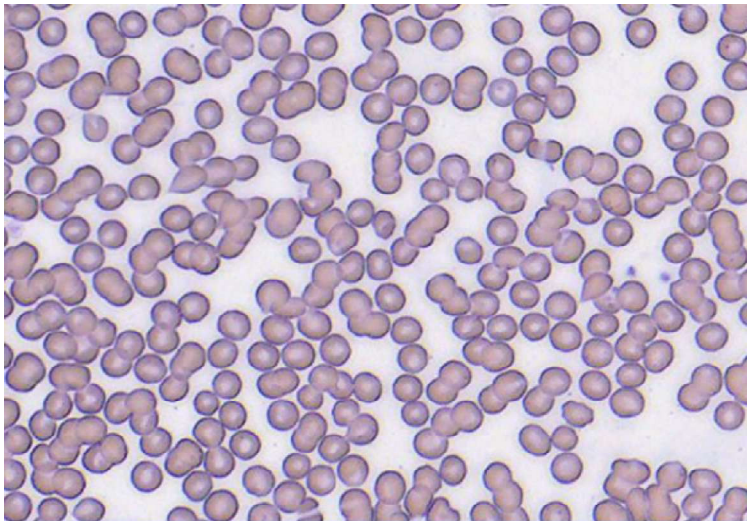
Spherocyte	Acanthocyte	Schistocyte	Normal
			
			

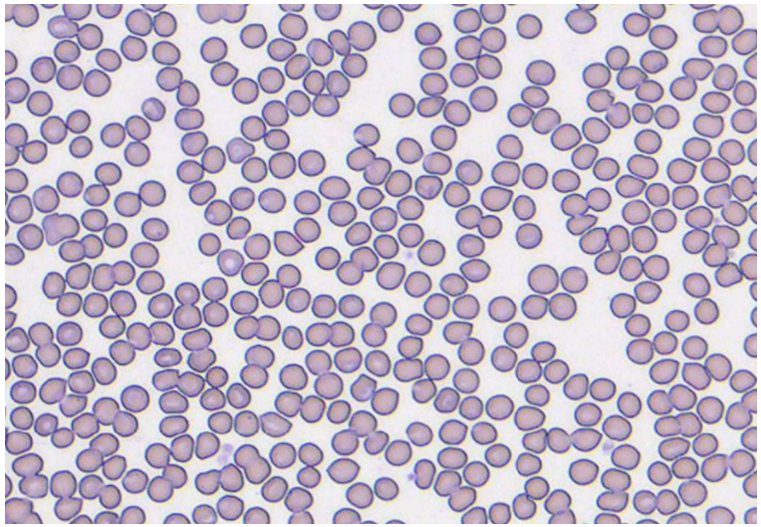
IDEXX

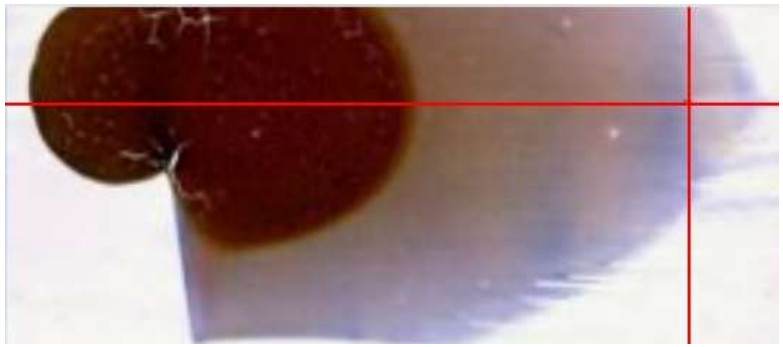
Blood morphology evaluation options

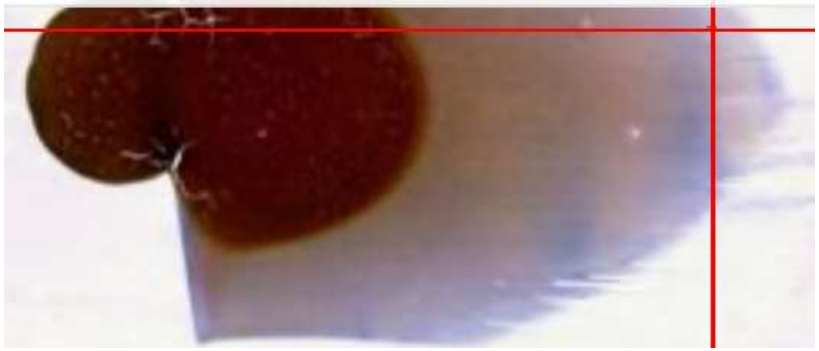
- In-house (vet techs/nurses/clinicians)
- Digital cytology - remote review of in-house slides (clinical pathologist; limited by quality of preparation)
- Reference laboratory (lab technicians, clinical pathologist)
- In-house automated analysis – e.g., InVue Dx

Glass slide limitations…
Are there spherocytes in either of these images?
If so what percent?

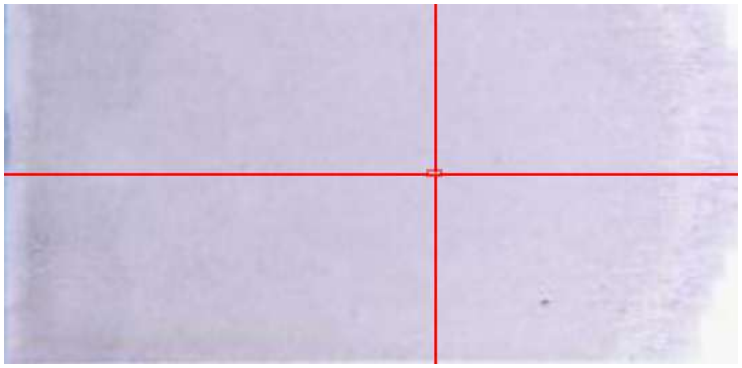


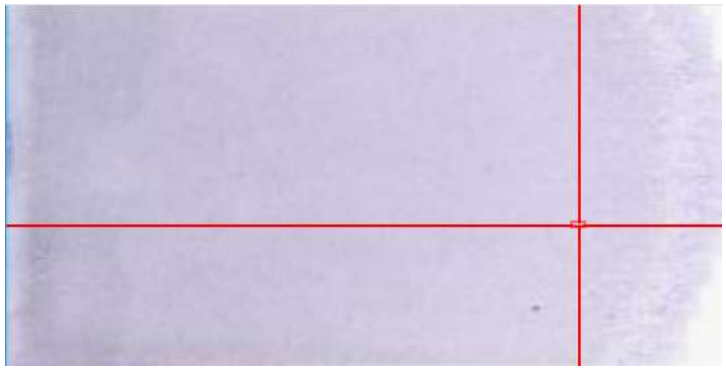


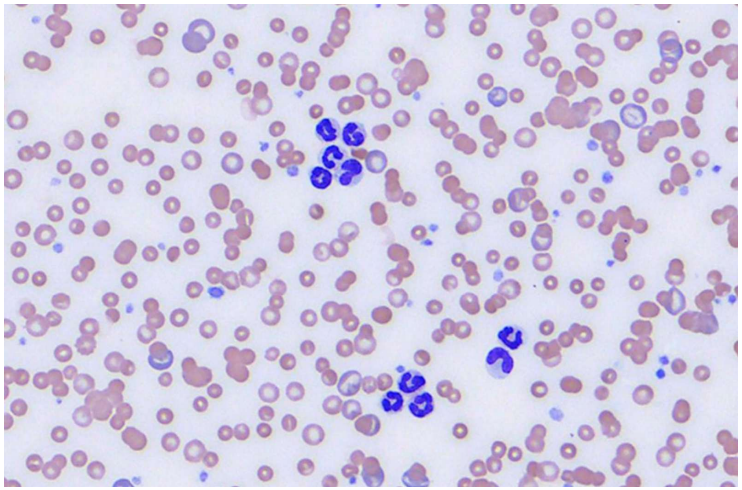


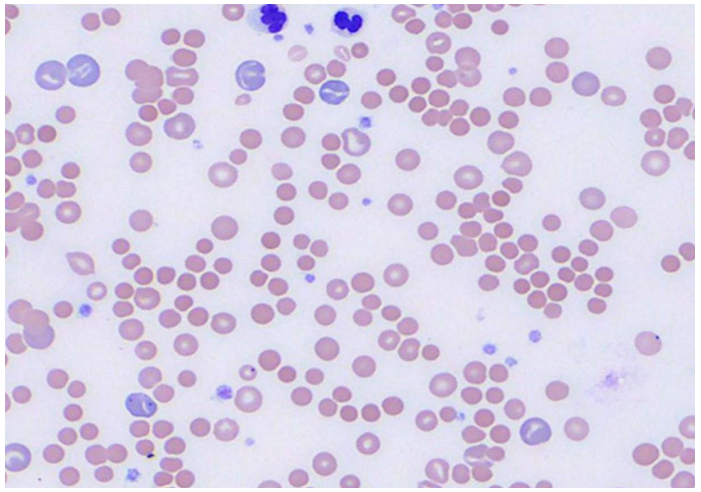


Glass slide limitations
Are there spherocytes?
If so what percent?



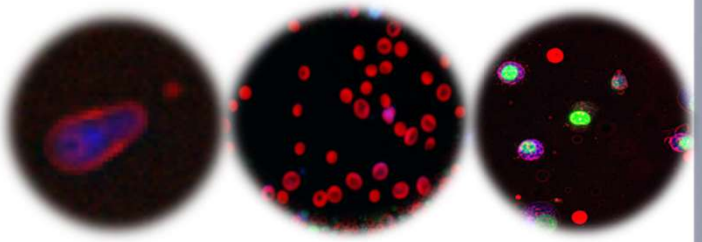






IDEXX InVue Dx- Innovating Point of Care Cytology

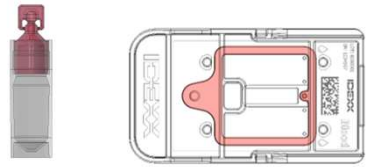
Results
in **10 min**



Ear Cytology | Blood Morphology | FNA Cytology

Launch | Coming Next

Revolutionary Workflow



+ Slide free
+ Load-and-go

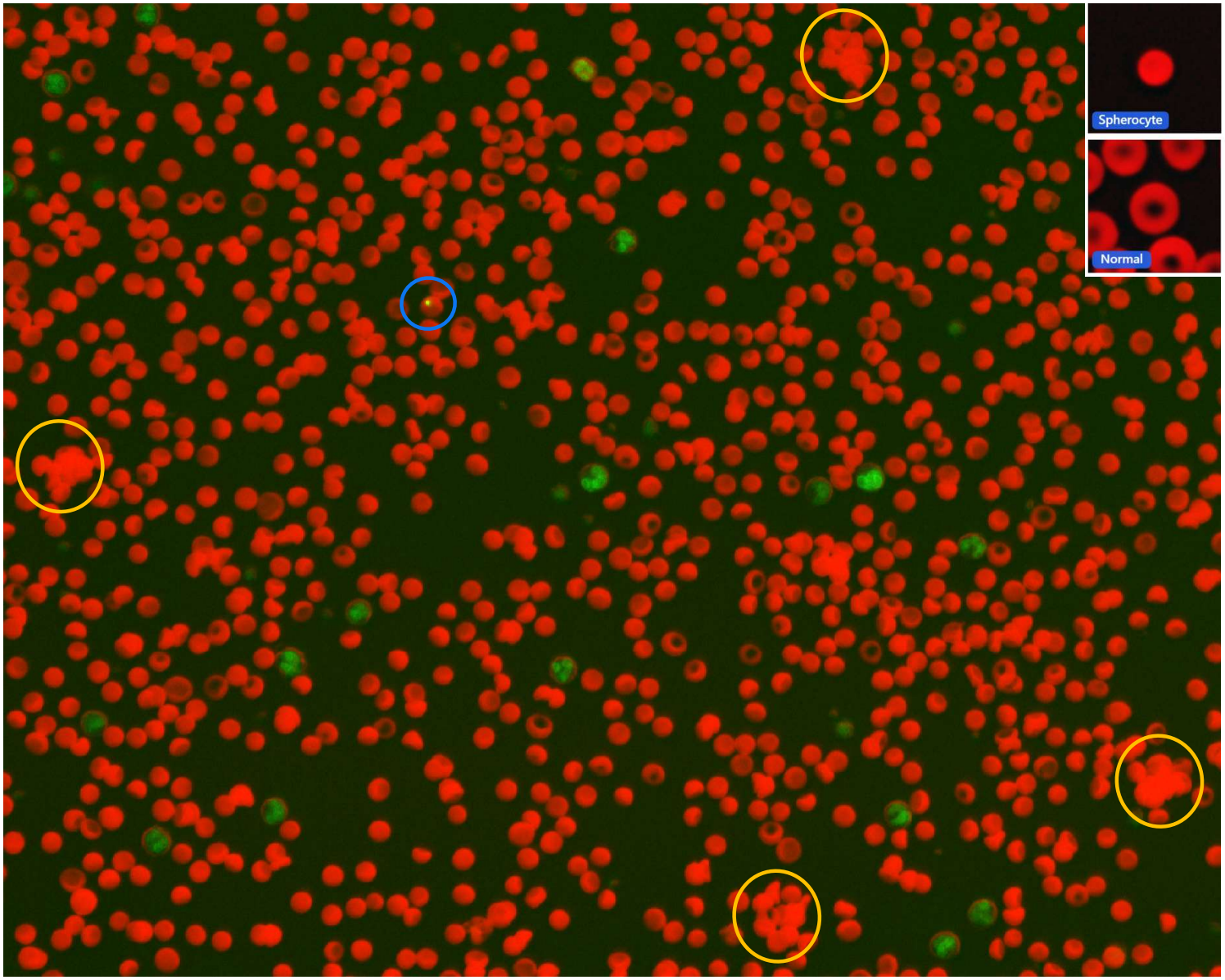
Expanded Insights

+ Pathologists trained AI
+ Technology for Life

IDEXX InVue Dx™ Comprehensive Hematology Results

Composite image:

+ Agglutination
+ Spherocytes
+ Howell Jolly body



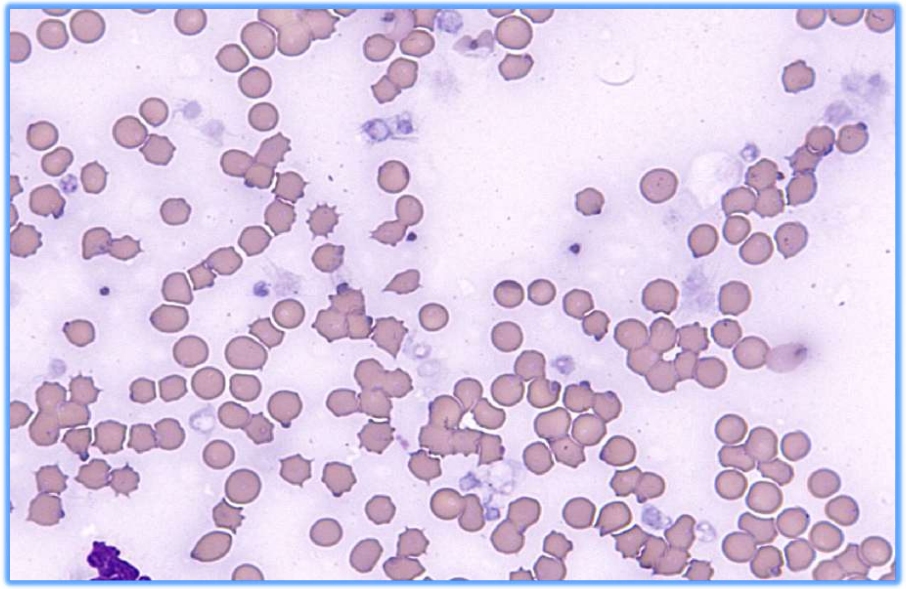
See cells like never before with IDEXX InVue Dx™

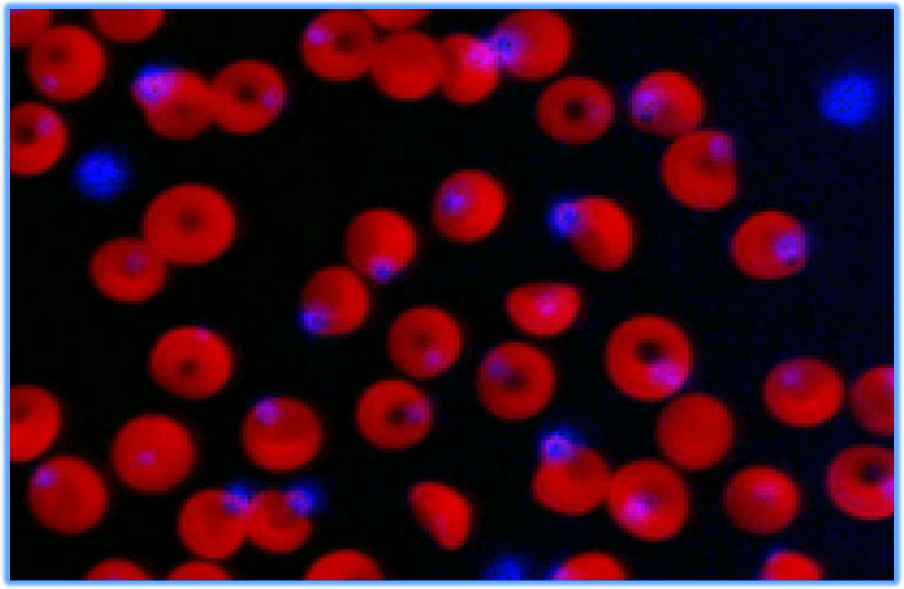
Traditional Slide Method

- Single image
- Single light source
- Aqueous/Alcohol-based stains
- Smear cells and uneven distribution

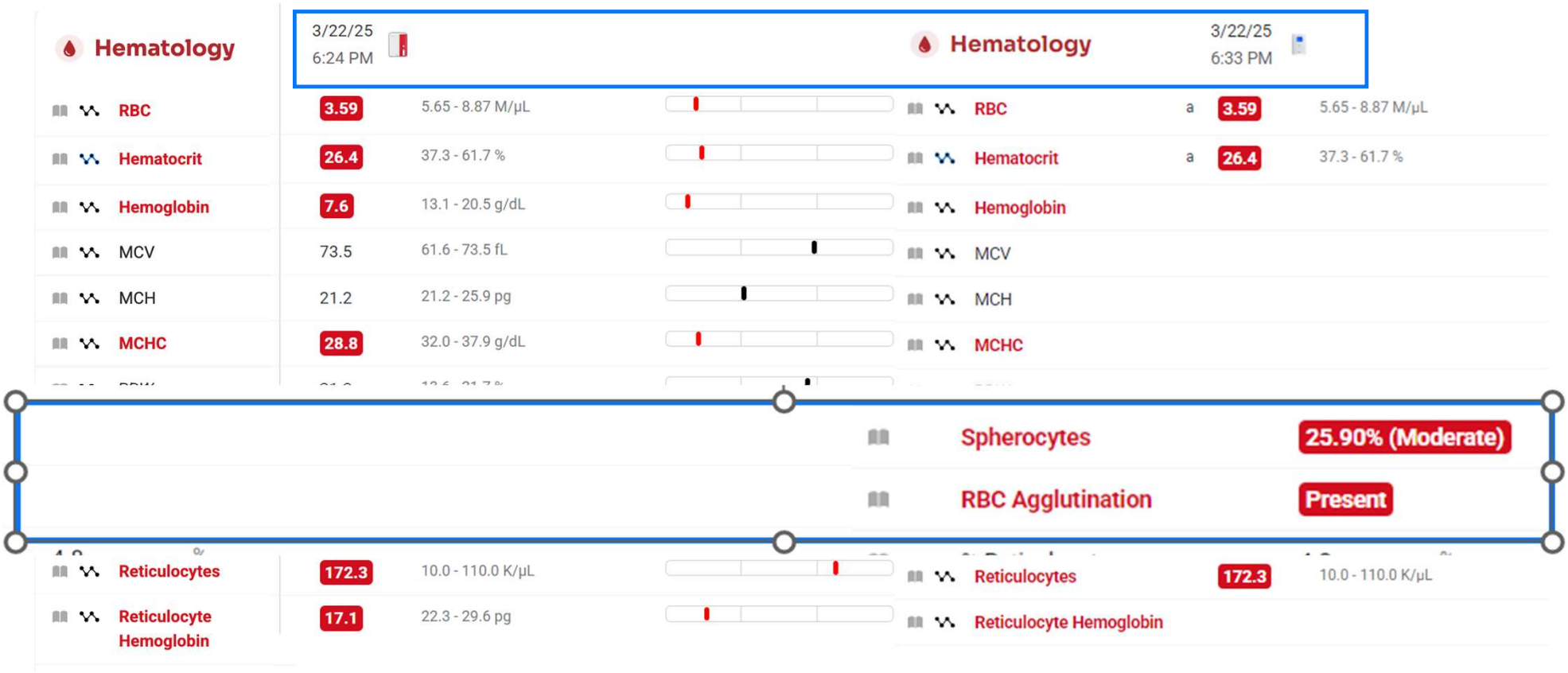
IDEXX InVue Dx

- 1000s of images for each sample
- Multiple wavelengths of light
- Fluorescent stains
- fluid system avoids smearing and distributes cells more evenly

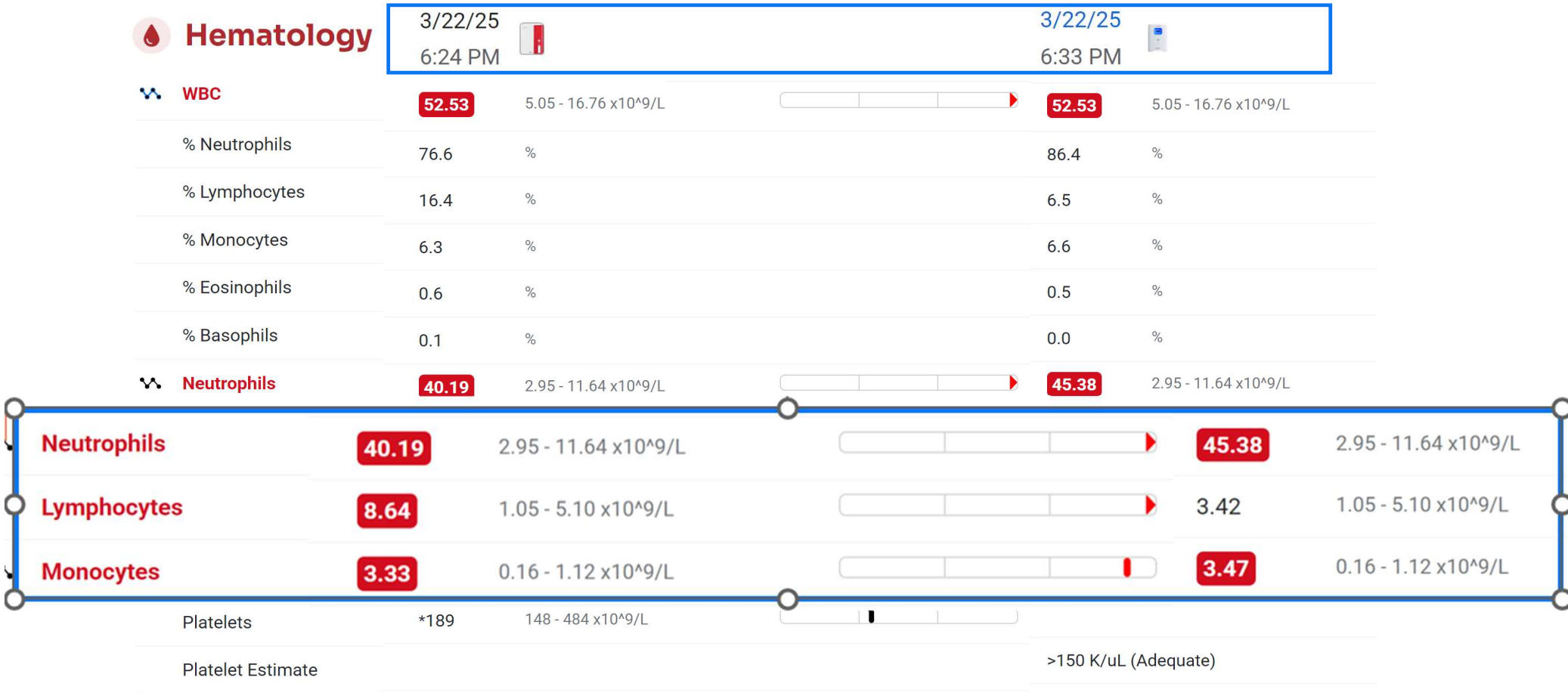




Jimmy’s hemogram revisited…



Jimmy’s leukogram revisited



Hematology	3/22/25 6:24 PM		3/22/25 6:33 PM	
WBC	52.53	5.05 - 16.76 x10^9/L	52.53	5.05 - 16.76 x10^9/L
% Neutrophils	76.6	%	86.4	%
% Lymphocytes	16.4	%	6.5	%
% Monocytes	6.3	%	6.6	%
% Eosinophils	0.6	%	0.5	%
% Basophils	0.1	%	0.0	%
Neutrophils	40.19	2.95 - 11.64 x10^9/L	45.38	2.95 - 11.64 x10^9/L
Lymphocytes	8.64	1.05 - 5.10 x10^9/L	3.42	1.05 - 5.10 x10^9/L
Monocytes	3.33	0.16 - 1.12 x10^9/L	3.47	0.16 - 1.12 x10^9/L
Platelets	*189	148 - 484 x10^9/L		
Platelet Estimate			>150 K/uL (Adequate)	

Procyte comments and InVue Dx WBC updates

ProCyte Dx

* Confirm with dot plot and/or blood film review.

Anemia with reticulocytosis - Likely regenerative anemia.

Monocytosis - Consider inflammation.

Low RETIC-HGB - Decreased iron availability (consider inflammation, iron deficiency, PSS, breed-related microcytosis).

IDEXX inVue Dx

a. Results imported from ProCyte.

b. WBC results imported from ProCyte. The white blood cell differential has been updated based on cytologic evaluation.

InVue annotations

Diagnostic Considerations	The presence of regenerative anemia, spherocytosis, and RBC agglutination are strongly suggestive of immune-mediated hemolytic anemia. Other clinical features may include icterus, hyperbilirubinemia/bilirubinuria (in the absence of liver dysfunction) or hemoglobinemia/uria. Investigate for underlying causes such as infection, neoplasia, concurrent inflammatory conditions, or history of recent dugs or vaccines. This platelet estimate incorporates enumeration of individual platelets and platelets within clumps. Platelet count is above 150 K/uL.

Treatment

Sassy

- 11-year-old FS shih tzu
- Presented for the evaluation of anemia diagnosed by his RDVM
- Past 24 hours: lethargic, hiding, does not want to go outside, trembling
- Episodic weakness and collapse

Sassy's physical exam

Temp: 104.2F

HR: 180 bpm

Pale mucous membranes

Tachypneic

Stress-intolerat

Grade II/VI heart murmur

Hepato-splenomegaly

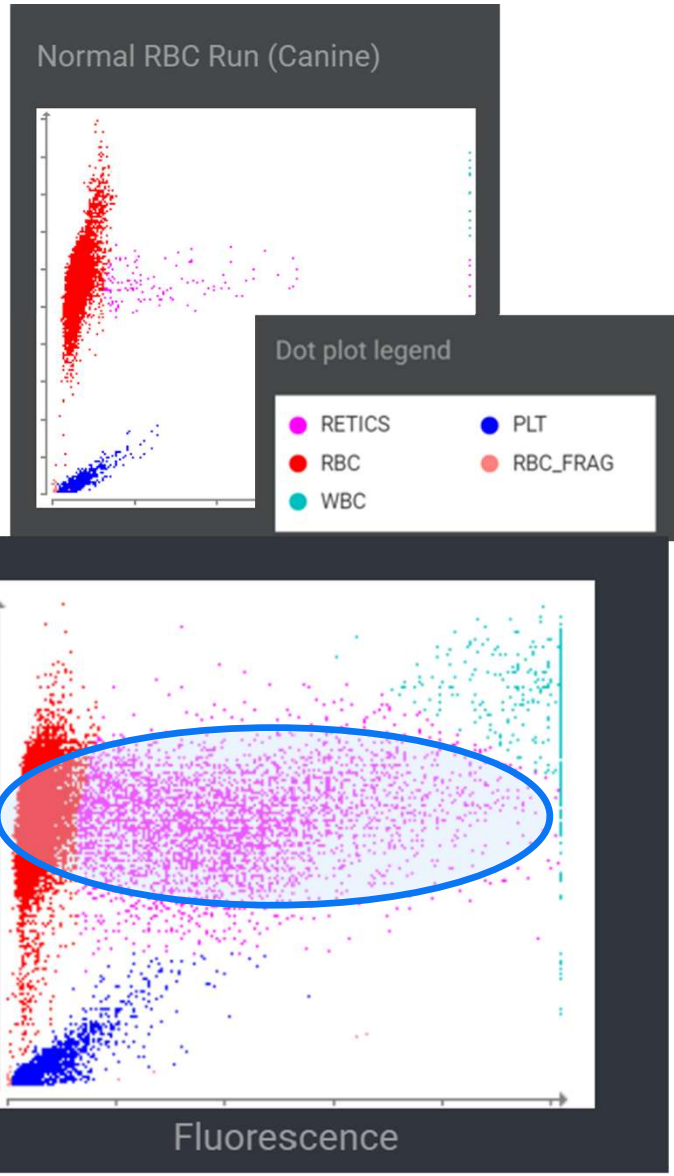
Sassy's hemogram and RBC dot plot

Canine | Shih Tzu | Male | 11 y

Hematology

10/1/18
2:30 PM

RBC	2.95	5.65 - 8.87 M/µL
Hematocrit	24.0	37.3 - 61.7 %
Hemoglobin	6.9	13.1 - 20.5 g/dL
MCV	81.4	61.6 - 73.5 fL
MCH	23.4	21.2 - 25.9 pg
MCHC	28.8	32.0 - 37.9 g/dL
RDW	28.7	13.6 - 21.7 %
% Reticulocytes	17.1	%
Reticulocytes	505.6	10.0 - 110.0 K/µL



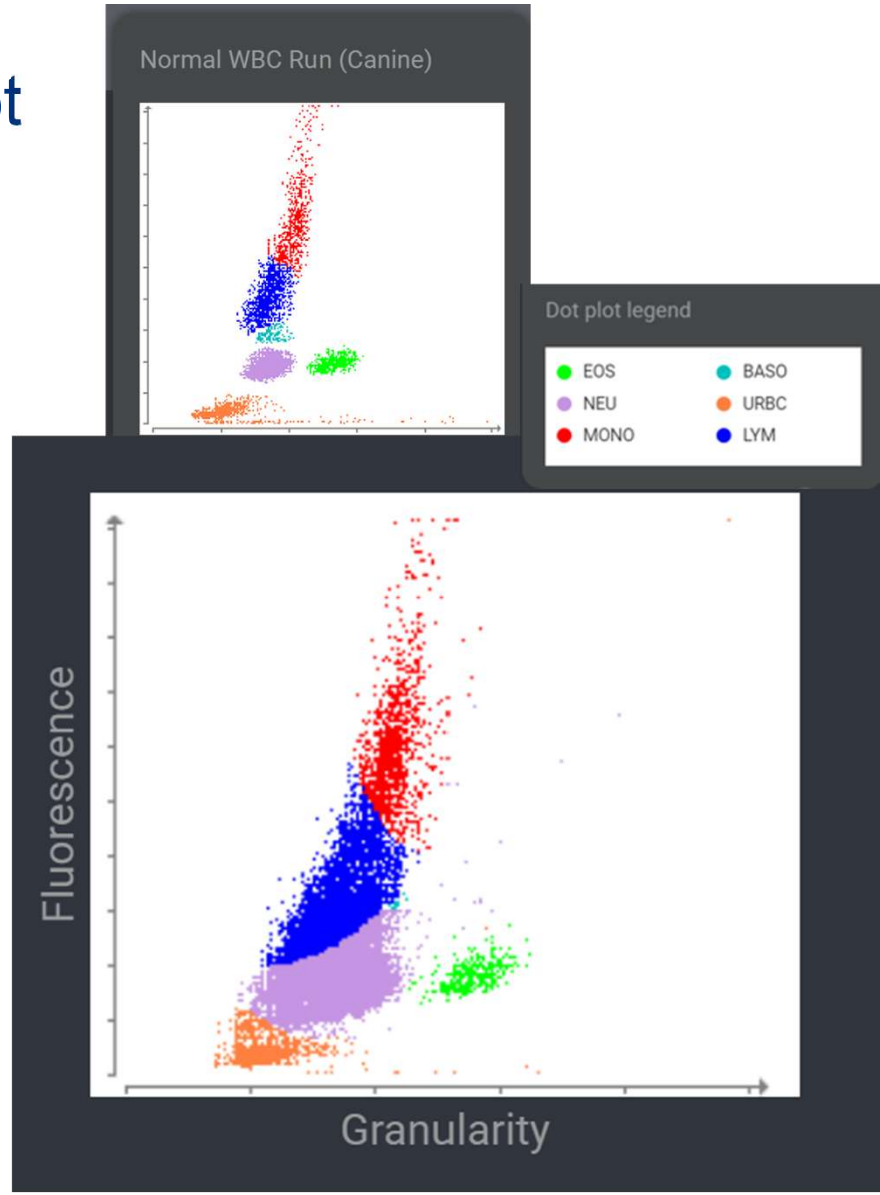
Pearl – degree of reticulocytosis can be indication of hemolysis (vs. hemorrhage)

Sassy's leukogram and WBC dot plot

Hematology

10/1/18
2:30 PM

WBC	*46.63	5.05 - 16.76 K/µL	
% Neutrophils	*64.4	%	
% Lymphocytes	*29.9	%	
% Monocytes	*4.5	%	
% Eosinophils	*1.2	%	
% Basophils	*0.0	%	
Neutrophils	*30.05	2.95 - 11.64 K/µL	
Bands	*Suspected		
Lymphocytes	*13.94	1.05 - 5.10 K/µL	
Monocytes	*2.08	0.16 - 1.12 K/µL	
Eosinophils	*0.54	0.06 - 1.23 K/µL	
Basophils	*0.02	0.00 - 0.10 K/µL	
Nucleated RBCs	*Suspected		
Platelets	254	148 - 484 K/µL	
PDW	14.7	9.1 - 19.4 fL	
MPV	10.4	8.7 - 13.2 fL	
Plateletcrit	0.26	0.14 - 0.46 %	



Sassy's blood smear

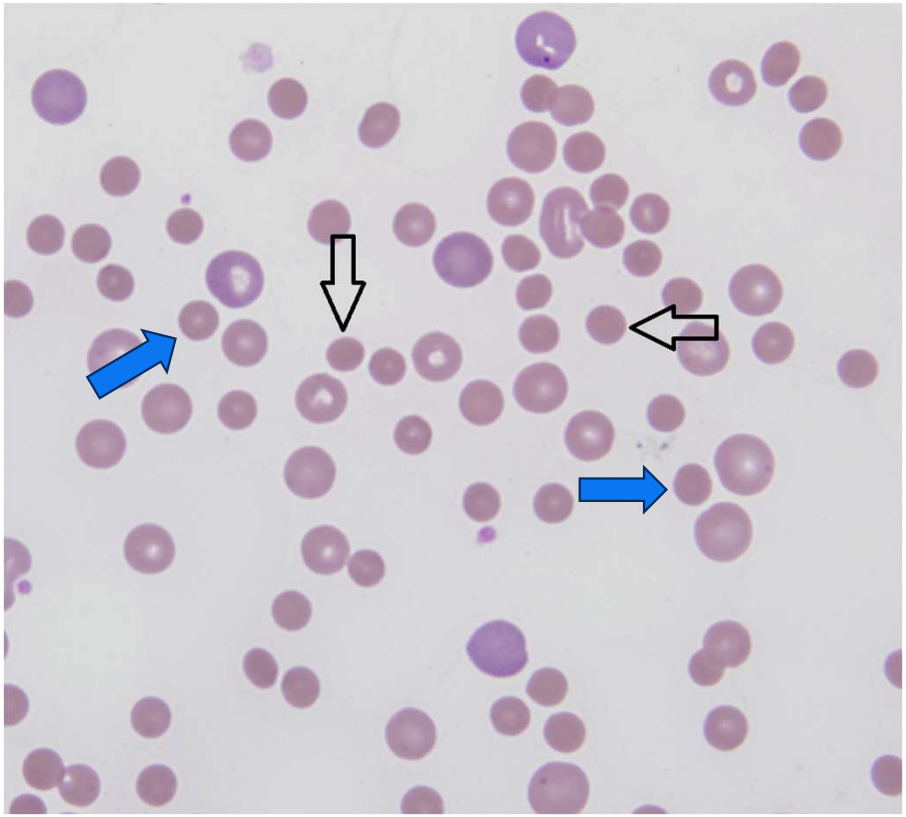


Image used with permission of Dr. Sylvie Beaudin Dipl. ACVP

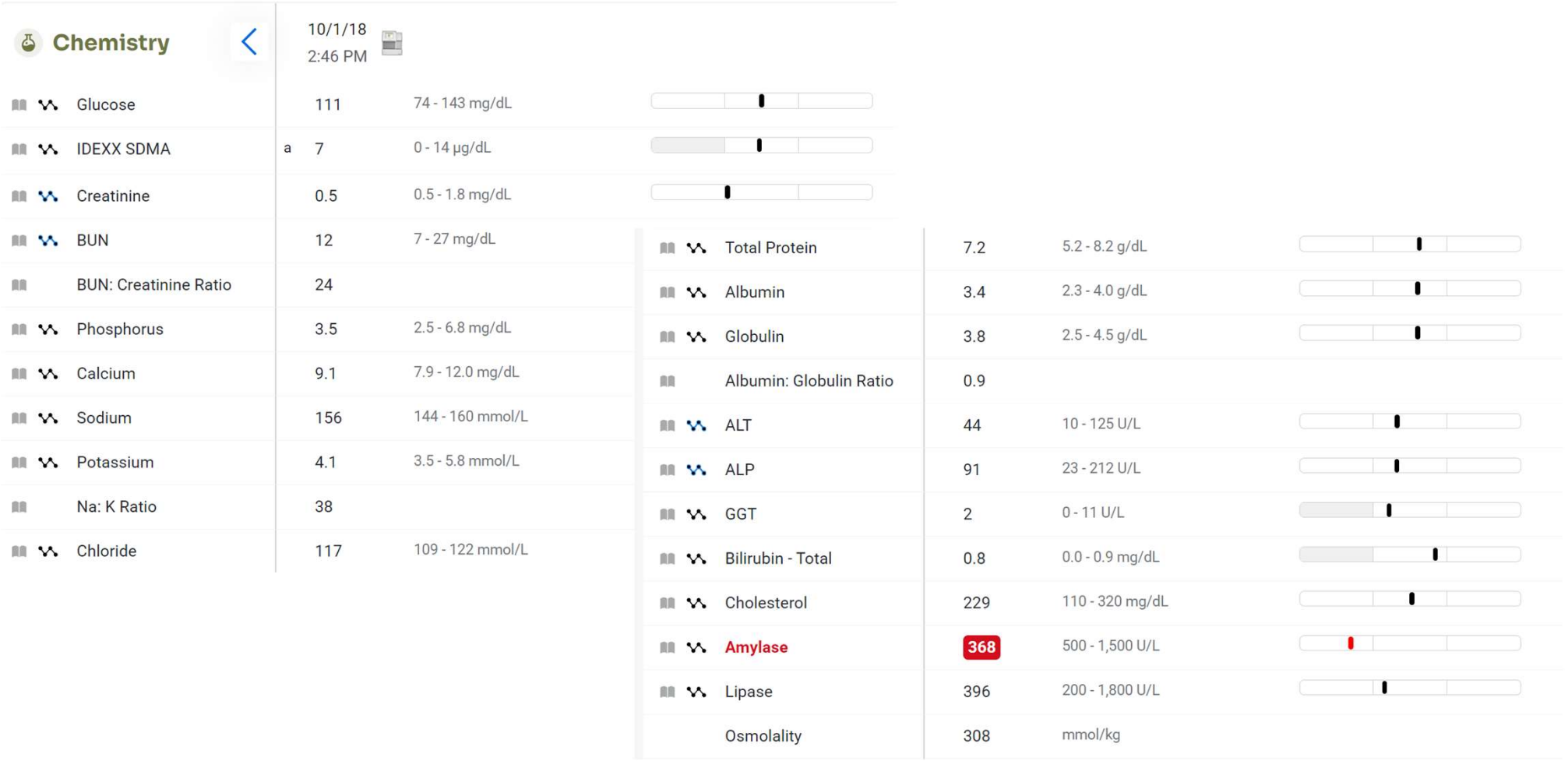
- 85-95% of IMHA cases have spherocytes
- * Interpret with caution if post transfusion review

Balch A, Mackin A. Canine immune-mediated hemolytic anemia: pathophysiology, clinical signs, and diagnosis. *Compend Contin Educ Vet.* 2007 Apr;29(4):217-25.

Complete CBC with slide review

- Mild to severe anemia (88% < 20% Hct)
- Strongly regenerative (reticulocytosis)
  - 1/3 non-regenerative
    - Too soon (takes 3-4 days to respond)
    - Antibodies directed against precursors in the bone marrow (PIMA/PRCA)
- Leukocytosis
  - Neutrophilia with left shift
    - Released by the bone marrow
    - Tissue hypoxia

Case



Chemistry		10/1/18 2:46 PM	
Glucose		111	74 - 143 mg/dL
IDEXX SDMA	a	7	0 - 14 µg/dL
Creatinine		0.5	0.5 - 1.8 mg/dL
BUN		12	7 - 27 mg/dL
BUN: Creatinine Ratio		24	
Phosphorus		3.5	2.5 - 6.8 mg/dL
Calcium		9.1	7.9 - 12.0 mg/dL
Sodium		156	144 - 160 mmol/L
Potassium		4.1	3.5 - 5.8 mmol/L
Na: K Ratio		38	
Chloride		117	109 - 122 mmol/L
Total Protein		7.2	5.2 - 8.2 g/dL
Albumin		3.4	2.3 - 4.0 g/dL
Globulin		3.8	2.5 - 4.5 g/dL
Albumin: Globulin Ratio		0.9	
ALT		44	10 - 125 U/L
ALP		91	23 - 212 U/L
GGT		2	0 - 11 U/L
Bilirubin - Total		0.8	0.0 - 0.9 mg/dL
Cholesterol		229	110 - 320 mg/dL
Amylase		368	500 - 1,500 U/L
Lipase		396	200 - 1,800 U/L
Osmolality		308	mmol/kg

Case

Urinalysis

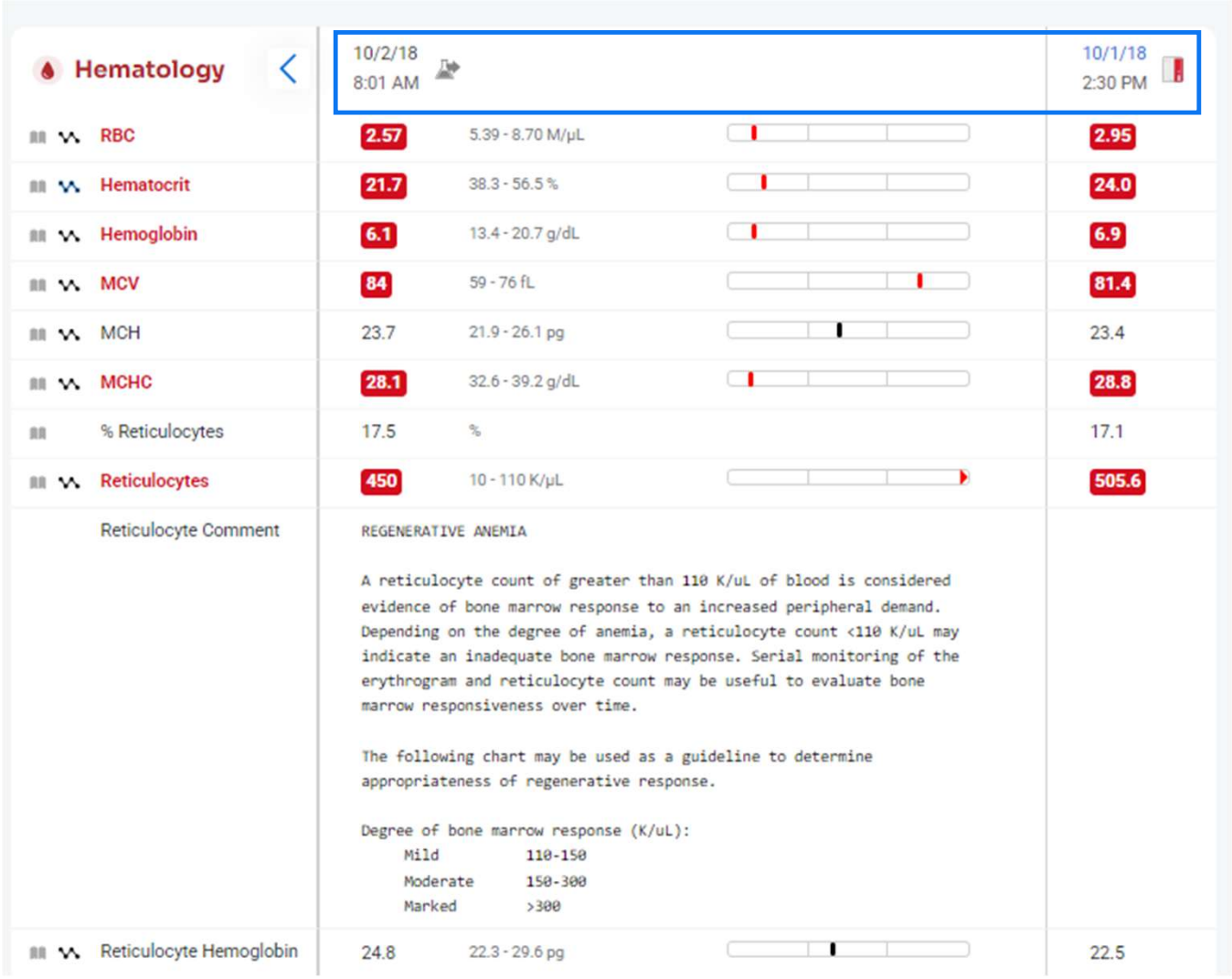
10/1/18 9:23 PM — 9:22 PM

Collection Method	Catheter	
Color	Amber	
Clarity	Clear	
Specific Gravity	1.015	
pH	8.0	
Urine Protein	neg	
Glucose	neg	
Ketones	neg	
Blood / Hemoglobin	neg	
Bilirubin	3	mg/dL
Urobilinogen	8	mg/dL
Leukocyte Esterase	neg	

Common questions regarding diagnostics

Question	Answer…
1. Must I always perform a Coomb's test?	1. No (IMHO)
2. What about an ANA or full immune-panel?	2. NO!!
3. Must I perform radiographs and ultrasound on every IMHA suspect?	3. Must you, no. (But you SHOULD, IMO)
4. Can I perform blood typing or Coomb's test if agglutination is present?	4. You can, but you should not
5. Should I withhold fluids because of the anemia?	5. NO, not if the patient needs fluids!

Sassy's hemogram revisited…



Hematology	10/2/18 8:01 AM		10/1/18 2:30 PM
RBC	2.57	5.39 - 8.70 M/µL	2.95
Hematocrit	21.7	38.3 - 56.5 %	24.0
Hemoglobin	6.1	13.4 - 20.7 g/dL	6.9
MCV	84	59 - 76 fL	81.4
MCH	23.7	21.9 - 26.1 pg	23.4
MCHC	28.1	32.6 - 39.2 g/dL	28.8
% Reticulocytes	17.5	%	17.1
Reticulocytes	450	10 - 110 K/µL	505.6
Reticulocyte Comment	REGENERATIVE ANEMIA A reticulocyte count of greater than 110 K/uL of blood is considered evidence of bone marrow response to an increased peripheral demand. Depending on the degree of anemia, a reticulocyte count <110 K/uL may indicate an inadequate bone marrow response. Serial monitoring of the erythrogram and reticulocyte count may be useful to evaluate bone marrow responsiveness over time. The following chart may be used as a guideline to determine appropriateness of regenerative response. Degree of bone marrow response (K/uL): Mild 110-150 Moderate 150-300 Marked >300		
Reticulocyte Hemoglobin	24.8	22.3 - 29.6 pg	22.5

Sassy's leukogram revisited

Hematology

	10/2/18 8:01 AM	10/1/18 2:30 PM	
WBC	29.2	*46.63	5.05 - 16.76
% Neutrophils	85.0	*64.4	%
% Lymphocytes	2.0	*29.9	%
% Monocytes	7.0	*4.5	%
% Eosinophils	3.0	*1.2	%
% Basophils	0.0	*0.0	%
Neutrophils	24.82	*30.05	2.95 - 11.64 K/µL
Bands	0.876	*Suspected	
Lymphocytes	0.584	*13.94	1.05 - 5.10 K/µL
Monocytes	2.044	*2.08	0.16 - 1.12 K/µL
Eosinophils	0.876	*0.54	0.06 - 1.23 K/µL
Basophils	0	*0.02	0.00 - 0.10 K/µL
Nucleated RBCs	47	*Suspected	
Platelets	534	254	148 - 484 K/µL
PDW		14.7	9.1 - 19.4 fL
MPV		10.4	8.7 - 13.2 fL
Plateletcrit		0.26	0.14 - 0.46 %

Polychromasia	MARKED
Anisocytosis	MODERATE
Remarks	Slide reviewed microscopically. WBC corrected for the presence of nucleated RBC's Neutrophils appear slightly toxic. OCCASIONAL TARGET CELLS SEEN Spherocytes-Marked Autoagglutination of erythrocytes is present and persists with saline dilution. This is a screening test that suggests an immune-mediated process. RBC count, HCT, MCV, MCH, MCHC & Retic count may be affected by RBC clumping. No parasites seen

Immunology

10/2/18 8:01 AM

Coombs' (37° C)	a	1:2048
Antinuclear Antibody	b	Negative
Rheumatoid Factor		NEGATIVE

Sassy's diagnosis?

Anemia

Bonus - regenerative

Diagnostic of IMHA	Supportive of IMHA	Suggestive of IMHA	Not IMHA
a) ≥2 signs of IM destruction b) ≥1 sign of hemolysis	a) ≥2 signs of IM destruction b) 0 signs of hemolysis	a) 1 sign of IM destruction b) 0 signs of hemolysis	a) 0 signs of IM destruction

OR

a) 1 sign of IM destruction
b) ≥1 sign of hemolysis

1. Absence of pretenders
2. Response to therapy

IDEXX

Transfer and presentation to ER

- Hct = 15%!!!!!
- More severely tachycardic and tachypneic
- Markedly stress-intolerant
- Lactate 3.3 mmol/L (0.5-2.0 mmol/L)

Sassy needs a transfusion STAT

- Blood typing impossible because of severe agglutination
  - Transfused with packed red blood cells DEA 1.1 negative

Additional testing

Ideal minimal database (ACVIM consensus)

- Thorough history
- Thorough PE with retinal exam
- CBC with blood film evaluation
- Biochemistry and urinalysis
- +/- Urine culture and fecal

Imagery

- In a study of dogs with IMHA:
  - 68% of thoracic radiographs were normal
  - 25% of abdominal ultrasounds were normal
- 76% of thoracic radiographs did not influence clinical course
- 50% of abdominal ultrasounds did not influence clinical course

CONCLUSION: up to the discretion of the clinician based on age, presenting clinical signs and other lab work anomalies

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;60(10):1065-1071

Infectious disease testing

Dogs

- *Babesia* spp.
- *Dirofilaria immitis*

- Others to consider:
  - *Anaplasma* spp.
  - *Ehrlichia* spp.
  - *Bartonella* spp.
  - *Leishmania* spp.

Cats

- *Babesia felis*
- Hemotropic *Mycoplasma* spp.
  - Lower incidence other feline *Mycoplasma* spp.
- FeLV

Garden OA, Kidd L, Mexas AM, Chang YM, Jeffery U, Blois SL, Fogle JE, MacNeill AL, Lubas G, Birkenheuer A, Buoncompagni S, Dandrieux JRS, Di Loria A, Fellman CL, Glanemann B, Goggs R, Granick JL, LeVine DN, Sharp CR, Smith-Carr S, Swann JW, Szladovits B. ACVIM consensus statement on the diagnosis of immune-mediated hemolytic anemia in dogs and cats. *J Vet Intern Med*. 2019;33(2):313-334. doi: 10.1111/jvim.15441

Back to Sassy

- Given age, decided to do additional work-up:
  - Abdominal US:
    - Hepatomegaly with 2 nodules suspected to be benign
    - Mild splenomegaly
      - Extramedullary hematopoiesis vs lymphoid hyperplasia
    - Chronic degenerative renal changes
    - Sediment in the bladder (Blood? Inflammatory cells? Other?)
    - Chronic focal pancreatitis
- 3 view chest films
  - Mild interstitial pattern with normal blood vessels
- SNAP® 4Dx® Test: Negative

General treatment of IMHA

Initial management is supportive

- Transfusions
  - Hct < 20% and presence of clinical signs
  - Hct < 12-15%
- Blood Typing
  - Autoagglutination can falsify result
  - 5 days to form new antibodies
- Packed Red Cells
  - Ideal blood product for anemia unless hypotensive
  - Whole blood is a reasonable alternative
- Oxyglobin
  - Controversial
- Fluids and Oxygen
  - YES! Anemic patients can have fluids

Other options:
- IVIG
- Plasmapheresis

Balch A, Mackin A. Canine immune-mediated hemolytic anemia: treatment and prognosis. *Compend Contin Educ Vet*. 2007;29(4):230-8.

Immunosuppressants

- Glucocorticoids
  - Dexamethasone if hyporexic
    - 0.2 – 0.4 mg/kg IV q 24hr
  - Prednisolone or prednisone at an initial PO dosage of 2 mg/kg/day, or 50-60 mg/m2/day for dogs >25 kg
  - Study showed that q 24hr administration was associated with less PU/PD than a dose divided q 12hr

Swann JW, Garden OA, Fellman CL, Glanemann B, Goggs R, LeVine DN, Mackin AJ, Whitley NT. ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs. *J Vet Intern Med.* 2019;33(3):1141-1172. doi: 10.1111/jvim.15463.

Swann, J.W., et al. Randomised controlled trial of fractionated and unfractionated prednisolone regimens for dogs with immune-mediated haemolytic anaemia. Vet Rec. 2019;184(25):771.

Common questions regarding long-term management

Question	Answer…
1. When, IF to start 2nd immunosuppressive?	1. It depends
2. When to start taper?	2. It depends
3. Taper what/which first and how?	3. It depends
4. Frequency of re-checks?	4. It depends
5. When to say successful response?	5. It's complicated
6. When to say failure of response?	6. It's complicated
7. What to do if relapse?	7. It depends
8. When should I recommend bone marrow sampling?	8. Persistent non-regenerative anemia, WBC morphology changes

Common questions regarding long-term management

Question	Answer…
9. Hct as dropped, does it mean relapse?	9. Maybe
10. Neutrophils are rising, is it because of the steroids?	10. Maybe
11. Should I ever vaccinate this pet again? a. What about titers?	11. It depends a. It depends

When to add a second agent?

1. Clinical features at presentation consistent with severe or immediately life-threatening disease.

2. The PCV/Hct does not remain stable, with an absolute decrease of ≥5% within 24 hours, during the first 7 days of treatment with a glucocorticoid drug.

3. Continued need for blood transfusions after 7 days of treatment.

4. Concern for significant adverse effects associated with glucocorticoids.

Swann JW, Garden OA, Fellman CL, Glanemann B, Goggs R, LeVine DN, Mackin AJ, Whitley NT. ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs. *J Vet Intern Med.* 2019;33(3):1141-1172. doi: 10.1111/jvim.15463.

Second immunosuppressive options

- Cyclosporine
  - Modified cyclosporine
  - T lymphocyte suppressor
  - Cyclosporine: 5 mg/kg PO q12h
    - Onset of action and pharmacokinetics are highly variable from dog-to-dog
    - Adjustment of this dosage may be guided by therapeutic drug monitoring (starting 1 week after administration)
  - Well tolerated and not myelotoxic
  - Gingival hyperplasia, hepatic toxicity, GI side effects, opportunistic infections

- Azathioprine
  - Purine analogue
  - 2 mg/kg or 50 mg/m2 PO q24h
    - After 2-3 weeks, the dosing interval may be increased to every other day (less toxicity)
  - Delay of onset of at least 11 days
  - Synergistic with glucocorticoids
  - Myelosuppression, hepatotoxicity, pancreatitis, GI signs

Archer TM, Boothe DM, Langston VC, Fellman CL, Lunsford KV, Mackin AJ. Oral cyclosporine treatment in dogs: a review of the literature. J Vet Intern Med. 2014;28(1):1-20. doi: 10.1111/jvim.12265

Balch A, Mackin A. Canine immune-mediated hemolytic anemia: treatment and prognosis. *Compend Contin Educ Vet*. 2007;29(4):230-8..

Second immunosuppressive options - part 2

Mycophenolate mofetil

- Purine synthesis inhibitor
  - Similar mechanism of action to azathioprine but 5-10x stronger and faster acting
- 10-15 mg/kg q 12hr
- Few side effects, GI signs more common with higher dosing (> 10 mg/kg q 12hr), hepatotoxicity and myelotoxicity are rare

Leflunomide

- Pyrimidine synthesis inhibitor
- 4 mg/kg q 24hr PO
- Used when other agents have failed
- Hepatoxicity and myelotoxicity are rare

Balch A, Mackin A. Canine immune-mediated hemolytic anemia: treatment and prognosis. *Compend Contin Educ Vet*. 2007;29(4):230-8..

Treatments to avoid

- Cyclophosphamide
  - No benefit, potentially detrimental
- Use of 3 or more immunosuppressive agents
  - More adverse effects
- Combining mycophenolate and azathioprine
  - Same mechanism of action

Swann JW, Garden OA, Fellman CL, Glanemann B, Goggs R, LeVine DN, Mackin AJ, Whitley NT. ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs. *J Vet Intern Med.* 2019;33(3):1141-1172. doi: 10.1111/jvim.15463.

Antithrombotics should be considered

- ACVIM: All dogs with IMHA, except those with severe thrombocytopenia (platelet count <30,000/µL)
  - Increased risk of thrombosis
  - Leading cause of morbidity and mortality in these patients
- Which antithrombotic?
  - Unfractionated heparin > low molecular weight heparin > oral Xa inhibitor (rivaroxaban) > clopidogrel (antiplatelet) > aspirin (antiplatelet)
- How long?
  - Until remission of disease and discontinuation of glucocorticoids

Swann JW, Garden OA, Fellman CL, Glanemann B, Goggs R, LeVine DN, Mackin AJ, Whitley NT. ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs. *J Vet Intern Med.* 2019;33(3):1141-1172. doi: 10.1111/jvim.15463.

Indications of a favorable response are multifactorial

- Stabilization of the anemia
- Resolution of agglutination
- Increase OR decrease in the amount of reticulocytes
- Decrease in the number of spherocytes
- Negative Coombs testing

- Most dogs will respond within 7 days with a maximal response within 2-4 weeks

Swann JW, Garden OA, Fellman CL, Glanemann B, Goggs R, LeVine DN, Mackin AJ, Whitley NT. ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs. *J Vet Intern Med.* 2019;33(3):1141-1172. doi: 10.1111/jvim.15463.

When to consider splenectomy?

- Only for refractory cases
- Ensure there is no underlying cause
- Maximize dose of glucocorticoids
- Second immunomodulatory agent added
  - Check cyclosporine levels
  - Switch second immunomodulatory agent
- When considering 3rd immunomodulatory agent

Swann JW, Garden OA, Fellman CL, Glanemann B, Goggs R, LeVine DN, Mackin AJ, Whitley NT. ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs. *J Vet Intern Med.* 2019;33(3):1141-1172. doi: 10.1111/jvim.15463.

Sassy’s treatment

Sassy's initial ER management

- Multiple transfusions
  - Rapidly hemolyzed
  - Could not cross-matching because of agglutination
  - Febrile during transfusions
- Dexamethasone 0.2 mg/kg IV q 24 hrs
- Added cyclosporine after the second transfusion
- Fluid therapy (for pyrexia and dehydration)
- Doxycycline, aspirin, nutritional support

Sassy's progress

- Sent home after a few days
  - Hct stabilized 18% without transfusions
  - Cardiovascularly stable
  - Financial limitations
- Home treatments
  - Prednisone, doxycycline, cyclosporine, aspirin
- Recheck 3 days later
  - Better general condition
  - Persistent episodes of weakness
  - Only eating when syringe fed
- Moment of truth….

  PCV/TP = 22%/6.8 g/dL

General medication weaning strategy

ACVIM
JOURNAL OF VETERINARY INTERNAL MEDICINE Open Access

CONSENSUS STATEMENT | Open Access

ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs

James W. Swann, Oliver A. Garden, Claire L. Fellman, Barbara Glanemann, Robert Goggs, Dana N. LeVine, Andrew J. Mackin, Nathaniel T. Whitley

First published: 07 March 2019 | https://doi.org/10.1111/jvim.15463 | VIEW METRICS

When PCV is stable and > 39% for 2 weeks with prior improvement in majority of measures of disease

- Single agent predniso(lo)ne: reduce by 20-25% q3 weeks
- Multimodal therapy: reduce predniso(lo)ne by 25-50%

If PCV remains stable and > 30%, continue weaning

- Predniso(lo)ne only: reduce dose by 25% q3 weeks
- Multimodal immunomodulatory therapy: reduce predniso(lo)ne by 25-33% q3 weeks or 25% q 2 weeks
- Wean completely wean corticosteroid unless adverse effects of 2nd immunosuppressive

Duration of therapy typically 3-6 months (steroid), 4-8 months all meds

When and what do I re-check?

- 1st re-check, generally ~ 1 week post discharge
  - PCV/TP, +/- full CBC/chem
- Assuming all is well, 3 weeks after that in anticipation of weaning a medication
  - PCV/TP
  - Wait for results!!
- Just before I am changing meds at any time
  - Wait for results!!
- 7-10 days post changing meds
  - At least PE and PCV/TP)
- Any time the patient declines for any reason

Sassy long-term follow-up

Day 3

- PCV/TP 22%/6.8
- Stable
- Doxy, pred, cyclosporine, aspirin (no change)

Day 10

- Clinically improved
- PCV = 29%
- Persistent moderate spherocytosis
- Persistent reticulocytosis
- No change in meds

Day 24

- Clinically improved
- Marked PU/PD
- PCV 37%
- Retics = 142K/*u*L
- No spherocytes
- Platelets = 529 K/*u*L
- Stopped aspirin
- No other changes in meds

Day 38

- Persistent, but less PU/PD
- Polyphagic
- Questionable jaundiced?
- PCV = 37%
- Retics = 150K
- Few spherocytes?
- Re-start aspirin, no change in other meds

Day 68

- PCV = 40%!!
- No retics or spherocytes
- Decreased pred by 25%
- Unchanged cyclosporine and aspirin
- Continued to taper pred over next many months then lost to follow-up

Relapse

Statistics

- 11-24% of cases
- 56% in the first 12 months
- Can be several years later

Reaction

- If still on immunosuppressants, return to previous dose
- If no longer on immunosuppressants, start over at the beginning
- Search for underlying cause/trigger

Sparrow R, Swann JW, Glanemann B. Comparison of timing of relapse in dogs with nonassociative immune-mediated hemolytic anemia, thrombocytopenia, or polyarthritis. *J Vet Intern Med.* 2024;38(2):1035-1042. doi: 10.1111/jvim.17004

Swann JW, Garden OA, Fellman CL, Glanemann B, Goggs R, LeVine DN, Mackin AJ, Whitley NT. ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs. *J Vet Intern Med.* 2019;33(3):1141-1172. doi: 10.1111/jvim.15463.

Common complications of IMHA

Complications of disease

- Anemia
- Hypoxemia
- Hypercoagulability
- Thromboembolic disease
- Fever

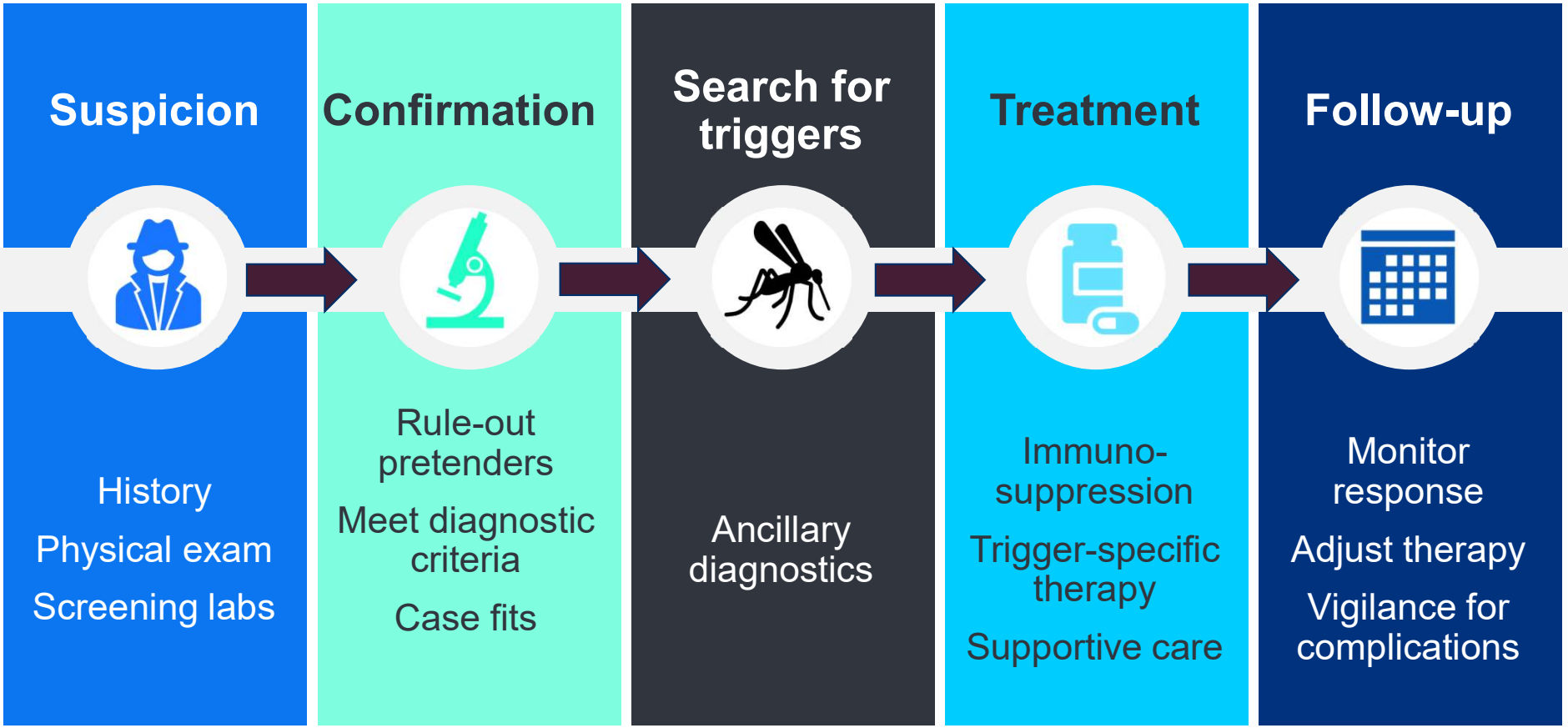
Complications of treatment

- GI side-effects
- Iatrogenic hyperadrenocorticism
- Hypercoagulability
- Thromboembolic disease
- Immunosuppression
- Bone marrow suppression
- Diabetes mellitus

Common faux pas

- Strictly cook-book approach
- Starting immunosuppressives without strong evidence of immune-mediated disease
- Sending patient home with pre-determined times to wean medications
- Inappropriately high doses of corticosteroids
- Combining too many immunosuppressives; polypharmacy in general
- Inadequate re-check
  - NOT pairing PCV with TP!!!
  - No periodic chemistries
  - No periodic urinalyses
- Unrealistic expectations; giving up too soon
- Not preparing pet parent for long-term management, when to be concerned/be seen

IMHA - Summary



Thank You!!

Don’t just keep up. Stay ahead with *The Curated Mind*, IDEXX’s monthly education newsletter.

Scan the code to stay in the know and receive updates about:

+ Upcoming live events
+ New on-demand education resources
+ The latest *Shake Up Your Workup* podcast
+ Articles from *The Vetiverse*
+ Upcoming in-person education opportunities