“See, I told you I was Sick!”
A case-based approach to feline anemia

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Definition
- Definition: Decrease in RBC mass
  - PCV - packed cell volume ("spun hematocrit")
  - HCT - hematocrit
  - \([\text{Hg}]\) - hemoglobin concentration
  - RBC number
- Remember the reference interval represents the central 95% of a normal population
- If uncertain, follow trends to detect developing anemia

Feline clinical signs
- Depression and weakness
- Anorexia
- Dehydration
- Pale mucous membranes
- Pica
- Tachycardia
- Bounding pulses
- Heart murmur
- Fever
- Tachypnea +/- dyspnea
- Splenomegaly
- Icterus
- Petechiae, ecchymoses
- Syncope
- Hypothermia
- Moribund

Classification of anemia
- Three schemes of classification are used:
  - A. Based on RBC morphology
  - B. Based on bone marrow responsiveness
    - Regenerative
    - Nonregenerative
  - C. Based on the major pathophysiologic mechanism
    - Red blood cell loss
    - Red blood cell destruction (lysis)
    - Failure of red blood cell production

RBC Morphology
- RBC indices measured:
  - MCV – mean cell volume
  - MCHC – mean cell hemoglobin concentration
The MCV and MCHC suggest the type of erythrocyte being produced by the marrow

- **MCV**: Normocytic, microcytic, macrocytic
- **MCHC**: Normochromic, hypochromic, **hyperchromic** (?) 

Examples:

- Normocytic, normochromic anemia
- Microcytic, hypochromic anemia

### Marrow Responsiveness

- **Regenerative**
- **Non-regenerative**

### Determination of regeneration

- **Reticulocytosis**
  - This is the MAIN characteristic of a regenerative anemia
  - It is evidence of response by the bone marrow to increase the number of circulating erythrocytes
  - Determined by staining RBCs with new methylene blue (NMB); this stains RNA within the RBC, resulting in a *reticulated* pattern
  - It can be easily measured (reticulocyte panel or on Procyte/Lasercyte)

Reticulocytes – unique features in cats

- Degree of regeneration is often not as dramatic as in dogs
- Two different types of reticulocytes - aggregate vs. punctate
  - **Aggregate**
    - Similar to reticulocytes of other species
    - Measured to determine reticulocyte index and absolute reticulocyte count
    - Reflects what is currently happening in the bone marrow (over ~12 – 24 hrs)
    - Account for up to 0.4% of erythrocytes in healthy cats
  - **Punctate**
    - Contain small, blue-stained spots
    - Derived from aged aggregate reticulocytes
    - Persist in circulation for at least two weeks

Using morphology to help determine regeneration

- **MCV** – Often *increased* with regeneration - **Macrocytosis**
- **MCHC** – Often *decreased* with regeneration - **Hypochromasia**
- **RDW** – red cell distribution width - (an index of the variation in size of the erythrocyte population)
  - Often increased with regeneration – **Anisocytosis**
- **NOTE**: Not all macrocytic and hypochromic anemias are regenerative. Conditions other than regeneration can result in these changes

Polychromasia and regeneration

- Polychromatophils are immature, non-nucleated erythrocytes
- They are normally only present in relatively low numbers
- They represent the last stage of erythrocyte maturation following the loss of the nucleus, which typically takes place in the marrow
- Remaining RNA stains with Wright stain; NMB stain would make these *aggregate* reticulocytes
- Polychromatophils may be found in the peripheral blood film when there is increased demand for and increased production of RBCs

Other morphologic changes in regenerative anemias

- Rubricytes (nRBCs)
- Codocytes (target cells)
- Howell-Jolly bodies
- (nuclear remnant in cytoplasm)
  - Basophilic stippling

How long to regeneration?
  - Don’t forget there is a lag time for the bone marrow to respond
    - Production Time: 5-7 days
    - 3-5 days before significant reticulocytosis

Non-regenerative anemia
  - Lacks all of the above characteristics
  - Don’t forget that pre-regenerative anemias will be non-regenerative until the bone marrow has time to respond

Classifying anemia based on underlying pathology
  - Based on the major pathophysiological mechanism
  - Regenerative
    - Red blood cell loss
    - Red blood cell destruction (hemolysis)
  - Non regenerative
    - Failure of red blood cell production

Causes of hemorrhage
  - External blood loss
    - Trauma
    - Gastrointestinal bleeding
    - Bleeding from the urinary tract
    - Flea infestation
  - Bleeding into a body cavity
    - Hemoabdomen
    - Hemothorax
    - Other?

External blood loss
  - Trauma – HBC, dog attack etc.
  - Gastrointestinal bleeding
    - GI parasites
    - Gastric/duodenal ulcers secondary to RF
    - Ulcerated tumors in the gastrointestinal tract
    - Gastric/peptic ulcer disease
    - Coagulopathy (factors/platelets)
  - Bleeding into the urinary tract
    - Neoplasia
    - Coagulopathy (factors/platelets)
    - Other? (Idiopathic cystitis, Idiopathic renal hematuria)
  - External parasites

Internal blood loss
  - Bleeding usually occurs into the abdomen or thorax
  - Causes include:
    - Trauma
    - Underlying neoplasia
    - Coagulation factor abnormalities
    - Platelet abnormalities
Coagulation factor abnormalities
  o Acquired:
    ▪ Vitamin K antagonism with anticoagulant rodenticide toxicity (eating mice?)
    ▪ Vitamin K absence with cholestasis (intra- or extrahepatic bile duct obstruction)
    ▪ Vitamin K deficiency with GI disease, severe anorexia, liver disease
    ▪ Secondary to hepatic lipidosis/other acquired liver disease
  o Congenital
    ▪ Hemophilia (A,B and even C!)
    ▪ Cats with significantly elevated PTT but no bleeding tendency?
      • Factor XII deficiency

Platelet abnormalities
  o Thrombocytopenia
    ▪ IMT
    ▪ Various bone marrow disorders
    ▪ FeLV and FIV
    ▪ Platelet consumption disorders
    ▪ DIC, other disorders
  o Thrombocytopenias (platelet dysfunction)
    ▪ Acquired thrombocytopenias
    ▪ Uremia, other conditions
    ▪ Drug induced (e.g. NSAID therapy, various sedative and anesthetic agents)
    ▪ Hereditary thrombocytopenias
    ▪ vWD and Ehlers-Danlos syndrome (both uncommon in cats)

Hemolysis
  o Hemolysis is excessive breakdown of red blood cells
  o Causes of hemolysis include
    ▪ Infectious (red blood cell parasites)
    ▪ Heinz body hemolytic anemia (toxins)
    ▪ Immune mediated
    ▪ Severe hypophosphatemia
    ▪ Erythrocyte defects
    ▪ Red cell fragmentation

Feline hemotropic mycoplasma (FHM)
  o Organism formerly known as Haemobartonella felis
  o Currently, 3 species considered clinically significant in cats
    ▪ Mycoplasma haemofelis
    ▪ Candidatus Mycoplasma haemominutum
    ▪ Candidatus Mycoplasma turicensis
  o M. haemofelis and FeLV?
  o Hemolysis is usually:
    ▪ Extravascular
    ▪ It may or may not be Coombs positive
    ▪ Typically causes a regenerative anemia, but may be nonregenerative under certain circumstances
  o Disease ranges from overt and life-threatening hemolytic anemia to subtle chronic anemias
  o Nonclinical/subclinical carriers are common
  o Spread by:
    ▪ Fleas (ticks and lice also?)
    ▪ Biting and aggressive behavior
    ▪ Blood transfusions
- From infected queen to kittens
  - Risk factors for infection: gender, age, season, lifestyle, other

**Diagnosis of FHM**
- Traditionally:
  - Identification of organisms in erythrocytes on blood smear
  - Sensitivity poor; often missed
  - Specificity poor; often misidentified e.g. stain precipitate
- Response to therapy
  - Not sure what is being treated
  - Delay in appropriate therapy if not FHM
- Currently:
  - We use PCR (Polymerase Chain Reaction) to detect organism nucleic acid
  - An enzyme ("DNA polymerase") is used in a series of *chain reactions* to copy a specific portion of DNA
  - This allows amplification of a minute amount of DNA to an amount that can be detected and analyzed

**Cytauxzoonosis**
- Caused by *Cytauxzoon felis*
- Transmitted by a tick vector
- Usually (but not always!) fatal
- Prepatent period is between 2 to 3 weeks
- Most cases presented from March through September
- Rapid course of severe illness
  - High fever
  - Icteric
  - Anemia (may be mild compared to the degree of icterus)
  - Thrombocytopenia
- Parasitized RBCs observed late in disease, during febrile episodes
- Treatment is imidocarb (two injections, one to two weeks apart)

**Heinz body anemia**
- Clumps of denatured hemoglobin
- Variable color with different stains
- Secondary to diseases (e.g. hyperthyroidism, CRF, diabetes mellitus, lymphoma)
- Due to toxins (e.g. onion or acetaminophen ingestion, propofol)

**Other causes of hemolysis**
- **Immune-mediated**
  - Primary IMHA uncommon in cats
  - Usually secondary to infections, neoplasia, drugs, or vaccines
  - Neonatal isoerythrolysis
- **Severe hypophosphatemia**
  - DKA with insulin therapy
  - Starvation-refeeding syndrome (hepatic lipidosis)
- **Erythrocyte defects**
  - PK deficiency, porphyria, osmotic fragility
- **Fragmentation (microangiopathic)**
  - DIC
  - Vasculitis
  - Hemangiosarcoma
  - Feline heartworm disease
Non-regenerative anemia
- Bone marrow disorder
- Erythropoietic disorder
- Rule out pre-regenerative anemias first

Bone marrow disorders
- Leukemias/Lymphomas
- Myeloproliferative disorders
  - Involves nonlymphoid cells
  - Leukemias, primary thrombocythemia, polycythemia vera
- Aplastic anemia
  - FeLV, FIV, estrogen, drugs
- Myelofibrosis
  - Excess fibrous connective tissue and collagen laid down in marrow
  - Cause is often unknown
- Myelodysplasia
  - Maturation defects

Erythropoietic disorders
- Anemia of inflammatory disease
  - Could be due to any inflammatory process
- Decreased erythropoietin
  - Renal failure
- Autoimmune disease
  - vs. erythroid stem cells
- Cytotoxic bone marrow damage
  - Chemotherapy drugs, estrogen
- FeLV infection
  - Selectively damages erythroid cells
- Nutrient deficiencies
  - Iron, folate and/or cobalamin

Overview of feline anemia:

The CBC:
- Perform comprehensive CBC with blood film review (plus biochemistry screen and assessment of retroviral status)
- Characterize severity of anemia and correlation to clinical picture
- Determine if anemia is regenerative or nonregenerative
- If regenerative, look for bleeding (external and internal)
- If regenerative and no obvious bleeding, consider hemolytic disease
- If hemolytic disease suspected, review retroviral status, history for possible toxin exposure, blood film morphology, test for infectious agents (FHM, *Cytauxzoon felis*)
- If nonregenerative, review retroviral status, assess renal function, investigate for evidence of inflammatory illness, perform FHM PCR test and consider bone marrow aspirate/biopsy

Beyond the CBC:
- Fecal examination
- Imaging tests
  - Radiographs
  - Ultrasound
- Endoscopy
- Coagulation testing
- Retrovirus testing
Test for Feline Hemotropic Mycoplasma

Beyond the CBC – The Bone Marrow Aspirate

- Bone marrow aspirate
  - Usually sufficient in most clinical cases
  - Bone core biopsy may be required
  - Thrombocytopenia is NOT a contraindication for BM aspiration!
  - When drawing back on the syringe, STOP as soon as you see blood coming into the needle hub!
  - If no anticoagulant in needle hub or syringe, make BM slides immediately
  - If anticoagulant is used, pick out marrow particles and make gentle squash preps within one hour of collection
  - Evaluate one or two slides (not the best ones!) for marrow islands

- Bone core biopsy
  - Similar landmarks, but require a Jamshidi marrow biopsy needle

The BM Aspirate – what can it tell us?

- Neoplasia
- Myelophthysis
- Myelofibrosis
- Erythroid hypoplasia
- Aplastic anemia
- Inappropriate cell line regeneration
- Marrow dysplasia
- Erythrophagocytosis
- Occasionally infectious agents
- Iron deficiency
- Iron sequestration
- Always send concurrent CBC for best marrow interpretation!