

Practical Hematology Non-Regenerative Anemias

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August 28-19, 2010

Practical Hematology

1. Determining the cause of anemia
2. Treating regenerative anemias
 - Blood loss
 - Hemolysis
3. **Treating non-regenerative anemias**
4. Blood & plasma transfusions in general practice
5. Determining the causing of coagulopathies
6. Treating coagulopathies in general practice
7. Finding the source of leukocytosis
8. Bone marrow sampling

Non-Regenerative Anemia

Etiologies

- Lack of iron (not due to blood loss)
- Lack of erythropoietin
- Lack of bone marrow cellular precursors
- Maturation abnormalities
- Anemia of chronic inflammation
 - Moderate non-regenerative anemia can be explained by signs of inflammation and systemic illness

Non-Regenerative Anemia

1. Absolute Reticulocyte Count

- $RBC/ul \times \% \text{ retics} = ARC$
- Non-regenerative $<50,000/ul$
- $>80,000/ul$ is a moderately regenerative response
- **Automated counts are not always reliable**
- **This is the preferred single index for assessing regenerative response**

If you can't calculate an absolute retic count, then corrected retic % (CRP) is second best

Non-Regenerative Anemia

2. Corrected Percent Reticulocytes

- If you don't know the RBC and can not calculate absolute retics, you can still correct retic % for anemia

$$\% \text{ retics} \times \frac{\text{patient PCV}}{\text{normal PCV}}$$

Cat normal PCV = 37%, Dog normal PCV = 45%

- $<0.5\%$ is non-regenerative
- $>1\%$ is a regenerative response

Non-Regenerative Anemia

3. Consider the erythropoietin (EPO) level

- The lower the HCT, the higher the EPO level should be
- Renal disease can be associated with inappropriately low EPO levels
- **EPO has four effects:**
 1. Stem cells differentiate to erythroid
 2. Decreases RBC maturation time
 3. Increases Hb per RBC
 4. Premature release of reticulocytes from bone marrow to blood

Non-Regenerative Anemia

Corrected Absolute Reticulocytes

$$\frac{\text{absolute retics}}{\text{retic circulation time}} \times \frac{\text{patient PCV}}{\text{normal PCV}}$$

Cat normal PCV = 37%, Dog normal PCV = 45%

Dog PCV	Cat PCV	Retic Circ Time (days)
45	32	1
35	24	1.5
25	16	2
15	10	2.5

<50,000 is non-regenerative

>80,000 is significantly regenerative

Diagnostics for Nonregenerative Anemia

- Make sure anemia has been present for at least 1 week before assessing regenerative response
- Bone Marrow Sampling
- EPO levels
- Iron testing

Lack of Erythropoietin

- **Renal Disease**
 - Lack of EPO production
- **Endocrinopathy**
 - Hypothyroidism – most common
 - Addison's disease
 - Growth hormone deficiency

Renal Disease – Poor EPO Production

- **Absolute reticulocyte count**
 - Less than 50,000/ul
- **Bone Marrow**
 - normal
- **Iron stores**
 - Usually normal
 - Iron may be redistributed to macrophages in bone marrow if chronic bleeding due to GI ulceration (iron deficiency anemia)
- **EPO levels**
 - Normal to modestly reduced
 - Lower in cats with CRF than in dogs
- **Uremic toxins suppress bone marrow activity (PTH)**

Renal Disease – Poor EPO Production

- **Treatment**
 - Treat renal disease
 - Human recombinant erythropoietin (extralabel)
 - 100 U/kg SC 3x weekly until PCV low-normal, then 1-2x weekly
 - Procrit, Epogen
 - Reserve for HCT <25% in dogs and <20% in cats
 - Correct iron deficiency first if present
 - Takes a few weeks to a few months for antibodies to develop
 - Sudden severe anemia may mean antiEPO antibodies have developed
 - Transfuse and stop EPO

Endocrinopathy

- **Decreased tissue oxygen consumption causes moderately low EPO levels**
- **Absolute reticulocyte count**
 - Less than 50,000/ul
- **Bone Marrow**
 - normal
- **Iron stores**
 - Serum iron decreased
- **EPO levels**
 - modestly reduced
- **Anemia resolves after 3-4 months of thyroxine therapy**
 - Less common with Addisons

Iron Deficiency Anemia

- **IDA becomes non-regenerative only if chronic blood loss is prolonged and severe, or if diet is lacking in iron**
- **Mother's milk contains little iron**
 - Neonates susceptible to non-regenerative IDA due to parasitism
- **Tissue iron stores depleted**
 - Liver, spleen, bone marrow
 - Soluble – ferritin
 - Insoluble – hemosiderin
- **Plasma transport to RBC Hb**
 - Transferrin (TIBC) increased
 - Copper helps transport iron across cell membranes

Iron Deficiency Anemia

- **Blood Smear**
 - Microcytic, hypochromic anemia
 - nRBC
- **CBC**
 - Decreased MCV, MCH, MCHC
- **Iron stores**
 - Serum iron & ferritin decreased
 - Transferrin/TIBC normal to increased
 - Increased UIBC/decreased transferrin saturation
- **Bone marrow**
 - Depleted iron stores
 - mild erythroid response
- **EPO levels**
 - increased

Anemia of Chronic Inflammatory Disease

- **Mild to moderate anemia**
- **The most common anemia in small animals**
- **Can develop within 7-10 days**
- **Iron is sequestered in the macrophages**
 - Physiologic metabolic response to deprive infectious organisms of iron
 - Apolactoferrin secreted by neutrophils
 - Chelated iron, especially at low pH of inflammation
 - Macrophages have lactoferrin receptors that internalize the chelated iron
 - Results in diversion of iron from ferritin (soluble) to hemosiderin (insoluble)

Anemia of Chronic Inflammatory Disease

- **Activated macrophages remove RBC from circulation**
- **Fever shortens RBC lifespan**
- **Iron stores**
 - Serum iron normal to decreased
 - Ferritin normal to increased
 - Transferrin/TIBC normal to decreased
- **Bone marrow**
 - **Increased hemosiderin in macrophages**
 - Lack of marked erythroid response
 - Myeloid hyperplasia

Anemia of Chronic Inflammatory Disease

- **EPO levels**
 - Normal to decreased
- **Treatment**
 - Treat underlying problem
 - Iron administration is of little help
 - EPO administration of little help

Pure Red Cell Aplasia

- **Severe anemia – PCV <20%**
 - Sometimes spherocytes and stomatocytes
- **Iron stores**
 - normal
- **Bone marrow**
 - Nearly absent erythroid precursors
- **Etiology**
 - FeLV
 - Immune mediated destruction of erythroid stem cells
- **Treatment**
 - Immunosuppression as for IMHA

Aplastic Anemia

- **Pancytopenia**
 - Pancytopenia often preceded by leukocytosis for several weeks
 - Neutropenia first
 - then thrombocytopenia
 - then anemia
- **Etiology**
 - Estrogen toxicity
 - Iatrogenic
 - Sertoli cell or granulosa cell tumor
 - Drugs
 - AZT, antineoplastics, azathioprine, phenylbutazone, TMPs, fenbendazole

Aplastic Anemia

- **Etiology**
 - Chloramphenicol causes mild, reversible nonregenerative anemia in dogs
 - Infection
 - Ehrlichia
 - Bacterial endotoxins
 - Aflatoxin B
 - Immune mediated – against stem cells
 - Idiopathic
- **Bone marrow**
 - Hypocellular bone marrow
 - May have myelonecrosis
 - Except plasmacytosis

Aplastic Anemia

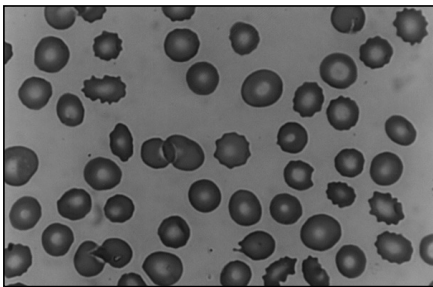
- **Treatment**
 1. Discontinue bone marrow toxins
 2. Doxycycline 5-10 mg/kg PO BID x 3 weeks
 3. If that fails, then immunosuppression
 - Prednisone 1 mg/lb/day
 - If not effective after 1-2 weeks, increase to 2 mg/lb/day x 1-2 weeks
 4. Prophylactic antibiotics
 - Amoxicillin 10 mg/lb BID if neutrophils 1500-2000/ul
 - add Baytril 5 mg/kg/day if neutrophils <1500/ul
 5. Avoid injury that can risk bleeding

WBC recover first, then platelets, then RBC

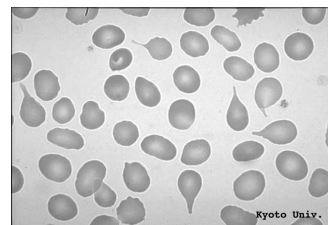
Myelophthisic Disease

- **Bone marrow has been replaced by something else**
 - Tumor cells
 - Fungal granuloma
 - Fibrous tissue
 - fat
- **Hemogram**
 - Normocytic, normochromic anemia
 - nRBC

Myelophthisic Disease



Myelophthisic Disease



- Poikilocytosis, dacryocytosis
- Large platelets or megaplatelets
- Leukocytosis with left shift

Myelophthisic Disease

- **Myelofibrosis**
 - neoplasia
 - Chronic sever hemolytic anemia
 - Congenital anemia
 - Idiopathic myelofibrosis
 - Nonregenerative anemia and thrombocytosis
 - Organomegaly due to EMH
 - Left shift in all 3 cell lines
 - Can not diagnose on bone marrow aspirate
 - Need bone marrow core biopsy

Myelophthisic Disease

- **Bone Marrow Neoplasia**
 - May or may not be associated with leukemia
 - Neoplastic cells in peripheral blood
 - Neoplastic cells found elsewhere
 - Liver, spleen, lymph nodes
 - Myeloproliferative neoplasia
 - Granulocytes and monocytic
 - "non-lymphoid leukemia"
 - Lymphoproliferative Neoplasia
 - Clinical Signs
 - Bone pain
 - Fever, infection, leukopenia
 - Anorexia, lethargy, vomiting, diarrhea
 - May progress to anemia and thrombocytopenia

Myelodysplasia

- **Also know as....**
 - Preleukemia
 - Subacute leukemia
 - dysmyelopoiesis
- **Many blast cells in the affected line**
- **But they don't mature in the usual way**
 - Neoplastic maturation arrest
 - Hyperplastic bone marrow with <30% blasts
- **Etiology**
 - drug induced
 - FeLV
 - idiopathic

Folate Deficiency

- **hemogram**
 - Macrocytosis (increased MCV)
- **B12 deficiency anemia not observed in dogs and cats**
- **Etiology folate deficiency**
 - Distal small intestinal disease
 - Prolonged TMPS administration
 - Increased requirements during pregnancy
- **Treatment**
 - Treat small intestinal disease
 - Supplement if giving TMPS for more than 30 days
 - Supplement during pregnancy

Feline Leukemia

- **Causes anemia in numerous ways**
 - AID by susceptibility to pathogens
 - Pure red cell aplasia
 - Aplastic pancytopenia
 - Hemolytic anemia due to hemoplasmas
 - IMHA
 - Myelodysplasia
 - Myelofibrosis

You can't treat FeLV anemia intelligently without a bone marrow

- **Hemogram**
 - Often macrocytic, normochromic
 - Megaloblastoic rubricytes
 - Usually non-regenerative

Treating FeLV Anemia

- **If myelodysplasia**
 - **EPO 100 U/kg SC 3x weekly until PCV low-normal, then 1-2x weekly**
 - **Prednisone 1-2 mg/lb/day, and taper over 60-90 days or more**
- **If regenerative anemia**
 - **Prednisone 1-2 mg/lb/day, and taper over 60-90 days or more**
 - **Doxycycline 5-10 mg PO BID x 3 weeks**
- **Antibiotics for infection, or if Neutrophils <1500/uI**

Sighthounds

Higher reference values – increased red cell mass

- HCT, Hb, RBC
- Also increased MCV (macrocytosis)

RBC life span half other dogs

- Normally 100-120 days
- Sight Hounds 50-60 days

Predisposed to Babesia infection

Differential Diagnosis

Macrocytic Anemia

Increased MCV

- **Regenerative anemia**
 - Blood loss
 - Hemolysis
- **Sighthound**
- **Folate deficiency**
- **Feline Leukemia infection**

Differential Diagnosis

- **Normocytic, normochromic anemia normal MCV, MCHC, MCH**
- **Acute Blood loss or Hemolysis**
- **Most non-regenerative anemias**
 - Anemia of chronic inflammatory disease
 - Renal disease
 - Endocrinopathy
 - Bone marrow failure
 - Immune response against marrow cells

Differential Diagnosis

Microcytic anemia

- **Microcytic but not hypochromic**
 - Akita, Shiba Inu, Chow chow
 - Puppies
 - **Dyserythropoiesis of Springer Spaniels** (polymyopathy, cardiac)
 - Chloramphenicol toxicity
- **Iron deficiency anemia**
 - Hypochromic
 - Low MCV, MCHC, MCH
 - Copper deficiency
- **Liver disease**
 - Especially portosystemic shunt

Differential Diagnosis

Spherocytes

- **IMHA**
- **Pure Red Cell Aplasia**
- **Hypophosphatemia**

Schistocytes

- **Microangiopathy**
- **DIC**
- **RBC fragility**
 - Congenital
 - Zinc toxicity
 - Iron deficiency

Differential Diagnosis

Chart