Anemia in Chronic Kidney Disease

JULIE DANNER, DVM
SMALL ANIMAL INTERNAL MEDICINE RESIDENT
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Anemia in Chronic Kidney Disease

- Estimated that 30-65% of cats and up to 71% of dogs with CKD develop anemia
- Prognostic? YES
  - Anemia → tissue hypoxia → adaptive mechanisms
- Quality of life issue? YES
  - Clinical signs – lethargy, exercise intolerance, decreased appetite

Outline

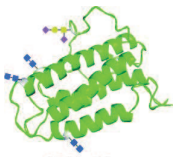
- Mechanisms
  - Decreased erythropoiesis
  - Shortened RBC survival
  - Increased RBC loss
- Management
  - Erythrocyte-stimulating agents (ESAs)
  - Iron supplementation
  - Transfusion medicine
  - Other
- Monitoring
  - CBC parameters
  - Iron testing

Mechanisms - Decreased Erythropoiesis

- Causes
  - **Lack of erythropoietin**
  - Inflammatory cytokines
  - Absolute iron deficiency
  - **Functional iron deficiency**
  - Uremic toxins
  - ACE inhibitors, angiotensin receptor antagonists, aluminum hydroxide
  - Hyperparathyroidism
  - Marrow fibrosis/inflammation

Erythropoietin

- Most important factor in anemia in chronic kidney disease
- Acidic glycoprotein, 30 kDa, 165 amino acids, four glycans
- Mainly produced by the peritubular interstitial cells in the inner medulla cortex and outer medulla of the kidney → less cells as kidney disease progresses
- Action of EPO can be augmented by several other hormones



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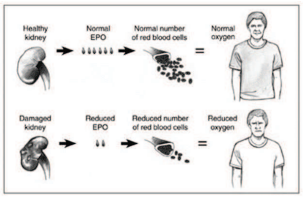
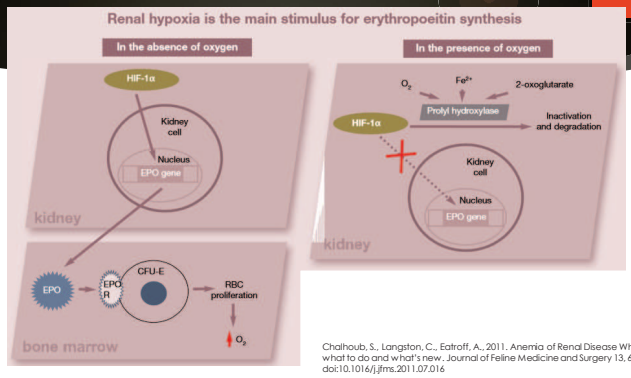
Erythropoietin

- Main stimulus for secretion = HYPOXIA
- Hypoxia → degradation of hypoxia-inducible factor 1α (HIF-1α) inhibited → HIF-1α free to bind to hypoxia-response elements of oxygen regulator genes → binding of HIF-1α stimulates an increased in production of erythropoietin
- Rate of production of erythropoietin is inversely proportional to the oxygen carrying capacity of blood



www.niddk.nih.gov



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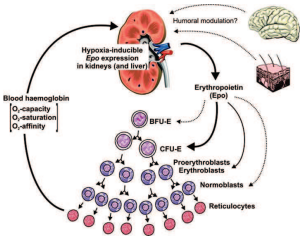
Erythropoietin

- Main site of action = BONE MARROW
- Binds to its receptor expressed on the surface of erythroid progenitor cells and lead to increased erythropoiesis
- Anti-apoptotic agent for erythrocyte progenitors
  - Mainly CFU-E
- Slow-acting process
- One main treatment target in anemia with CKD



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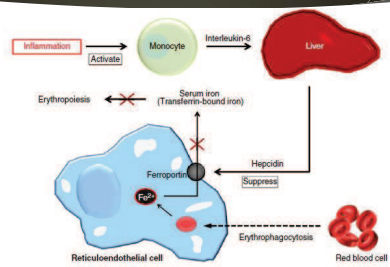
Mechanisms - Iron Deficiency

- Starts mainly with production of inflammatory cytokines
  - Both acute and chronic
  - Interferon-α, ß, γ; tumor necrosis factor-α, interleukin-1, interleukin-6**
  - Create a relative/fuctional iron deficiency by induction of hepcidin
- Hepcidin
  - Central regulator of systemic iron homeostasis
  - Acute phase protein
  - Produced by liver → stimulated by iron presence and inflammation
    - CKD increases hepcidin via decreased renal clearance
  - Suppressed by iron deficiency or erythropoietic activity

www.buzzle.com

Iron Deficiency



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Decreased Erythropoiesis – Other Factors

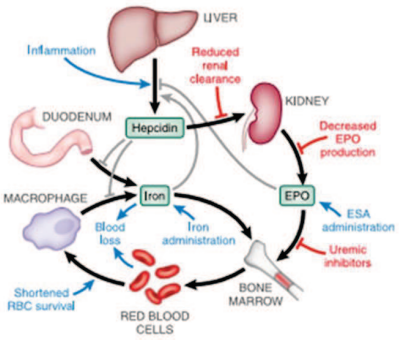
- Inflammatory cytokines
- Absolute iron deficiency
- Uremic toxins
- ACE inhibitors, angiotensin receptor antagonists, aluminum hydroxide
- Hyperparathyroidism
- Marrow fibrosis/inflammation

Mechanisms – Shortened RBC Survival

- Uremia - pathogenesis unclear
  - Possible low-grade hemolysis as uremia progresses
  - Increased lipid-peroxidation of the red blood cell membrane may occur as uremia progresses → premature clearance by the reticuloendothelial system

Mechanisms – RBC loss

- Uremia
  - Can affect platelets (uremic thrombocytopathy)
    - Manifests as GI bleeding, mucocutaneous bleeding, etc.
- GI blood loss
  - Gastric pathology common in dogs with CKD, but ulceration is uncommon
  - Gastrin: cleared by kidneys → elevated levels in people and cats with CKD, but gastric hyperacidity and ulcers are variably present
  - Key signs: anemia that is disproportionate to level of azotemia, unusual rapid decline in hematocrit, and an elevation in the BUN/creatinine ration
  - Trial with H2-receptor antagonist/sucralfate → increase hematocrit → supports diagnosis



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Management of Anemia - ESAs

- Erythrocyte-stimulating agents (ESAs)
  - Recombinant erythropoietin discovered in 1985
  - Multiple products available – epoetin alfa (Epogen), epoetin beta (Neo-Recormen), darbepoetin alfa (Aranesp) and continuous EPO receptor activators (Mircea)
  - Products vary in glycosylation
- Canine EPO – 81.3% homology
- Feline EPO – 83.3% homology

Management of Anemia - ESAs

- Due to possible complications, should only be used in pets with:
  - Fairly advanced CKD
  - Clinical signs attributable to anemia
  - Hematocrit values of <22%

Epoitin alfa - Epogen

- First ESA used in client-owned pets with naturally occurring CKD
- Starting dose 100 IU/kg SC three times weekly until PCV reaches target goal (>25% in cats)
  - Once reached, maintenance dose of 50-100 IU/kg twice weekly is needed
  - Response is usually seen in 3-4 weeks
- Cost: ~ $170/bottle (10,000 units)
  - Ex: 5 kg cat – would provide 20 100 IU/kg doses (approximately 2 months worth if target reached in 1 month)
    - $85/month
  - Ex: 25 kg dog – would provide 4 100 IU/kg doses
    - Two months worth = $850
    - $425/month

www.7daypharmacy.net

Darbopoieten (Aranesp)

- Developed in the 1990's
- Difference from Epogen?
  - Contains five N-linked carbohydrate chains → increases the amount of sialic acid chains → increased circulating half-life → administered less often!
- No published data on half-life in cats; in dogs has shown to have three-fold increase in half-life compared to Epogen
- No published dose information in companion animals

Darbopoietin

- Starting dose: 1.0-1.5 mcg/kg once weekly, then decrease to once every 2-3 weeks after target reached
  - 1 mcg of DPO = 200 units of EPO
- 100 mcg = $775
  - 5 kg cat: 100 mcg = 20 doses = ~9 months = $86/month (if giving every 2 weeks for maintenance)
  - 25 kg dog: 100 mcg = 4 doses = 1 month = $775 for first month, then $387/month if giving every 2 weeks

ESA Therapy - Monitoring

- Initially
  - Weekly PCV, reticulocyte count, blood pressure until stable
  - TARGET: <25% with 1-3% increase/week
    - Faster increase in PCV = more likely chance of hypertension
- Long-term monitoring
  - CBC, chemistry/renal panel, blood pressure and PE every 1-3 months depending on status of CKD
  - Patient parameters: strength, appetite, weight gain, TPR, etc.

ESA Complications - PRCA

- Pure red blood cell aplasia
  - Caused by production of anti-EPO antibodies that cross-react with ALL ESAs, as well as endogenous EPO
  - Rare in humans receiving ESAs (<300 cases worldwide)
    - Majority have been associated with the use of Epogen
  - Veterinary medicine – occurs in 25-30% of pets getting Epogen; <10% for darbopoietin
    - Anti-EPO antibodies are directed at the protein backbone
    - Complete lack of homology of canine and feline EPO to the ESAs is thought to be the cause of increased incidence of PRCA

Complications - PRCA

- Characterized by severe non-regenerative anemia with complete lack of bone marrow RBC precursors
  - Become concerned when the reticulocyte count and PCV are both decreasing
- Bone marrow aspirate – variable in companion animals
  - M:E ratios range from 4:1 – 299:1
- Treatment
  - Antibodies can persist for up to 8 months
  - Immediate cessation of ESAs, possibly initiation of immunosuppressive medication
    - No best protocol
  - Patients become transfusion dependent (can be required weekly)

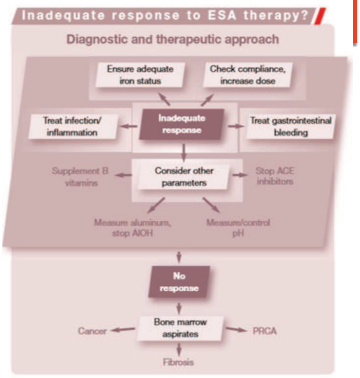
ESA Complications

- Hypertension
  - Side effect of EPO administration in 40-50% of dogs and cats; similar in darpopoietin
  - Reasons: Increased blood viscosity, improved cardiac output, reduced vasodilation as compensation for anemia, imbalance of vasoactive hormones with increased vascular response
- Seizures
- Iron deficiency
- Arthralgia
- Fever
- Polycythemia

ESA – Treatment Failure

- Defined as:
  - Significant decrease in hemoglobin level at a constant ESA dose
  - Significant increased in ESA dose to maintain hemoglobin level
  - Failure to raise the hemoglobin level to greater than 11 g/dl despite an ESA dose equivalent to greater than 500 IU/kg/week of Epogen or 1.5 mcg/kg/week of darbopoietin
- Must evaluate multiple parameters

- Iron deficiency
  - Present in 25-38% of anemic people with CKD and is the leading cause of failure to ESA treatment
  - Changes to the CBC are not sensitive indicators of iron deficiency
- Infection/inflammation
  - Have dramatic impact on erythropoiesis and EPO resistance
  - Thoroughly search for infectious complications (UTI, dental disease, etc.)
- If the PCV does not improve after checking these issues…
  - Address the less common issues (stop ACE inhibitors, check for primary hyperparathyroidism, etc)



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Management – Iron Supplementation

- Iron deficiency is the leading cause of treatment failure in humans receiving ESAs
  - SHOULD BE ADMINISTERED TO ALL PATIENTS RECEIVING ESAS!
- May represent…
  - Utilization of iron
  - Inadequate GI absorption
  - Sequestration of iron in storage sites
- Evaluation of serum iron parameters should be monitored at the start of ESA therapy and then monthly (MCV and MCHC not reliable tools as they can be decreased with BOTH absolute and relative iron deficiency)
  - True iron deficiency: Low serum iron*, low ferritin*, low TIBC, low % saturation
    - Serum ferritin and serum iron are the best indicators of total body iron stores in cats

Management – Iron Supplementation

- Supplementation
  - IM injection of iron dextran (50 mg/cat) should be provided at the time of the injection and then monthly
  - Oral iron (ferrous sulfate) : 50-100 mg/cat of elemental iron q24h
    - Pet-Tinic has 12.5 mg elemental iron per 5 ml
    - Tablets range from 35-100 mg of elemental iron per tablet

www.entirelypets.com

Management - Other

- Transfusion therapy
  - Indicated when there is acute blood loss or when the patient has severe clinical signs of anemia
  - Disadvantages: immune reactions, donor-recipient incompatibility, reduced life-span of infused products in uremic patients, cost, **lack of long-term effectiveness**
- Anabolic steroids
  - Nandrolone and stanzolol have been used in humans
  - Overall not recommended

Management - Other

- Vitamin supplementation
  - Most kidney diets are sufficient in vitamins, though anorexia can make levels low
  - B-vitamins (B12, folic acid, niacin, and pyridoxine) are necessary for erythropoiesis
  - L-carnitine
    - May increased CFU-E and stimulation erythropoiesis
    - Deficiency common in people on dialysis
    - No data on cats with CKD

www.iherb.com

Future Directions?

- Oral prolyl hydroxylase inhibitor
  - Prevents degradation of HIF-1α → enhances native EPO production
- Canine recombinant erythropoietin
  - JVIM 2004
  - Used canine recombinant EPO for dogs with CKD and in dogs that had PRCA from human recombinant EPO
  - Appeared to be safe alternative
    - Dogs followed for 1 year with no evidence of PRCA
    - Was NOT effective in restoring erythropoiesis in dogs with PRCA from human recombinant EPO
  - Patent submitted in 2009?
- Oral darbopoeitin?

Questions?

Feel free to contact:
Julie Danner, DVM
Email: Jdanner2@illinois.edu

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