Anemia To Blood Doping: Hematological Issues In Athletes

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I have no commercial, financial, or research relationships or interests within the past 12 months that affect my ability to provide a fair and balanced presentation for the proposed CME activity.
OUTLINE

- Laboratory Evaluation of Anemia
- Sports Anemia (Dilutional Pseudo-Anemia)
- Iron Deficiency Anemia
- Foot Strike Hemolysis
- Sickle Cell Trait
What Is Ideal Hematocrit?

- ~ 40% for a long life?
- ~ 50% to win the big marathon?
- ~ 60% to climb Mt. Everest without an oxygen tank?
- ~ 60% to die from blood doping?
Who Gets Anemia?

- Heavy menses
- Vegetarian
- Calorie cutter
- Breakfast skipper
- Sky-high carb diet
Work up for Anemia

- Detailed history
  - Symptoms of: fatigue, sob, decreasing performance, palpitations, tachycardia, pica
  - GI, urinary bleeding
  - Menstrual history
  - Nutritional practices
  - Training
  - Use of medications
Physical Exam

- Resting bp, pulse, orthostatics
- Skin – pallor, jaundice
- Cardiopulmonary
- Abdominal
- Possibly rectal exam
Laboratory Studies

- Hemoglobin/Hct including MCV, MCH
- Reticulocyte count <2%
- Possible smear – for abnormal cells
- Serum iron, ferritin
- Total iron-binding capacity/transferrin
- LDH, bilirubin, haptoglobin
- Possibly further GI/GU evaluation
- Consider CRP, ESR, TSH, electrophoresis if ruling out other dz
Sports Anemia

- Also called “Dilutional Pseudoanemia”
- Not true anemia
- Increased plasma volume in response to exercise
  - Increase in aldosterone, renin, ANF, vasopressin
  - increased renal retention of water and salts
  - Increase in plasma proteins
  - Increased hydration
Sports Anemia

- Endurance athletes mainly
- Expanded plasma volume
- Dilutes Hgb down 1.0-1.5 g/dl
- In men, most common “anemia”
- Waxes and wanes with training
- Benefit, not a detriment
Iron Deficiency Anemia

- #1 Nutritional Deficiency in U.S.
  - Iron Deficiency ~ 11% of women
  - Iron Deficiency Anemia 1-2% adults
- #1 cause of Anemia in Athletes
  - Up to 12.5% of athletes
- ↓ Dietary intake
- Menstruation
- ↑ Loss from other sources (GI, GU, hemolysis, sweating)
- ↓ Absorption
Iron Deficiency Anemia

- Hg <12 g/dL (36 Hct) Female
- Hg < 14 g/dL (42 Hct) Male
- MCV < 75
  - (if < 60 consider hemoglobinopathy)
- Ferritin <12
- Low Serum Iron w/ High TIBC
- High Hg – think doping/steroids
Iron Deficiency Anemia

- **Stage 1** - “prelatent anemia”
  - Depleted Iron Stores
  - ↓Ferritin NL-TIBC/Iron NL-HCT

- **Stage 2** - “iron-deficient erythropoiesis”
  - above plus ↓Ferritin ↑TIBC ↓IRON, Mild ↓HCT
  - Normocytic to mildly microcytic, mild Hypochromic

- **Stage 3** - overt Microcytic and Hypochromic anemia
  - ↓Ferritin ↑TIBC ↓IRON ↓HCT
Gastrointestinal Hemorrhage in Athletes

- Particularly in distance runners, triathletes
- Following endurance events stool occult positive 13-85%
  - Overt hematochezia was reported in 6%
- Increased blood loss with increased intensity
- Mixed results on increased blood loss with concurrent use of NSAIDs
- Blood loss can be trivial to severe
Gastrointestinal Hemorrhage in Athletes

- **Visceral ischemia** due to decreased splanchic perfusion
- **Gastritis** and **esophagitis** most frequently noted abnormalities on endoscopy – but also cases of small bowel and colonic ischemia
  - Exercising at 70% of VO2 max reduces blood flow to the gastrointestinal tract by 60-70%; more intense exercise may cause reductions in excess of 80% - worsened by dehydration
  - Up and down motion of running appears to be risk factor - ? Direct trauma to viscera
Genitourinary System Losses

- Exercise-induced hematuria
- Typically microscopic
- Usually resolves within a few days of event
- Renal causes
  - Renal vasoconstriction
  - decreased renal plasma flow with damage to nephron
  - direct trauma to GU system
- Intravascular hemolysis causing hemoglobinuria
Iron Deficiency Anemia - Impact on Performance

- Reduction in aerobic capacity, endurance and energetic efficiency due to decreased oxygen delivery
- Correction of anemia with iron supplementation improves performance
- ? No improvement in performance shown with iron supplementation in nonanemic, iron-deficient athletes
Iron Deficiency Anemia - Treatment

- Discuss Dietary consumption
  - Males require 10mg/day, female 15mg/day
  - Heme iron (meats) more bioavailable (10-35%) vs non-heme iron (2-5%)
  - Handouts/Websites - www.fwhc.org/health/iron.htm

- Consider Iron Replacement
  - Stage 1&2?, Stage 3 yes
Iron Replacement
need 150-200mg/day

- Ferrous vs Ferric
  - Ferrous is absorbed better
  - sulfate 325mg(65mg)
  - gluconate 325mg(36mg)
  - Replace w/ palatable forms
  - Increased absorption w/ Vitamin C (Ascorbic Acid)

- GI side effects
  - Take w/ food (but can ↓absorp up to 65%)

- Do not use enteric coated forms (do not dissolve in stomach)

- Drug Interactions (H2 blockers, PPI, tea and coffee tannates, Caffeinated drinks)
Iron Deficiency Anemia - Treatment

- Re-evaluate
  - CBC in 1 month
  - Reticulocytes and MCV increase first
  - If HCT not up despite therapy – consider further evaluation

- Replaced Iron stores complete when Ferritin = 50

- Can take 4-6 months to treat then maintenance therapy
To Prevent Anemia

- Lean red meat
- No coffee at meals
- OJ with breakfast
- Iron cookware
- Mixed meals
- Supplements

Intravascular Hemolysis

- Also called “Foot Strike Hemolysis”
  - Caused by RBC destruction from repeated trauma
- Elevated temperature in muscle, turbulence and acidosis may also be involved

Robinson et al, MSSE 38:480-83, 2006
Foot Strike Hemolysis
Diagnosis

- ↑ Bilirubin
- ↓ Haptoglobin
- ↑ Schistocytes
- Slight ↑ MCV & Reticulocytes
  - Preferential breakdown of older rbcs
- Hemoglobinuria
- Anemia resolves w/ d/c exercise

Foot Strike Hemolysis
Treatment

- Change Shoes
- Change Running Surfaces
- Modification of Training Program

- Search for other causes of hemolysis
  - Drugs (ABX, INH)
  - Acute Illnesses (Mycoplasma, Mono, Sepsis, Viral)
  - Chronic Illnesses (Autoimmune)
  - Heredity (G6PD, Thalassemia, Sickle Cell)
Intravascular hemolysis in non-foot strike sports

- Swimmers
  - Compression from contracting muscles
- Cyclists, other sports
  - ? Increase in body temperature may increase red cell turnover
  - oxidative and osmotic stress
Sickle Cell

- Inherited disease of abnormal hemoglobin S
  - Polymerizes under physiologic stress = destruction of rbcs
- Sickle disease – usually incompatible with participation in intense physical activity
- Sickle Trait - Heterozygous state where Hgb S is present with Normal Hgb A in RBC
  - < 50% Hgb is Hgb S
  - Usually Asymptomatic w/ no anemia
  - Up to 8% of African Americans
  - 1/10,000 Whites
Sickle Cell Risks

- Gross hematuria
- Splenic infarction
- Exertional heat illness
  - Rhabdomyolysis
  - Heat stroke
  - Renal failure
- Idiopathic sudden death
- Physiologic changes associated with exercise
  - (Regional hypoxemia, acidosis, dehydration, hyperthermia) – all increase risk of sickling
Sickle Cell Trait

SPLENIC INFARCTION

- Rare in sickle cell trait – 47 reported cases
- Due to microvascular occlusion
- Severe Hypoxia - Elevations > 10,000 feet
- Descend to lower height, O2, hydration
Sickle Cell – Treatment/Prevention

- Train wisely
- Stay hydrated
- Avoid heat and elevation
- Rest when sick
- Report hematuria
- Respect pain – abdominal, muscles, cardiac
Blood Doping
Erythropoietin (EPO)

- Glycoprotein hormone regulating RBC production
- Produced by renal cortex (90%), brain, lung & uterus
- Binds to CFU erythroid stem cells in bone marrow
- EPO regulation controlled by gene on chromosome 7 with hypoxic inducible factor
- New circulating erythrocytes seen 1-2 days after EPO levels rise
Blood Doping

- Increasing the number of red blood cells in the body to increase the oxygen carried to muscle
  - Administration of blood, red blood cells, or related blood products
  - Erythropoietin (EPO) or rHuEPO
    - Stimulates bone marrow to produce red blood cells
Blood Doping

- 1968 Mexico City Olympics (Alt. 7300 ft)
  - Most endurance race winners from highlands
  - Athletes from high altitude had “thick blood”
- Elblom et al (1972)*
  - 3 men, 800ml autologous transfusion (4 weeks)
    - 13% increase in Hg
    - 9% increase in VO2max
    - Run time to exhaustion increase 23%
- 1976 Blood Transfusions Banned by IOC
- 1987 rHuEPO first available in Europe
- 1990 – IOC prohibited use of EPO

Blood Doping - Does It Work?

- **Performance Studies** - (Williams and Branch summarized study findings)
  - 7% increase in Hgb
  - 5% increase in VO2 max
  - 34% increase in time to exhaustion at 95% VO$_2$ max
  - 44 second improvement in 5 mile treadmill run time
Blood Doping - Side Effects

- Infections with transfusions
- Inhibit endogenous EPO production
- Increased viscosity of blood
  - Stroke, MI, venous thromboses, PE
  - HTN (direct relation to dose), CHF
Recombinant Human Erythropoietin (rHuEPO)

- rHuEPO isolated from Chinese hamster ovaries
  - SQ administration, 50-300 u/kg, 2-3/week
  - Hct increases noted after 2-6 weeks

- Clinical Applications:
  - treatment of anemias related to renal failure, chemotherapy, HIV infection, prematurity, hemoglobinopathies, autoimmune disease and malignancy

- Adverse Effects:
  - headache, fever, nausea, anxiety, lethargy
  - hypertension & hyperkalemia in dialysis population
  - hyperviscosity syndromes
  - Seizures and hyperkalemia (rare)
rHuEPO

- 1987-1991, 20 top European cyclists died unexpectedly, suspected EPO use
- 1998-2000, 18 more cyclists with suspected EPO use died of thromboembolic complications (PE, CVA, MI)

Ergogenic Effectiveness*
  - Hct increase from 43% to 51%
  - 7% increase VO2max
  - 9% increase in run time to exhaustion
  - Effects lasted up to 3 weeks after EPO stopped

Detection of rHuEPO Misuse

- 1990 rHuEPO banned by IOC, later USOC & NCAA
- Nearly identical in structure and metabolism to endogenous EPO form, rapid half life (24 hours)
  - Cleared from body within 2-3 days
- 1997 International Cycling Union created Hct cutoffs
  - Males (50%), Females (47%)
- 2000 Mathematical Model
  - measuring indirect blood markers associated with rHuEPO
  - Hb, EPO level, reticulocyte %, soluble transferrin
- 2000 Isoelectric Focusing & Immunoblotting
  - possible to separate rHuEPO and endogenous EPO based on differences in charge status of glycosylated side chains
  - rHuEPO slightly more acidic than EPO
  - Also able to detect Darbopoietin (rHuEPO analogue)
Detection of Blood Transfusion

- Advancement of rHuEPO testing, indirectly leads to a return to older practices of blood transfusion
  - Autologous transfusions currently undetectable
  - Homologous transfusions can be detected by flow cytometry after labeling RBC membrane proteins
    - Multiple RBC populations
    - Enhanced production of RBC line
Additional Blood-Boosting Methods

- **High Altitude Training / Altitude Tents**
  - In low pO2, Hg binds O2 more efficiently
  - Natural stimulus for erythropoiesis, over 3-4 weeks

- **Artificial Oxygen Carriers**
  - Hemoglobin Oxygen Carriers (ex. Hemopure)
    - No positive effect on endurance or VO2max*
    - Hypertension, GI hypertonicity, renal toxicity
  - Perfluorocarbons Emulsions
    - Synthetic liquid dissolves oxygen 100x greater than plasma, requires oxygen supplementation
    - Flu-like symptoms, thrombocytopenia, allergic reactions, hepatosplenomegaly, organ failure

Summary

- **Sports Anemia** – dilutional due to increase plasma volume
  - Rule out other causes
  - No treatment needed

- **Iron Deficiency Anemia**
  - Order appropriate labs
  - Evaluate nutritional intake
  - Evaluate for possible losses including GI, GU
  - Training adaptations

- **Hemolytic Anemia**
  - Order appropriate labs
  - Training adaptations

- **Sickle Cell Trait**
  - Higher risk for sickling crisis with heat, exertion, dehydration, altitude
References