ANEMIA AND INFLAMMATORY DISEASE

ACOI Meeting, San Francisco, October 2010

Naushira Pandya M.D., CMD
Professor and Chair
Department of Geriatrics
Director, Geriatrics Education Center
Nova Southeastern University College of Osteopathic Medicine
Ft. Lauderdale, FL
The Prevalence of Anemia in Older Adults Increases With Age

Aging and anemia

- Aging by itself is unlikely to cause anemia
- Anemia should always be investigated—may allow timely diagnosis of serious illnesses
- Aging may predispose individuals to anemia
  - Decreased hematopoietic reserve
  - Reduced absorption of essential nutrients
  - Decline in GFR and erythropoietin secretion
- Aging associated with increased concentrations of cytokines—inhbit erythropoiesis and response to growth factors
- Age may be associated with a relative erythropoietin deficiency

WHY IS ANEMIA IMPORTANT IN THE ELDERLY?

- Associated with
  - Frailty with decreased muscle strength\(^1,2\)
  - Mobility impairment\(^3\)
  - Falls and related fractures\(^4,5,10\)
  - Increased cardiac complications (LVH and CHF)\(^6,7\)
  - Depression\(^8\)
  - Cognitive impairment\(^9\)
  - Increased mortality\(^1\)

Theoretical model showing why anemia of aging may be self-maintained and may aggravate the manifestations of aging.

Balducci L. JAGS 51(Suppl):S1 2003
Mortality risk of anemia in the elderly

- Community based study of 755 people aged > 85 yr
- Risk of mortality in people with anemia over 5 yr:
  - Men: RR=2.29
  - Women: RR=1.6
- Mortality risk in persons with anemia was increased two fold
- Mortality from malignant disease or infections was higher in persons with anemia

Isaks G.J. et al. JAMA 1999;281:1714-1717
Anemia and adverse outcomes in older adults

ANEMIA

- Decreased Exercise Tolerance
- Decreased Cardiovascular Fitness
- Falls Instability
- Decreased Immobility
- Muscle Wasting

- Frailty
- Functional Loss
- Depression
- Increased care needs
- Institutional long-term care

• Anorexia, nausea
• Fatigue
• Cold intolerance
• Decreased activity level or endurance
• Increase in falls
• Dizziness
• Increased confusion
• Headache

SYMPTOMS MAY BE ATYPICAL IN THE ELDERLY
• **Possible Causes**
  - Failure of bone marrow to produce red-blood cells due to
    - Erythropoietin resistance
    - Cancer (hematologic and solid tumor)
    - Arthritis
    - Autoimmune (RA, SLE, vasculitis, sarcoidosis, IBD)
    - Chronic infections (TB, Osteomyelitis, chronic wounds)
    - Viral infections inc. HIV
    - Fungal and parasitic infections
    - Chronic kidney disease and inflammation
    - Chronic rejection after solid organ transplantation
  - Age-associated alterations in cytokine levels
    - (IL 6) and proinflammatory cytokines

**Anemia of chronic disease/chronic inflammation**
- Dysregulation of Iron Homeostasis
- Impaired Proliferation of Erythroid Progenitor Cells
- Blunted Erythropoietin Response

PathophysiologicaMechanisms
Underlying Anemia of Chronic Disease

Weiss and Goodnough. NEJM Mar 10, 2005
The role of HEPCIDIN in chronic anemia

The image depicts the regulation of iron metabolism in the context of chronic anemia. Key elements include:

- **Inflammation and infection** triggering the production of Hepcidin.
- **Dietary iron** and **duodenal absorption** of iron leading to higher transferrin levels.
- **Transferrin receptor** and **heme** acting as iron sources.
- **Ferritin** and **RBC precursors** as sites of iron storage and release.

Hepcidin, as a negative regulator, controls the release of iron from the liver and macrophages, and its levels are increased in response to inflammation and infection to limit iron availability.
Pathophysiological Mechanisms Underlying Anemia of Chronic Disease.

Weiss and Goodnough. NEJM Mar 10, 2005
Factors that aggravate anemia of chronic inflammation

- Bleeding episodes
- Vitamin deficiencies (e.g., of cobalamin and folic acid)
- Hypersplenism
- Autoimmune hemolysis
- Renal dysfunction
- Radio- and chemotherapeutic interventions
Serum Interleukin-6 and Hemoglobin as Physiological Correlates in the Geriatric Syndrome of Frailty  

S. Leng et al. JAGS Aug 2002

- Frailty determined by weight loss, fatigue, low levels of physical activity, grip strength and walking speed
- Frail subjects have evidence of inflammation and lower Hb (12.1 vs 13.9) and Hct levels
- Frail group had more diseases (4.3 vs 2.6)
- IL-6 and other proinflammatory cytokines inhibit hematopoiesis
• Low reticulocyte count
• Normocytic, normochromic anemia with normal or elevated iron stores
• Elevated sedimentation rate
• Elevated C-reactive protein
• Elevated Interleukin-6
• EPO level is not helpful

Diagnostic Criteria of ACI
Algorithm for the Differential Diagnosis among Iron-Deficiency Anemia, Anemia of Chronic Disease, and Anemia of Chronic Disease with Iron Deficiency

Weiss and Goodnough. NEJM Mar 10, 2005
<table>
<thead>
<tr>
<th>Blood Test</th>
<th>ACI</th>
<th>IDA</th>
<th>ACI + IDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>TIBC</td>
<td>↓</td>
<td>↑</td>
<td>LN or ↓↑</td>
</tr>
<tr>
<td>% Transferrin saturation</td>
<td>↓ or N</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ferritin</td>
<td>↑ or N</td>
<td>↓</td>
<td>↓ or N</td>
</tr>
<tr>
<td>Soluble transferrin receptor</td>
<td>N</td>
<td>↑</td>
<td>↑ or N</td>
</tr>
</tbody>
</table>

**Differentiating Iron-Deficiency Anemia From Anemia of Chronic Disease on the Basis of Lab Values**

ACI: anemia of chronic inflammation; IDA: iron-deficiency anemia; N: normal; LN: low normal; TIBC: total iron-binding capacity.
Adapted from Weiss
N=512 85 yr olds
34.8% male

The prevalence of anemia was 23.8%

Low ferritin associated with OR 2.2 for anemia

Low ferritin and high CRP associated with 7x risk of anemia

The predictive use of low ferritin in older persons with anemia, with and without inflammation; Leiden 85-plus study  
*JAGS Aug 2010*
- Blunted response documented in cancer and RA
- Evidence for response to EPO with advanced age varies

EPO response in the institutionalized elderly with anemia  

Drinka et al. JAGS Mar 2004
0.5% to 5% prevalence for overt hypothyroidism
5% to 20% for subclinical hypothyroidism in women aged 60 to 65 and older
N=316 inpatients (IM and Ger wards)
155 (49%) had anemia, mean Hb 10.7g/dL

20% with anemia had hypothyroidism vs.
9% without anemia had hypothyroidism
Hb levels improved with treatment of hypothyroidism

Screening for Hypothyroidism in older hospitalized patients with anemia
G. Vitlae et al. JAGS Sept 2010
Rationale

- Anemia can be deleterious in itself (especially to older pts with CAD, COPS, CKD)
- Associated with poor prognosis

- Treat or stabilize the underlying disease
  - Anemia may improve (e.g. anti-TNF antibodies in RA)

- Blood transfusion for severe anemia (<8 g/dL) or life-threatening anemia (<6.5 g/dL)
  - Increased survival after MI
  - Increased mortality though in critically ill

Treatment options of ACI
Iron therapy
- Poorly absorbed
- Low iron may be protective (reduces pathogens)
- Iron down regulates cellular immune function (may improve RA and IBD)
- Required for absolute or functional iron deficiency in conditions of intense erythropoiesis
- Not recommended for patients with anemia of chronic disease who have a high or normal ferritin level (above 100 ng per milliliter), owing to possible adverse outcomes in this setting

Treatment options of ACI
• Erythropoietic Agents
  ◦ Currently approved for use in cancer chemotherapy, CKD, and patients with HIV infection who are undergoing myelosuppressive therapy
  ◦ There is some response in patients with anemia of chronic disease (25% in MDS, 80% in multiple myeloma, up to 95% in RA with CKD)
  ◦ The therapeutic effect involves counteracting the antiproliferative effects of cytokines, along with the stimulation of iron uptake and heme biosynthesis in erythroid progenitor cells
  ◦ Long-term effects may be anti inflammatory in RA
  ◦ However, some malignant cell lines may have EPO receptors

Treatment options of ACI
Table 4. Therapeutic Options for the Treatment of Patients with Anemia of Chronic Disease.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Anemia of Chronic Disease</th>
<th>Anemia of Chronic Disease with True Iron Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of underlying disease</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Transfusions*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Iron supplementation</td>
<td>No</td>
<td>Yes†</td>
</tr>
<tr>
<td>Erythropoietic agents</td>
<td>Yes‡</td>
<td>Yes, in patients who do not have a response to iron therapy</td>
</tr>
</tbody>
</table>

* This treatment is for the short-term correction of severe or life-threatening anemia. Potentially adverse immunomodulatory effects of blood transfusions are controversial.
† Although iron therapy is indicated for the correction of anemia of chronic disease in association with absolute iron deficiency, no data from prospective studies are available on the effects of iron therapy on the course of underlying chronic disease.
‡ Overcorrection of anemia (hemoglobin >12 g per deciliter) may be potentially harmful to patients; the clinical significance of erythropoietin-receptor expression on certain tumor cells needs to be investigated.