Anemia in the Elderly

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“Anemia should not be accepted as an inevitable consequence of aging”

A cause is found in approximately 80 percent of elderly patients
Anemia: Geriatric Patients

- Common occurrence, although usually mild
- High prevalence in nursing homes - 31.4%
  - (a) anemias due to causes more common in the elderly;
  - (b) anemias without special predilection for the elderly;
  - (c) anemias of unknown cause (up to 17%)
Geriatric-Related Anemia

- Anemia of chronic disease
- Renal insufficiency
- Blood loss
- Bone marrow infiltration
- Nutritional deficiency
- Hemolysis
- Chemotherapy/radiation therapy
Etiologies of Nursing Home Anemia

The most common diagnosis was:

- anemia of chronic disease (65.6%),
- followed by anemia of chronic renal failure (13.2%)
- anemia primarily due to iron, vitamin B12 or folate deficiency was found to be only 4%.
- In 15.9% of these cases the main cause of anemia could not be resolved.

## Underlying Causes of Anemia of Chronic Disease

<table>
<thead>
<tr>
<th>Associated Diseases</th>
<th>Estimated Prevalence * percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections (acute and Chronic)</td>
<td></td>
</tr>
<tr>
<td>Viral / HIV</td>
<td>18-95</td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
</tr>
<tr>
<td>Parasitic</td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
</tr>
<tr>
<td>Cancer †</td>
<td>30-77</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td>8-71</td>
</tr>
<tr>
<td>RA</td>
<td></td>
</tr>
<tr>
<td>SLE/ CTD</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td></td>
</tr>
<tr>
<td>Chronic rejection after transplantation</td>
<td>8-70</td>
</tr>
<tr>
<td>Chronic kidney disease and inflammation</td>
<td>23-50</td>
</tr>
</tbody>
</table>

* Values shown are ranges. Epidemiologic data are not available for all conditions associated with the anemia of chronic disease. The prevalence and severity of anemia are correlated with stage of underlying condition and appear to increase with advanced age.

† The prevalence of anemia in patients with cancer is affected by therapeutic procedures and age. A high prevalence was reported in one study in which 77 percent of elderly men and 68 percent of elderly women with cancer were anemic. In another study, anemia was observed in 41 percent of patients with solid tumors before radio-therapy and in 54 percent thereafter.

Prevalence of Anemia in the U.S. Population

Data from the Third National Health and Nutrition Examination Survey (NHANES III)
NHANES III Survey

- The National Health and Nutrition Examination Survey [NHANES] is a population-based survey conducted by the National Center for Health Statistics to collect health and nutrition information on the U.S. population.

- NHANES III is the most recent survey with publicly available data:
  - 33,994 persons surveyed between 1988-1994
  - Designed to obtain nationally representative information
<table>
<thead>
<tr>
<th>Condition</th>
<th>Measure</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Serum ferritin ng/ml</td>
<td>&lt;15 ng/ml</td>
</tr>
<tr>
<td>Vitamin $B_{12}$ deficiency*</td>
<td>Serum $B_{12}$ pg/ml</td>
<td>&lt;200 pg/ml</td>
</tr>
<tr>
<td>Folate deficiency</td>
<td>RBC folate ng/ml</td>
<td>&lt;102.6 (MEC only)</td>
</tr>
<tr>
<td></td>
<td>Serum Folate ng/ml</td>
<td>&lt;2.6 (home only)</td>
</tr>
</tbody>
</table>

*Serum $B_{12}$ not available in phase I of NHANES III
## Distribution of Types of Anemia in Persons Age 50+

<table>
<thead>
<tr>
<th>Type of Anemia</th>
<th>Est. U.S. Population</th>
<th>% Anemic, Age 50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency only:</td>
<td>323,698</td>
<td>7.3%</td>
</tr>
<tr>
<td>Folate deficiency only:</td>
<td>238,385</td>
<td>5.4%</td>
</tr>
<tr>
<td>B12 deficiency only:</td>
<td>176,490</td>
<td>4.0%</td>
</tr>
<tr>
<td>Folate and B12 deficiencies:</td>
<td>59,806</td>
<td>1.3%</td>
</tr>
<tr>
<td>Iron with folate and/or B12 deficiencies:</td>
<td>100,697</td>
<td>2.3%</td>
</tr>
<tr>
<td>None of the above:</td>
<td>3,539,007</td>
<td>79.7%</td>
</tr>
</tbody>
</table>

Source: NHANES III, MEC + home exam population, Phase II only; excludes persons with null/blank Hb values
Normal Erythropoietin Production and Hemoglobin Levels

Anemia: Symptoms

- Fatigue
- Exhaustion (decreased energy)
- Weakness
- Impaired concentration
- Decreased cognition
- Respiratory distress
- Tachycardia

Leads to

- Impaired quality of life
- Diminished physical capacity

Do You Have Tired Blood?

Consequences of Geriatric Anemia
associated with:
- increased mortality
- poor health
- fatigue
- functional dependence
- falls
- can lead to cardiovascular and neurological complications

Anemia, Cancer, and Cognitive Impairment

- Anemia affects the young and elderly alike.
- Cancer and cancer treatment cause anemia and have been linked to cognitive impairment.
- Anemia can exacerbate cognitive deficits, particularly in the elderly.

Normal Erythropoiesis

RE = reticuloendothelial

Anemia: Cancer-Related Inflammatory Mechanism

AIS=anemia-inducing substance; TNF=tumor necrosis factor; EPO=erythropoietin; BFU-E=burst-forming unit erythroblasts; CFU-E=colony-forming unit erythroblasts.

Anemia of Chronic Disease

- Inflammation, neoplasia
- Blunted erythropoietin response
- Impaired iron utilization
  - Bone marrow stores adequate
  - Low serum iron

Differentiating IDA from ACD

- Serum ferritin level
- Soluble transferrin receptor level

Soluble transferrin receptor and soluble transferrin receptor-ferritin index for evaluation of the iron status in elderly patients

Serum Levels That Differentiate Anemia of Chronic Disease from Iron-Deficiency Anemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACD</th>
<th>FE (-)</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Transferrin</td>
<td>↓ / ↔</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ferritin</td>
<td>↔ / ↑</td>
<td>↓</td>
<td>↓ / ↔</td>
</tr>
<tr>
<td>Soluble transferrin receptor</td>
<td>↔</td>
<td>↑</td>
<td>↔ / ↑</td>
</tr>
<tr>
<td>Ratio of soluble transferrin receptor to Log ferritin</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cytokine levels</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
</tr>
</tbody>
</table>

Pathophysiologic Factors in Anemia of Chronic Disease.

- Pathologic Iron Homeostasis
- Impaired Erythropoiesis
- Blunted Erythropoietin Response
Pathologic Iron Homeostasis

<table>
<thead>
<tr>
<th>Key Factors</th>
<th>Mechanisms</th>
<th>Systemic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α or IL-1</td>
<td>Induces ferritin transcription</td>
<td>Hypoferremia, hyperferritinemia</td>
</tr>
<tr>
<td></td>
<td>Leads to a decreased erythrocyte half-life, mediated by TNF-α</td>
<td>Erythrophagocytosis</td>
</tr>
<tr>
<td>IL-6</td>
<td>Induces ferritin transcription or translation</td>
<td>Hypoferremia, hyperferritinemia</td>
</tr>
<tr>
<td></td>
<td>Stimulate formation of hepcidin</td>
<td></td>
</tr>
<tr>
<td>INF-γ or LPS</td>
<td>Stimulates DMT1 synthesis; down-regulates ferroportin 1 expression</td>
<td>Hypoferremia</td>
</tr>
<tr>
<td>IL-10</td>
<td>Induces transferrin-receptor expression; stimulates ferritin translation</td>
<td>Hypoferremia, hyperferritinemia</td>
</tr>
<tr>
<td>Erythrophagocytosis</td>
<td>Reduces erythrocyte half-life through increased uptake of erythrocytes damaged by TNF-α</td>
<td>Hypoferremia, anemia</td>
</tr>
</tbody>
</table>

DMT1 denotes divalent metal transporter 1, LPS lipopolysaccharide
# Impaired Erythropoiesis

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<tr>
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<th>Mechanisms</th>
<th>Systemic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF-γ, IL-1 or TNF-α</td>
<td>Inhibits proliferation and differentiation of CFU-E and BFU-E</td>
<td>Anemia with normal or decreased reticulocyte counts</td>
</tr>
<tr>
<td></td>
<td>Causes hypoferremia through diversion of iron to the RES</td>
<td>Anemia with increased levels of tetrapotoporphyrin</td>
</tr>
<tr>
<td></td>
<td>Induces formation of nitric oxide</td>
<td>Anemia with increased levels of levulinic acid</td>
</tr>
<tr>
<td>α-1-antitrypsin</td>
<td>Limits iron uptake by erythroid cells</td>
<td>Anemia</td>
</tr>
<tr>
<td>Tumor cells or microbes</td>
<td>Infiltrate bone marrow</td>
<td>Anemia, pancytopenia or both</td>
</tr>
<tr>
<td></td>
<td>Produce soluble mediators</td>
<td>Anemia, pancytopenia of both</td>
</tr>
<tr>
<td></td>
<td>Consume vitamins</td>
<td>Systemic deficiency of folate or cobalamin</td>
</tr>
<tr>
<td>Hypoferremia</td>
<td>Caused by cytokine-mediated diversion of iron into the RES and reduced iron absorption</td>
<td>Anemia</td>
</tr>
</tbody>
</table>

RES denotes reticuloendothelial system
## Blunted Erythropoietin Response

<table>
<thead>
<tr>
<th>Key Factors</th>
<th>Mechanisms</th>
<th>Systemic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin deficiency</td>
<td>Inhibits erythropoietin production by IL-1 and TNF-α</td>
<td>Decreased levels of circulating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>erythropoietin</td>
</tr>
<tr>
<td>Hypoferremia</td>
<td>Reduces erythropoietin responsiveness of progenitor cells</td>
<td>Anemia, hypoferremia</td>
</tr>
<tr>
<td></td>
<td>owing to iron restriction</td>
<td></td>
</tr>
<tr>
<td>INF-γ, IL-1, &amp; TNF-α</td>
<td>Impair responsiveness of progenitor cells to erythropoietin</td>
<td>Anemia</td>
</tr>
</tbody>
</table>

Geriatric-Related Anemias: Initial Evaluation

- Patient should be assessed for deficiencies
  - Iron (total iron-binding capacity, serum iron, ferritin)
  - Folate (serum homocysteine)
  - Vitamin B$_{12}$ (serum methylmalonic acid)
  - R/O renal insufficiency

- Treatment must be individualized
  - Correct nutritional and metabolic deficiencies
  - Treat underlying infections or inflammatory processes
  - R/O MDS
  - Manage hemolytic diseases, occult blood loss

NCCN. Available at: www.nccn.org.
Anemia
Biochemical or clinical evidence of inflammation
Transferrin saturation < 16
Rule out other causes of anemia
Ferritin
- Ferritin < 30 ng/ml
  - Iron deficiency anemia
- Ferritin 30-100 ng/ml
  - Determination of soluble transferrin receptor
    - sTfR/log ferritin > 2
      - Anemia of chronic disease with true iron deficiency
  - sTfR/log ferritin < 1
    - Anemia of chronic disease
- Ferritin > 100 ng/ml
  - Anemia of chronic disease

Randomized Placebo-Controlled Trial

Hgb=hemoglobin; SEM=standard error of mean.

Recombinant Human Erythropoietin: Indications in Cancer

- Anemia in cancer patients on chemotherapy
  - For treatment of anemia in nonmyeloid malignancies when the anemia is caused by chemotherapy
  - To decrease the need for transfusions in patients who will receive concomitant chemotherapy for a minimum of 2 months

- Not indicated for treatment of anemia caused by iron or folate deficiencies, hemolysis, or gastrointestinal bleeding

rHuEPO Treatment: Summary of Potential Benefits

- Increased hemoglobin concentrations
- Reduced need for transfusions
- Fewer adverse effects
- Outpatient treatment possible
- Improved quality of life
- Improved survival rate?

rHuEPO = recombinant human erythropoietin.
rHuEPO Treatment: Caveats and Drawbacks

- Effective in only 50% to 60% of patients
- Slow time to response
- Frequent injections – inconvenience
- Patient compliance
- Suboptimal response to rHuEPO may be related to iron deficiency and other factors
- Cost can be significant

rHuEPO = recombinant human erythropoietin.
Darbepoetin Alfa vs rHuEPO: Time to Hgb Response

95% confidence intervals for cumulative percentage of patients responding by week 13. Kaplan-Meier proportions; rHuEPO=recombinant human erythropoietin; Hgb=hemoglobin.


- Darbepoetin alfa 4.5 µg/kg/qw (n=29)
- rHuEPO 150 U/kg/tiw (n=53)

rHuEPO dose doubled for nonresponders. No darbepoetin-alfa dose increase allowed.
Aranesp® (darbepoetin alfa) in Anemia of Cancer: Summary of Safety

- Adverse events similar to those observed in cancer patients
- No safety issues associated with less frequent dosing
- No evidence of antibody formation to darbepoetin alfa
- Aranesp® was well tolerated beyond 12 weeks of treatment


<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>Aranesp®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>27%</td>
<td>17%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0%</td>
<td>16%</td>
</tr>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Limb Pain</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

Patients (%)

<table>
<thead>
<tr>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Aranesp®</td>
<td>Placebo</td>
<td>Aranesp®</td>
<td>Placebo</td>
<td>Aranesp®</td>
</tr>
</tbody>
</table>
Aranesp® (darbepoetin alfa) in Anemia of Cancer: Summary of Efficacy

- **Q4W Dosing**
- Hematopoietic response in up to 70% of patients
- Mean change in Hb at 6.75 mcg/kg Q4W dose of Aranesp®
  - 1.22 using the ITT approach
  - 1.38 g/dL using the completers’ analysis
- RBC transfusion rates for 6%-16%, compared with 21% for placebo group

Aranesp™ (darbepoetin alfa)
Chemotherapy-Induced Anemia

- Aranesp™ is contraindicated in patients with uncontrolled hypertension. Erythropoietic therapies may increase the risk of thrombotic and other serious events; dose reductions are recommended if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period.

- The most commonly reported side effects in Aranesp™ trials were fatigue, edema, nausea, vomiting, diarrhea, fever, and dyspnea; no important differences were observed between Aranesp™ and Epoetin alfa.

Summary

- Anemia is prevalent in geriatric patients with cancer as a result of:
  - Chemotherapy and radiation treatments
  - Chronic disease

- The impact of anemia has been underappreciated
  - Association between anemia and quality of life is well established
  - Potential impact upon outcomes

- Weekly dosing of epoetin alfa significantly improves Hb and quality of life

- Every other week Darbopoietin dosing more convenient

- The association between anemia, cognitive function, and survival is still being explored
Geriatric-Related Anemia: Effects of Erythropoietin

- ↑ Hemoglobin (p<0.001)
- ↓ Transfusions (p=0.0057)
- ↑ Quality of life (p<0.01)