UNEXPLAINED ANEMIA OF THE ELDERLY
Grand Rounds
Department of Medicine
Case Western Reserve University
and
University Hospitals Case Medical Center

October 18, 2011

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Hanna Payne Professor of Experimental Medicine
Professor, Medicine, Biochemistry, Genetics and Oncology
Director, Center for Science, Health & Society
Case Western Reserve University
WHO criteria for anemia

<table>
<thead>
<tr>
<th>Sex</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men:</td>
<td>&lt; 13.0 g/dL</td>
</tr>
<tr>
<td>Women:</td>
<td>&lt; 12.0 g/dL</td>
</tr>
</tbody>
</table>

World Health Organization, 1968
Changes of Hemoglobin in BLSA Participants

For Men:
- Age at Study Entry:
  - <30
  - 30-39
  - 40-49
  - 50-59
  - 60-69
  - 70-79
  - ≥80

For Women:
- Age at Study Entry:
  - <30
  - 30-39
  - 40-49
  - 50-59
  - 60-69
  - 70-79
  - ≥80

Courtesy L. Ferrucci.
Longitudinal Changes of Hemoglobin in Japanese Cohorts

Geriatric Outcomes And Anemia
Anemia in the Elderly

- Not a normal finding
- Morbidity Increased
- Mortality doubled
- Secondary to
  - Nutritional Deficiency (Iron, Folate, B-12)
  - Organ Failure (Kidneys, Liver)
  - Bone Marrow Infiltration
    - Myelodysplasia, Myeloma, Leukemia
  - Bleeding (Especially Gastrointestinal)
  - Inflammation (Other Malignancies)
  - Medications
- Blood Donation
- Unexplained Anemia of the Elderly
- Slow Response to replacement therapy

Prevalence of WHO Anemia Increases With Age

## Anemia in Geriatric Populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>% Anemic (WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guralnik J, et al</td>
<td>Community (NHANES III)</td>
<td>11%</td>
</tr>
<tr>
<td>Ble A, et al</td>
<td>Community (InCHIANTI)</td>
<td>10%</td>
</tr>
<tr>
<td>Arch Intern Med. 2005;165:2222-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ershler W, et al</td>
<td>Community, Internal Medicine practices</td>
<td>27%</td>
</tr>
<tr>
<td>unpublished</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joosten, et al</td>
<td>Hospitalized</td>
<td>24% (&lt;11.5)</td>
</tr>
<tr>
<td>Gerontology 1992; 38:111-117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinson, et al</td>
<td>Nursing Home (NGRC)</td>
<td>60%</td>
</tr>
<tr>
<td>JAGS 2007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WHO: Hb < 13 g/dL for men, < 12 g/dL for women
Racial/Ethnic Variation in Anemia in the Elderly

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Men, %</th>
<th>Women, %</th>
<th>Total, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>9.2</td>
<td>8.7</td>
<td>9.0</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>27.5</td>
<td>28.0</td>
<td>27.8</td>
</tr>
<tr>
<td>Mexican American</td>
<td>11.5</td>
<td>9.3</td>
<td>10.4</td>
</tr>
<tr>
<td>Other</td>
<td>20.4</td>
<td>7.5</td>
<td>14.0</td>
</tr>
<tr>
<td>Total</td>
<td>11.0</td>
<td>10.2</td>
<td>10.6</td>
</tr>
</tbody>
</table>

Anemia in the Elderly is Associated with Substantial Morbidity

- Frailty\(^1\)
- Depression\(^2\)
- Decreased physical performance\(^5\)
- Decline in physical performance\(^3\)
- Recurrent falls\(^4\)
- Increased disability\(^5\)
- Increased hospitalization\(^6\)
- Cognition
- Mortality\(^7\)

\(^1\) Chaves, P. et al. J Geront, 2005; 60A: 729.  
\(^7\) Chaves et al. JAGS 2004. 52: 1811-1816.
Anemia and Cognition: Impaired Executive Function in Mildly Anemic Community-Dwelling Women Aged 70 to 80

Cumulative Incidence of Mobility Disability by WHO-defined anemia status among race-sex subgroups of older adults

Kaplan-Meier survival curves by WHO-defined anemia status among race-sex subgroups of older adults.

### Distribution of Anemia Subtypes, NHANES III

<table>
<thead>
<tr>
<th>Anemia</th>
<th>No. in the United States</th>
<th>Type, %</th>
<th>All anemia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With nutrient deficiency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron only</td>
<td>467 000</td>
<td>48.3</td>
<td>16.6</td>
</tr>
<tr>
<td>Folate only</td>
<td>181 000</td>
<td>18.8</td>
<td>6.4</td>
</tr>
<tr>
<td>$B_{12}$ only</td>
<td>166 000</td>
<td>17.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Folate and $B_{12}$</td>
<td>56 000</td>
<td>5.8</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Iron with folate or $B_{12}$ or both</strong></td>
<td>95 000</td>
<td>9.9</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>965 000</td>
<td>100.0</td>
<td>34.3</td>
</tr>
<tr>
<td><strong>Without nutrient deficiencies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency only</td>
<td>230 000</td>
<td>12.4</td>
<td>8.2 (33%)</td>
</tr>
<tr>
<td>ACL no renal insufficiency</td>
<td>554 000</td>
<td>30.0</td>
<td>19.7</td>
</tr>
<tr>
<td>Renal insufficiency and ACL</td>
<td>120 000</td>
<td>6.5</td>
<td>4.3</td>
</tr>
<tr>
<td>UA</td>
<td>945 000</td>
<td>51.1</td>
<td>33.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1 849 000</td>
<td>100.0</td>
<td>65.7</td>
</tr>
<tr>
<td>Total, all anemia</td>
<td>2 814 000</td>
<td>NA</td>
<td>100.0</td>
</tr>
</tbody>
</table>

NA indicates not applicable.

Anemia of Aging

- Anemia is an independent predictor of morbidity and mortality in the elderly
- NHANES III study:
  - Incidence of anemia over age 65
    - Men 11%
    - Women 10%
  - Etiology of anemia
    - 1/3 patients with nutritional deficiencies
    - 1/3 patients with anemia of chronic inflammation (ACI)
    - 1/3 patients with “unexplained anemia” (UA)
- Incidence of anemia exhibits wide ethnic disparity
  - 3X higher in non-Hispanic blacks vs. non-Hispanic whites
# Laboratory Studies

## Routine

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, smear, retic</td>
</tr>
<tr>
<td>Fe, TIBC, ferritin</td>
</tr>
<tr>
<td>TSH, B12, Folate</td>
</tr>
<tr>
<td>Estimated GFR</td>
</tr>
<tr>
<td>Liver Tests</td>
</tr>
<tr>
<td>CRP</td>
</tr>
<tr>
<td>Serum EPO</td>
</tr>
</tbody>
</table>

## As Indicated

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal occult blood</td>
</tr>
<tr>
<td>Haptoglobin, Coombs</td>
</tr>
<tr>
<td>SPEP, UPEP</td>
</tr>
<tr>
<td>MMA, Homocysteine</td>
</tr>
<tr>
<td>Testosterone</td>
</tr>
<tr>
<td>Hb Electr., alpha thal</td>
</tr>
<tr>
<td>PCR</td>
</tr>
</tbody>
</table>
# Criteria For Common Anemia Etiologies

## Table 2. Prospective Definitions of Anemia Etiologies

<table>
<thead>
<tr>
<th>Anemia Etiology*</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Serum ferritin &lt; 50 ng/mL&lt;br&gt;Exception: 3-month trial of iron therapy with an increase in ferritin above 50 ng/mL without an erythroid response* and no evidence of bleeding</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>B12 level &lt; 200 pg/mL or &lt; 300 pg/mL with a methylmalonic acid level &gt; 0.4 μmol/L&lt;br&gt;Exception: 3-month trial of vitamin B12 without an erythroid response*</td>
</tr>
<tr>
<td>Folate deficiency</td>
<td>Serum folate &lt; 4.0 ng/mL or RBC folate &lt; 316 ng/mL&lt;br&gt;Exception: 3-month trial of folic acid repletion without an erythroid response*</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>Thyrotropin &lt; 0.1 mU/mL or &gt; 10 mU/mL&lt;br&gt;Exception: corrective thyroid therapy without an erythroid response*</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>Requiring confirmation by bone marrow examination defined by 2001 World Health Organization criteria&lt;br&gt;Exception: corrective thyroid therapy without an erythroid response*</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Estimated glomerular filtration rate &lt; 30 mL/min/1.73m² body surface area by Modification of Diet and Renal Disease Study Group (25)</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>Presence of a diagnosed subacute or chronic inflammatory condition without above conditions</td>
</tr>
<tr>
<td>Thalassemia trait</td>
<td>MCV &lt; 82 fl with a normal RBC number, no iron deficiency, no inflammatory disease, and the appropriate ethnic group&lt;br&gt;Confirmation highly encouraged with elevated hemoglobin A2 on hemoglobin electrophoresis or two deletions by alpha-thalassemia polymerase chain reaction. If only a single alpha-thalassemia deletion, hemoglobin stability over 2 years required</td>
</tr>
<tr>
<td>Other</td>
<td>Clinical conditions with a reasonable likelihood of causing anemia</td>
</tr>
<tr>
<td>Unexplained anemia</td>
<td>No anemia etiology discovered or a &gt; 1.0 g/dL decline in hemoglobin in a patient with thalassemia trait</td>
</tr>
</tbody>
</table>

*Notes: Categories mutually exclusive and listed in order of preference of assignment (eg, if iron deficiency and anemia of inflammation present, only recorded as iron deficiency). MCV = mean corpuscular volume; RBC = red blood cell.

* Erythroid response defined as either a 1.0 g/dL increase in hemoglobin or exceeding anemic thresholds.

Artz & Thirman, J. Geront., 2011, 66A, 925-932
Other includes (hemolysis = 4, alcohol = 3, hypothyroidism = 1, vitamin B12 deficiency = 1, medication = 1)
# Unexplained Anemia in the Elderly

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>76 yrs</td>
</tr>
<tr>
<td>Male</td>
<td>69 (39.7)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>46 (26.4)</td>
</tr>
<tr>
<td>AA</td>
<td>117 (67.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>69 (39.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>138 (79.3)</td>
</tr>
<tr>
<td>Both diabetes and hypertension</td>
<td>65 (37.3)</td>
</tr>
<tr>
<td>Transfused in prior 3 months</td>
<td>29 (16.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Values (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (median)</td>
<td>61.5 mL/min/1.73</td>
</tr>
<tr>
<td>CRP ≥ 3 mg/mL</td>
<td>81 (52.6)</td>
</tr>
<tr>
<td>Epo (median)</td>
<td>18.4 U/L</td>
</tr>
<tr>
<td>Hb (mean)</td>
<td>10.2 gm/dL</td>
</tr>
<tr>
<td>MCV (mean)</td>
<td>88.5</td>
</tr>
<tr>
<td>Reticulocytes (mean)</td>
<td>58,000</td>
</tr>
</tbody>
</table>

Artz et al. ASH 2010
SO IT IS REALLY HOPELESS. CAN'T YOU DO ANYTHING?

OH YES. I CAN SEND YOU A "GET WELL-CARD"!
PARTNERSHIP FOR ANEMIA: CLINICAL AND TRANSLATIONAL TRIALS IN THE ELDERLY

PARTICIPATING INSTITUTIONS

Case Western Reserve University
Duke University
Howard University
Johns Hopkins University
Stanford University
University of California-Los Angeles
University of Chicago
University of Utah

Supported by NIH/NIA Grant U54 AG034661
The PACTTE Hypothesis

UAE corrective therapy, including improved function, can be individualized based upon pathogenesis.

Mechanism

- Iron Deficiency → IV Iron
- Inflammation → Salsalate
- Hypoxia sensing/ESA defect → ESA’s
- Myelodysplasia → lmids
- Hormonal deficiency

Tx
Intravenous Iron For Treatment of Fatigue in Nonanemic Premenopausal Women with Low Serum Ferritin Concentration

- Study of efficacy of IV iron for treatment of fatigue in nonanemic patients with low serum ferritin concentration
- Randomized, double-blind, placebo controlled study
- 90 Premenopausal women presenting with fatigue, serum Ferritin ≤ 50 ng/mL and Hemoglobin ≥ 12.0 g/dL
- Randomized to receive either 800mg IV Iron Sucrose or Placebo
- Fatigue (assessed by Brief Fatigue Inventory) and Serum Iron Status assessed at baseline, 6 and 12 weeks
- Fatigue Improved in 65% Iron treated group vs. 34-40% in placebo treated group
- Improvement in Fatigue associated with increase in serum ferritin

Krayenbuehl et al, Blood 2011, 118:3222-3227
Intravenous Iron For Treatment of Fatigue in Nonanemic Premenopausal Women with Low Serum Ferritin Concentrates

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Iron group</th>
<th>Placebo group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31 ± 8</td>
<td>32 ± 7</td>
<td>ns</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166 ± 6</td>
<td>166 ± 6</td>
<td>ns</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>60 ± 8</td>
<td>59 ± 7</td>
<td>ns</td>
</tr>
<tr>
<td>Blood pressure systolic, mmHg</td>
<td>117 ± 13</td>
<td>117 ± 13</td>
<td>ns</td>
</tr>
<tr>
<td>Blood pressure diastolic, mmHg</td>
<td>73 ± 8</td>
<td>72 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td>Heart rate, 1/min</td>
<td>72 ± 10</td>
<td>71 ± 9</td>
<td>ns</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>133 ± 6</td>
<td>133 ± 7</td>
<td>ns</td>
</tr>
<tr>
<td>Mean red blood cell volume, fl</td>
<td>90 ± 5</td>
<td>90 ± 5</td>
<td>ns</td>
</tr>
<tr>
<td>Serum ferritin concentration, ng/mL</td>
<td>24 (10, 32)</td>
<td>20 (14, 28)</td>
<td>ns</td>
</tr>
<tr>
<td>Transferrin saturation, %</td>
<td>20 (14, 30)</td>
<td>25 (16, 32)</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>77 (72, 82)</td>
<td>78 (72, 84)</td>
<td>ns</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>17 (13, 21)</td>
<td>17 (15, 23)</td>
<td>ns</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>20 (17, 26)</td>
<td>21 (18, 24)</td>
<td>ns</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, mIU/L</td>
<td>1.5 (1.0, 2.0)</td>
<td>1.4 (0.8, 2.0)</td>
<td>ns</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.1 (1.1, 1.1)</td>
<td>1.1 (1.1, 1.1)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Results are presented as means ± 1 SD or as median values (quartiles Q1, Q3). P values were calculated by t test or the Mann-Whitney U test. ns indicates not significant and no trend (P > .10).

Krayenbuehl et al, Blood 2011, 118-3222-3227
Anemia of Inflammation

• Innate immune response in individuals with inflammatory disease
• Normocytic, normochromic anemia
• Low serum iron
• Adequate/Increased macrophage iron
• Erythropoietin hyporesponsiveness
• Decreased erythrocyte survival
Overview of systemic iron homeostasis

Key components:
- Hypoxia signal
- Erythropoietic signal
- Iron signal (via HJV, HFE, TFR2)
- Inflammatory signal
- Liver
- Macrophage
- FPN
- Fe$_2$-Tf
- RBCs
- Bone marrow
- Duodenum

Key processes:
- Fe loss
- Bone marrow production
Hepcidin, A Central Regulator of Iron Homeostasis

- Hepcidin binds to iron exporter, ferroportin, resulting in its internalization and degradation.
- Ferroportin degradation blocks iron release from macrophages, duodenal cells and hepatocytes
- Hepcidin causes iron sequestration and blocks iron utilization
- Hepcidin synthesis in liver is regulated by
  - body iron stores
  - Erythropoietic needs
  - inflammation
- Hepcidin is an antimicrobial peptide
  - Direct antimicrobial activity in vitro
  - Reduces iron availability - prevents bacterial growth
Hepcidin and Ferroportin

**Macrophage**

**Enterocyte**

C. Roy   Education Program   ASH  2010
Decreased Fe recycling

Decreased dietary uptake
Inflammatory markers in older non-anemic controls compared with participants with unexplained anemia.

<table>
<thead>
<tr>
<th></th>
<th>Older controls</th>
<th>Unexplained anemia</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>11</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Male frequency (%)</td>
<td>7 (64%)</td>
<td>23 (92%)</td>
<td>0.057¹</td>
</tr>
<tr>
<td>Age (years) median, IQR</td>
<td>69 (68–75)</td>
<td>75 (73–78)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemoglobin (g/dl) mean, SD</td>
<td>14.2 ± 0.8</td>
<td>11.7 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESR (mm/h) mean, SD</td>
<td>7 ± 3.3</td>
<td>17.9 ± 12.7</td>
<td>0.004²</td>
</tr>
<tr>
<td>IL-6 (mfi) mean, SD</td>
<td>26.4 ± 6.1</td>
<td>25.6 ± 10.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Hepcidin (ng/ml) mean, SD</td>
<td>44.0 ± 35.8</td>
<td>142.8 ± 78.0</td>
<td>0.003²</td>
</tr>
<tr>
<td>Ferritin (ng/ml) mean, SD</td>
<td>57 ± 62</td>
<td>128 ± 96</td>
<td>0.007⁴</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; mfi = mean fluorescent intensity. Note: three samples were missing for IL-6 analysis and four samples were missing for hepcidin analysis.

¹ Fisher’s exact test.
² Logarithm transformed for purposes of hypothesis testing.
# UA vs Controls, AI

<table>
<thead>
<tr>
<th></th>
<th>Elderly controls</th>
<th>UA</th>
<th>AI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>11</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>7 (64%)</td>
<td>19 (91%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>69 (68-75)</td>
<td>76 (65-90)</td>
<td>74 (66-88)</td>
</tr>
<tr>
<td><strong>Hb (g/dL)</strong></td>
<td>14.2 ± 0.8</td>
<td>11.7 ± 0.6</td>
<td>11.3 ± 1.2</td>
</tr>
<tr>
<td><strong>ESR (mm/hr)</strong></td>
<td>7 ± 3.3</td>
<td>17.9 ± 12.7 (p=0.0004)</td>
<td>42.7 ± 41.0</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td>26.4 ± 6.1</td>
<td>25.7 ± 10.8 (p=0.8042)</td>
<td>38.8 ± 25.2</td>
</tr>
<tr>
<td><strong>Hepcidin (ng/mL)</strong></td>
<td>57.1 ± 35.8</td>
<td>142.8 ± 77.8 (p=0.003)</td>
<td>272.6 ± 272.9</td>
</tr>
<tr>
<td><strong>Ferritin (ng/mL)</strong></td>
<td>57 ± 62</td>
<td>122 ± 97 (p=0.007)</td>
<td>249.7 ± 109.2</td>
</tr>
</tbody>
</table>
Erythropoietin and Anemia of Aging

• Epo production and Epo responsiveness may change with age

• Baltimore Longitudinal Study on Aging (n=143)
  ➢ Epo levels rise with age in healthy, non-anemic individuals
  ➢ Slope of the rise is greater in those without diabetes or hypertension
  ➢ Anemic individuals had a lower slope of rise
  ➢ Hypothesis: Anemia reflects failure of a normal compensatory rise in Epo levels, reflecting age-related co-morbidities

N. Berliner ASH 2010
EPO Increases Over Time in the Non-Anemic Elderly

Data from a single individual over time (years)
EPO Increases Over Time in the Non-Anemic Elderly

Iron Deficiency Anemia

"Unexplained" Anemia

$r^2=0.21$

$r^2=0.05$

*Erythropoietin Level expressed as a natural log
Stem Cell Frequency and Function in the Elderly

- Hierarchy of hematopoietic progenitors in man

Hematopoietic Stem Cell (HSC) → Multipotent Progenitor (MPP) → Common Myeloid Progenitor (CMP) → Granulocyte/Macrophage Progenitor (GMP) → Megakaryocytic/Erythroid Progenitor (MEP)

Increased frequency of MEP in UAE bone marrow compared to young and elderly normal bone marrow

Impaired erythroid lineage differentiation of HSC and MEP from UAE bone marrow

A

Number of Colonies

Normal HSC

UAE HSC

CFU-Mix

CFU-GM

BFU-E

CFU-E

B

Number of Colonies

Normal CMP

UAE CMP

CFU-Mix

CFU-GM

BFU-E

CFU-E

C

Number of Colonies

Normal MEP

UAE MEP

BFU-E

CFU-E
Stem Cell Frequency and Function in the Elderly - Conclusions

- In the normal, non-anemic elderly, HSC are increased and have a bias toward myelopoiesis and against lymphopoiesis
- In UAE, HSC are even more increased, GMP are reduced, MEP are increased, but the cloning efficiency of these MEP is reduced (i.e. they give rise to fewer erythroid bursts and erythroid colonies)

Stem Cell Frequency and Function in the Elderly - Interpretation

• With aging, an increase in Epo levels may be needed to maintain a normal or near-normal Hb, and this need for increased Epo is reflected by the reduced efficiency of MEP to differentiate fully to erythroid precursors

• In the UAE, Epo levels do not increase appropriately and that, in combination with a reduced ability of MEP to differentiate, results in anemia

PACTTE Planned Interventions

- Iron
- Anti-inflammatory agents
- Anti-IL-6
- Anti-hepcidin
- Erythropoietic stimulating agents
- Imids
A Randomized, Open-Label, Wait-list Control Trial To Evaluate the Efficacy of Intravenous Iron in Older Adults with Unexplained Anemia and a Serum Ferritin Between 20 and 100 ng/mL

On behalf of the PACTTTE Investigators
PACTTE
Partnership for Anemia: Clinical and Translational Trials in the Elderly

• A multi-center Phase II study to evaluate the efficacy and safety of intravenous iron sucrose in older adults with unexplained anemia and a serum ferritin between 20 and 100 ng/mL

• Primary endpoint: functional improvement
  - 6 minute walk test

• Secondary endpoint: rise in Hb

• Studies will evaluate cognitive function
Intravenous iron can improve mean 6 Minute Walk Test (6MWT) by at least 50 meters in adults 65 years and older with unexplained anemia and a serum ferritin between 20 and 100 ng/mL.

Intravenous iron will lead to an increase in hemoglobin (Hb) in adults 65 years and older with unexplained anemia and a serum ferritin between 20 and 100 ng/mL.
Why not oral iron?

- Poorly absorbed
- Poorly tolerated: nausea, gastritis, constipation
  -> poor compliance
- Not as potent as intravenous iron
  - Longer time to replenish stores, restore hemoglobin
- Efficacy of orally administered high-dose iron is limited by inflammatory conditions, which inhibit iron absorption
Study: Primary Objective

- To determine whether the administration of 1000 mg of intravenous iron sucrose to older adults with unexplained anemia and a serum ferritin between 20 and 100 ng/mL leads to improvement in 6MWT results.

Study: Primary Endpoint

- Change of 6MWT distances from baseline to 12 weeks.
Study: Secondary Objectives

- To assess the efficacy of IV iron sucrose in improving Hb
- To assess the safety of IV iron sucrose in older anemic adults with a serum ferritin between 20 and 100 ng/mL
- To quantify the impact of anemia treatment by IV iron sucrose on the following functional and self-report outcome measures as assessed by the geriatric evaluation panel (GEP) consisting of the following:
  - Trail-Making Test and CogState cognitive tests
  - Short-Form 36 and physical component score (PCS) subscale
  - Functional Assessment in Chronic Illness Therapy-Anemia (FACIT-An)
  - Four components of the frailty index:
    - Grip strength
    - 4 meter walk speed
    - Self-reported exhaustion
    - Self-reported activity level
- To investigate the correlation between baseline serum ferritin and other measures of iron status (e.g. transferrin saturation, soluble transferrin receptor and soluble receptor/log ferritin) and response to IV iron sucrose.
Study Design

- **Screening Visit** (Days -14 to 0)
- **Randomization** (Day -2 to 0) No Visit needed
- **Observation Period**
  - Treatment Visit 1
  - Treatment Visit 2
  - Treatment Visit 3
  - Treatment Visit 4
  - Treatment Visit 5
- **Follow up Period**
  - Follow up Visit 1
  - Follow up Visit 2
- **Wait List Control Group**
- **Immediate Intervention Group**
- **Treatment Period**
  - Treatment Visit 1
  - Treatment Visit 2
  - Treatment Visit 3
  - Treatment Visit 4
  - Treatment Visit 5
- **Follow up Period**
  - Follow up Visit 1
  - Follow up Visit 2
  - Follow up Visit 3
  - Follow up Visit 4

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice
Inclusion Criteria

- Age ≥ 65 years old
- Hb concentration ≥ 9.0 g/dL and < 11.5 g/dL for women and ≥ 9.0 to < 12.7 g/dL for men
- Unexplained anemia (see Appendix 2 for definition)
- Serum ferritin level ≥ 20 and ≤ 100 ng/mL
- Able to walk without the use of a walker, motorized device or the assistance of another person.
- Must be able to understand and be willing to provide written informed consent in the absence of dementia, defined as a Montreal Cognitive Assessment (MoCA) score ≥ 22
- Must be able to understand and speak in English
Exclusion Criteria

- Red blood cell transfusions within the past 3 months
- Use of erythropoiesis stimulating agents (ESA) in the past 3 months
- Intravenous Iron Infusions within the past 3 months
- History of unstable angina or myocardial infarction in the past 3 months
- Distance on 6MWT above the median for age and sex adjusted population medians (see Table 2 Section 5.7.2)
- History of stroke or transient ischemic attacks in the past 3 months
Exclusion Criteria cont…

- Uncontrolled hypertension defined as greater than the average diastolic blood pressure > 100 mm Hg or systolic blood pressure > 160 mm Hg on 2 separate occasions on 2 separate days during screening.
- Positive fecal occult blood test within the screening period
- Elevated AST (SGOT) or ALT (SGPT) ≥ 2x upper limit of normal
- Documented anaphylactic reaction to iron sucrose infusion in the past
- Subjects initiated on oral iron supplementation within the last 6 weeks, or those initiated on oral iron within the last 3 months who have had at least a one g/dL improvement in Hb since starting oral iron supplementation
PACTTE Trial 2: Salsalate

Randomized Controlled trial of Salsalate for UAE with elevated Interleukin-6
Salsalate Draft Schema

1. Clinic visits
2. CBC, chemistries and laboratory blood work
3. Salicylate level
4. Geriatric Panel

Visits:
- Screen
- 1 pill BID
- 2 pills BID
- 750 mg BID
- 1500 mg BID
- Post-treatment Phase

Month:
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7

Salsalate 1500 mg BID
Placebo

Month 0-7

1 pill BID
2 pills BID
Take-Home Messages

- Anemia of aging is common, associated with increased morbidity and mortality, and is a rising public health problem as the population ages.
- Unexplained anemia in the elderly is predominantly mild, but nonetheless is associated with increased morbidity, frailty, and mortality.
- Unexplained anemia may reflect an age-related inflammatory state leading to increased EPO-resistance which may be rooted in the marrow progenitor compartments.
- Interventions that may be used to treat anemia in elderly patients, and whether and how such therapy will improve outcomes, are being tested.
Geriatric Anemia Clinic

Suggested Referral Characteristics

• **Age ≥ 65 Years Old**

• **Hb Concentration**
  - Women < 11.5 g/dL
  - Men < 12.7 g/dL

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