# A Comprehensive Approach to Evaluating Anemia

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Professor of Clinical Medicine

## Productive State
- **Hyper-productive**
  - Elevated reticulocyte count
  - Acute blood loss
  - Replacement of a deficient nutrient
  - Hemolysis
- **Hypo-productive**
  - Normal or inadequately elevated reticulocyte count
  - Everything else

## Anemia by Cell Size

<table>
<thead>
<tr>
<th>Microcytic (&lt;80 fL)</th>
<th>Normocytic (80-100 fL)</th>
<th>Macrocytic (&gt;100 fL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe deficiency</td>
<td></td>
<td>Megaloblastic</td>
</tr>
<tr>
<td>ACD</td>
<td></td>
<td>vitamin B12 deficiency</td>
</tr>
<tr>
<td>Pb toxicity</td>
<td></td>
<td>folate deficiency</td>
</tr>
<tr>
<td>Sideroblastosis</td>
<td></td>
<td>DNA synthesis blockers</td>
</tr>
<tr>
<td>Thalassemia</td>
<td></td>
<td>Non-Megaloblastic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>liver failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>thyroid failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hemolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>marrow failure</td>
</tr>
</tbody>
</table>

## Size Does Not Answer All Questions

Be aware of mixed anemias!
**RBC Size Classification**

- **Microcytic**
  - Iron deficiency
  - Anemia of chronic disease
  - Thalassemia
  - Lead toxicity
- **Normocytic**
  - Anything but thalassemia
- **Macrocytic**
  - Megaloblastic
  - Non-megaloblastic

**Microcytic Anemias**

<table>
<thead>
<tr>
<th>Hypo-productive</th>
<th>Hyper-productive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Thalassemia*</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td></td>
</tr>
<tr>
<td>Lead toxicity</td>
<td></td>
</tr>
</tbody>
</table>

*normal or elevated RBC count

**Microcytosis Plus Elevated RBC Count**

- Normal Ferritin
  - Thalassemia
  - Thalassemia plus Iron deficiency
- Low Ferritin
  - Polycythemia vera
  - Plus Iron deficiency

**Macrocytic Anemia**

<table>
<thead>
<tr>
<th>Smear</th>
<th>Megaloblastic</th>
<th>Non-Megaloblastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear</td>
<td>• macroovalocytes</td>
<td>• target cells</td>
</tr>
<tr>
<td></td>
<td>• hypersegmented neutrophils</td>
<td>• other poikilocytosis</td>
</tr>
<tr>
<td>Diseases</td>
<td>Vitamin B12 deficiency</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Folate deficiency</td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>DNA synthesis inhibitors</td>
<td>Hemolysis</td>
<td></td>
</tr>
</tbody>
</table>
Anemia of Chronic Disease

**relative or absolute hypoerythropoietemia**

- Anemia of inflammation** - sideropenia
  - Malignancy
  - Granulomatous disease
  - Autoimmune rheumatologic disorders
  - Chronic infection
  - Hospitalized patient with subacute illness
  - Heart failure
  - Chronic kidney disease
  - Unknown
- "Anemia" of endocrine deficiency - euferria
  - Hypothyroid
  - Panhypopituitarism
  - Hypoadrenalism
  - Hypogonadism (males)
- Anemia of visceral organ failure - variable serum iron
  - Renal failure
  - Hepatic failure

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Anemia of Inflammation - Hepcidin and Ferroportin

- Blunted response to erythropoietin
- Shortened RBC survival
- Pro-inflammatory cytokines restrict erythropoiesis and sequester iron in splenic macrophages
  - TNFα, IL-1β, macrophage migration inhibitory factor, acute phase reactants
- IL6 mediates hepcidin transcription which promotes the internalization and degradation of ferroportin
  - Reduced iron absorption across intestinal lumen
  - Impaired release of iron in macrophages to marrow erythroid progenitors

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**Geriatrics 1992: 47: 47-57**

**Hematology 2010; 276-280**
Iron Deficiency vs ACD

<table>
<thead>
<tr>
<th>Test</th>
<th>Iron deficiency</th>
<th>ACD</th>
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</thead>
<tbody>
<tr>
<td>MCV</td>
<td>low, normal</td>
<td>low, normal</td>
</tr>
<tr>
<td>MCH</td>
<td>low, normal</td>
<td>low, normal</td>
</tr>
<tr>
<td>serum iron</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>transferrin</td>
<td>normal, <em>high</em></td>
<td>normal, low</td>
</tr>
<tr>
<td>% saturation</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>ferritin</td>
<td>normal, <em>low</em></td>
<td>normal, <em>high</em></td>
</tr>
<tr>
<td>sol. transferrin receptor</td>
<td><em>high</em></td>
<td>normal</td>
</tr>
</tbody>
</table>

* <30 ng/mL

Anemia of Inflammation

Iron Deficient

Iron Replete

Iron Responsive

Iron Non-Responsive

Diagnostic Tests to Determine Iron Deficiency Coincident with Inflammation

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulocyte Hgb concentration</td>
<td>&lt;28 pg</td>
<td>Functional iron deficiency</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>&lt;30 ng/mL</td>
<td>Iron deficient</td>
</tr>
<tr>
<td>sTransferrin receptor / log Ferritin ratio (sTfR units = ng/L)</td>
<td>&gt;1.5 0.8-1.5 &lt;0.8</td>
<td>Iron deficient  Iron replete  Iron deficient with inflammation</td>
</tr>
</tbody>
</table>

Etiologies of Anemia in the Elderly

Blood 2004; 104: 2263
Anemia of the Elderly

- Incidence
  - 10%, ≥65 years
  - 20%, ≥85 years

- Race/Ethnicity
  - Non-Hispanic blacks 3-fold more likely than Non-Hispanic whites to be anemic

- Pathophysiology of ‘Unexplained Anemia’
  - Epo-resistance in the aging hematopoietic stem cell
  - Reduced Epo production from the aging kidney
  - Increased elaboration of inflammatory cytokines with age

Vitamin D Deficiency and Anemia of the Elderly

- Vitamin D deficient (<20 ng/dL)
  - OR 1.47 for any anemia (1.06, 2.05; p=0.02)
  - OR 1.88 for anemia of inflammation (1.64, 2.07; p<0.05)

- Independent of age, sex, race/ethnicity

  • Not associated with “unexplained anemia”

Blood 2011; 117: 2800
Vitamin D Deficiency and Anemia in Older People

NHANES 2001-6

Evaluating Anemia: Initial Diagnostic Tests

- Productive state
  - Reticulocyte count
  - Direct Coomb’s test
- Morphology
  - Blood smear
- Nutrients
  - Iron, ferritin
  - Vitamin B12 ± methyl malonic acid
  - RBC folate
  - TSH, free T4
  - Cr, eGFR (± EPO)
  - ? Vitamin D

Evaluating Anemia: Secondary Diagnostic Tests

- Distinguish iron deficiency from anemia of Inflammation
  - sTransferrin receptor/log ferritin ratio
  - Reticulocyte Hgb concentration
  - Bone marrow biopsy - iron stain
- Rule out uncommon causes of anemia
  - Serum and Urine Immunofixation Electrophoresis
  - Hgb Electrophoresis
- Rule out bone marrow pathology - biopsy
  - Primary (aplastic anemia, pure red cell aplasia, MDS)
  - Infiltrative disease - malignancy, infection, granulomatous disease
- Therapeutic and Diagnostic Trial
  - IV iron trial

ESAs: Treatment of Anemia of Chronic Diseases

- Anemia of Inflammation
  - RA, SLE, IBD
  - HIV treated with AZT
  - Hepatitis C
- Anemia of Malignancy
  - Treated with chemotherapy
  - Palliative intent
- CKD
- MDS
Treating Iron Replete Anemia with Parenteral Iron

- “Functional iron deficiency” = iron restricted erythropoiesis
  - Immediate circulating plasma iron briefly available to the erythron
- Indications
  - ESRD
  - Cancer with myelosuppressive chemotherapy
- Combine with ESA (erythropoietic stimulating agent)
  - Epoetin
  - Darbepoetin

Drive Trial

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**Drive Trial**

![Graph showing response proportions over time](image)

Reprinted with permission from the American Society of Nephrology

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**Anemia of Cancer**

<table>
<thead>
<tr>
<th>Decreased Production</th>
<th>Increased Destruction</th>
<th>Blood Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia of Inflammation</td>
<td>Hemolysis</td>
<td>Acute</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Chronic</td>
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<tr>
<td>Nutritional deficiency</td>
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<td></td>
</tr>
<tr>
<td>Bone marrow infiltration</td>
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<tr>
<td>Chronic kidney disease</td>
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</table>

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**Anemia of Cancer**

![Diagram showing various causes and effects of anemia](image)


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**Competing Effects of ESAs in the Treatment of the Anemia of Cancer**

![Diagram illustrating the effects of ESAs](image)

Reprinted with permission from Annual Reviews

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ESA Meta Analysis in Cancer Patients: Overall Survival

*Lancet 2009: 373: 1532-42*

ESA Meta Analysis in Cancer

Survival

*Br J Cancer 2010; 102: 301*

ESA Meta Analysis in Cancer

Overall Survival

*Br J Cancer 2010; 102: 301*

ESA Meta Analysis in Cancer

Cancer Progression

*Br J Cancer 2010; 102: 301*
### ESA Meta Analysis in Cancer Venothromboembolic Events

Reprinted with Permission from the Nature Publishing Group

### Randomized Trials of ESA Plus Parenteral Iron in Cancer Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>ESA</th>
<th>Design</th>
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<th>%Transfused</th>
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<tbody>
<tr>
<td>Hadenus</td>
<td>67</td>
<td>E</td>
<td>IV vs oral</td>
<td>93 √</td>
<td>7</td>
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<td></td>
<td>53</td>
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<td>Pedrazzoli</td>
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<td>7</td>
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<td>D</td>
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<td>82 √</td>
<td>36 √</td>
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<tr>
<td></td>
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<td></td>
<td>63</td>
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<td>40</td>
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</tbody>
</table>

Hematology 2010: 351-6

E, epoetin  D, darbepoetin

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### Hemoglobin Response To IV Iron In Cancer Patients Receiving Chemotherapy and Darbepoetin

Reprinted with Permission from the American society of Clinical Oncology
Take Home Points -1-

- Classify the Anemia
  - RBC indices
  - Reticulocyte count
- Order routine RBC nutrient tests
- Order tests as directed by the anemia classification and review of the blood smear
- Iron pathophysiology has become more complicated
  - Ferritin
  - Reticulocyte Hgb concentration
  - Soluble Transferrin receptor to log ferritin ratio
  - Bone marrow biopsy - iron stain

Take Home Points -2-

- Vitamin D deficiency is more prevalent in patients with the anemia of inflammation
- ESAs have a therapeutic role
  - CKD
  - Malignancy treated with chemotherapy
  - Rheumatologic disorders, hep C, HIV (AZT)
  - MDS
- Iron restriction complicates anemia of inflammation in iron replete settings
- IV iron improves Hgb response and reduces the need for transfusions when added to ESAs
  - ESRD
  - Malignancies treated with chemotherapy

References