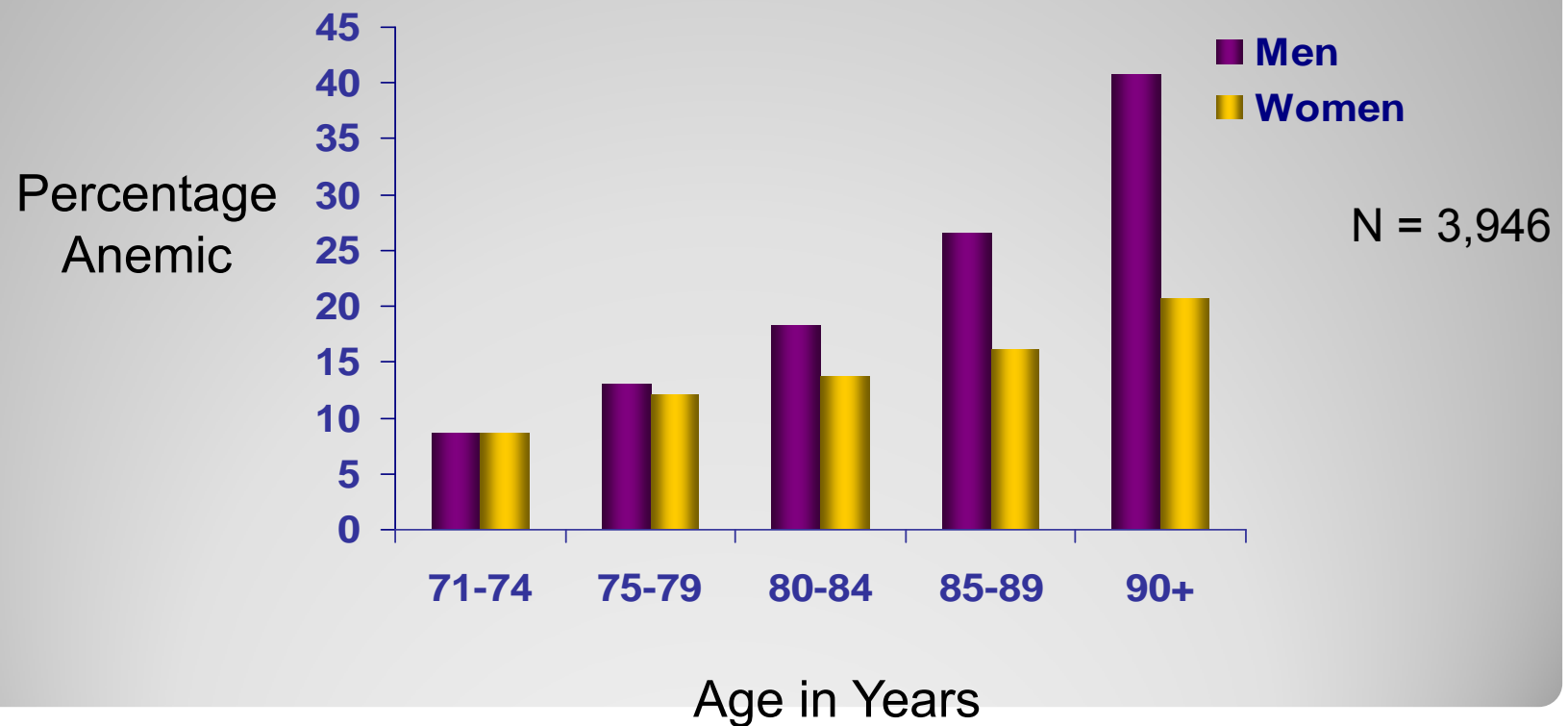


ANEMIA AND INFLAMMATORY DISEASE

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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- inhibit erythropoiesis and response to growth factors
- Age may be associated with a relative erythropoietin deficiency

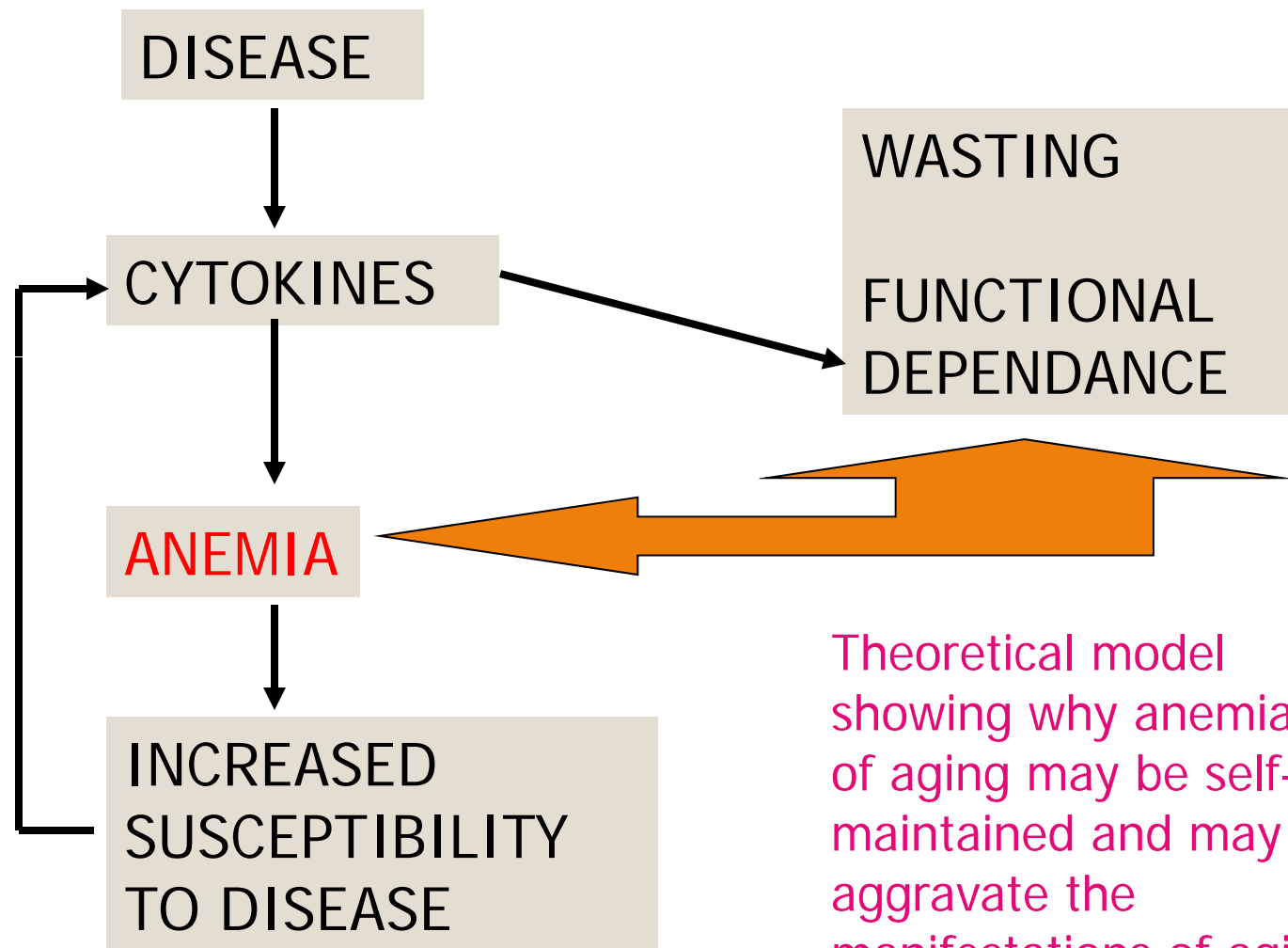
Nafziger et al. Am J Hematol 1993;43:172-176

WHY IS ANEMIA IMPORTANT IN THE ELDERLY?

- **Associated with**

- **Frailty with decreased muscle strength^{1,2}**
- **Mobility impairment³**
- **Falls and related fractures^{4,5,10}**
- **Increased cardiac complications (LVH and CHF)^{6,7}**
- **Depression⁸**
- **Cognitive impairment⁹**
- **Increased mortality¹**

1. Kamenetz Y, Beloosesky Y, Zelter C, et al. Relationship between routine hematological parameters, serum IL-3, IL-6 and erythropoietin and mild anemia and degree of function in the elderly. *Aging Clin Exp Res* 1998; 10: 32-38.
2. Penninx BW, Pehor M, Cesari M, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc* 2004; 52(5): 719-724.
3. Chaves P, Ashar T, Guralnik JM, et al. Looking at the relationship between hemoglobin concentration and previous mobility difficulty in older women: Should the criteria used to define anemia in older people be changed? *J Am Geriatr Soc* 2002; 50: 1257-1264.
4. Dharmarajan TS, Avula S, Norkus EP. Anemia increases risk for falls in hospitalized older adults: An evaluation of falls in 362 hospitalized, ambulatory, long term care and community patients. *J Am Med Dir Assoc* 2006; 7: 287-293.
5. Penninx BW, Pluijm SM, Lips P, et al. Late-life anemia is associated with increased risk of recurrent falls. *J Am Geriatr Soc* 2005; 53(12): 2106-2111.
6. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes; insights from a cohort of 12,065 patients with new-onset heart failure. *Circulation* 2003; 107: 223-225.
7. Levin A. The role of anaemia in the genesis of cardiac abnormalities in patients with chronic kidney disease. *Nephrol Dial Transplant* 2002; 17: 207-210.
8. Penninx BW, Pehor M, Cesari M, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc* 2004; 52(5): 719-724.
9. Beard CM, Kokmer E, O'Brien PC, et al. Risk of Alzheimer's disease among elderly patients with anemia: Population based investigations in Olmstead County, Minnesota. *Ann Epidemiol* 1997; 7(3): 219-224.
10. Pandya N. et al. Study of anemia in long-term care. *CMRO* 2008



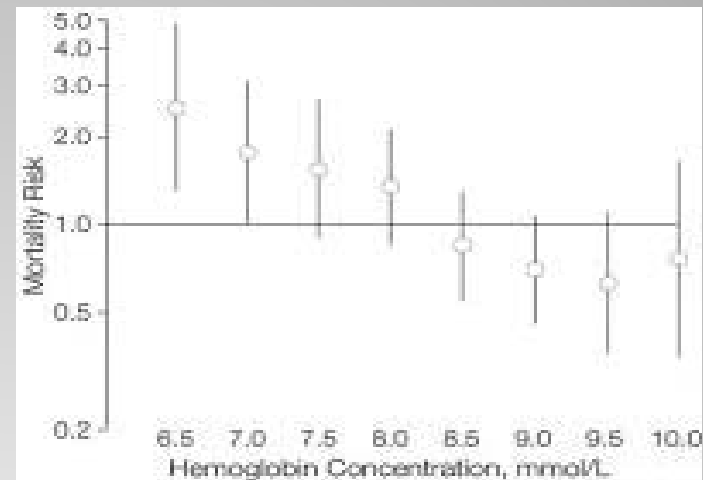
Theoretical model showing why anemia of aging may be self-maintained and may aggravate the manifestations of aging

Balducci L. JAGS 51(Suppl):S1 2003

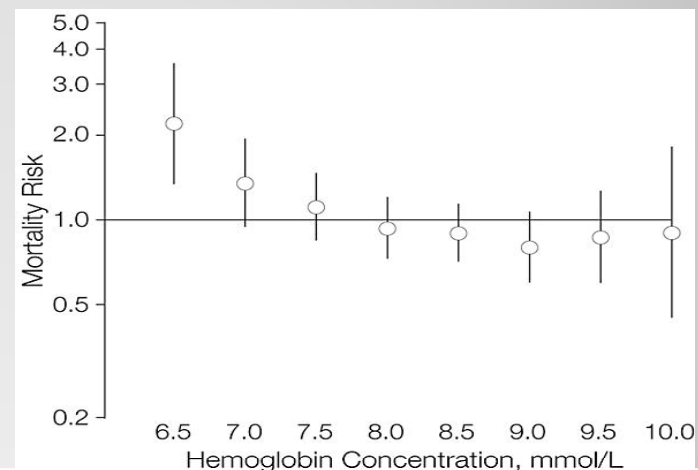
Mortality risk of anemia in the elderly

- 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*

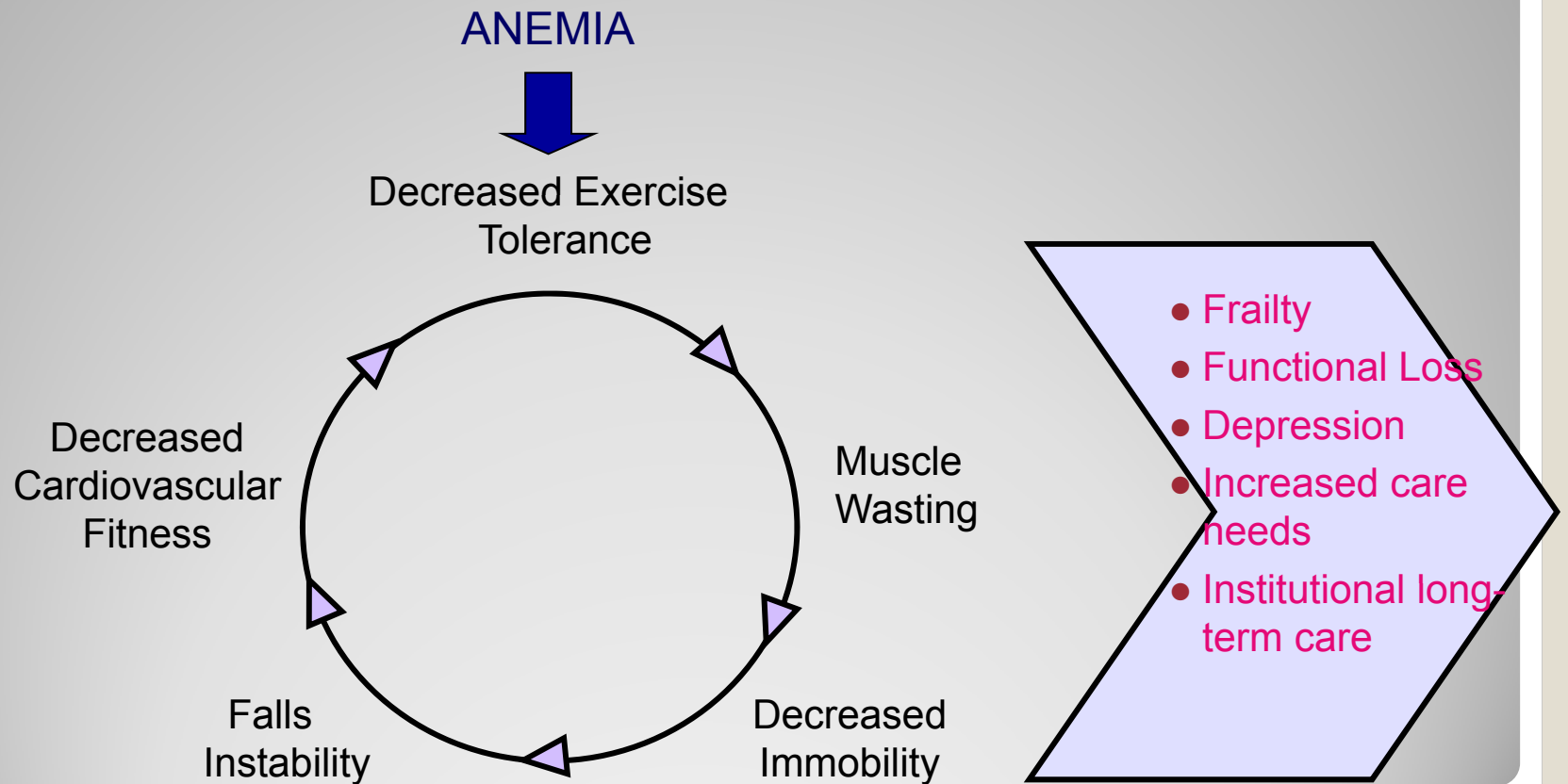


Men



Women

Anemia and adverse outcomes in older adults



Robinson B. *J Am Geriatr Soc.* 2003;51:S14-S17.

- 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

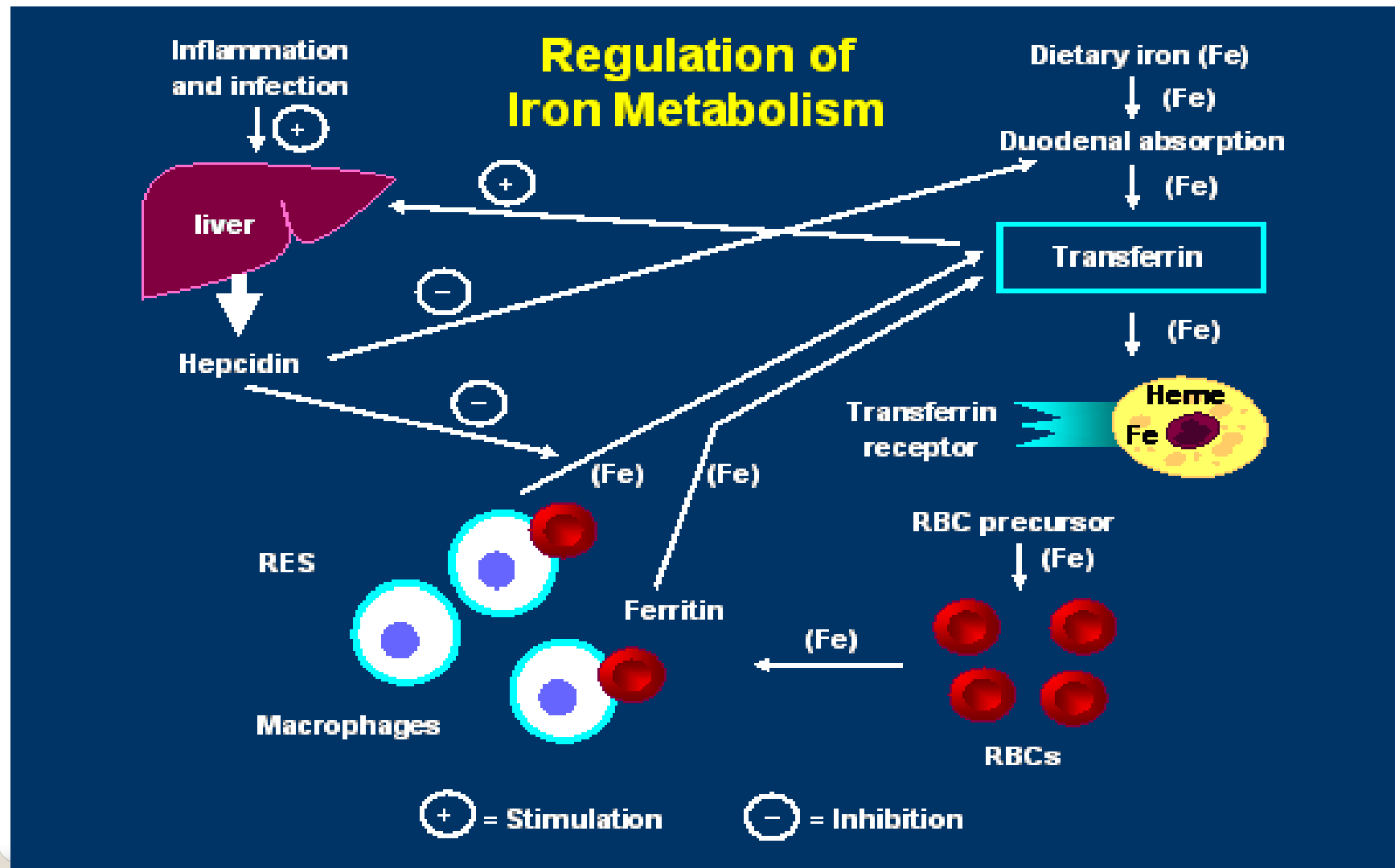
**Anemia of chronic
disease/chronic inflammation**

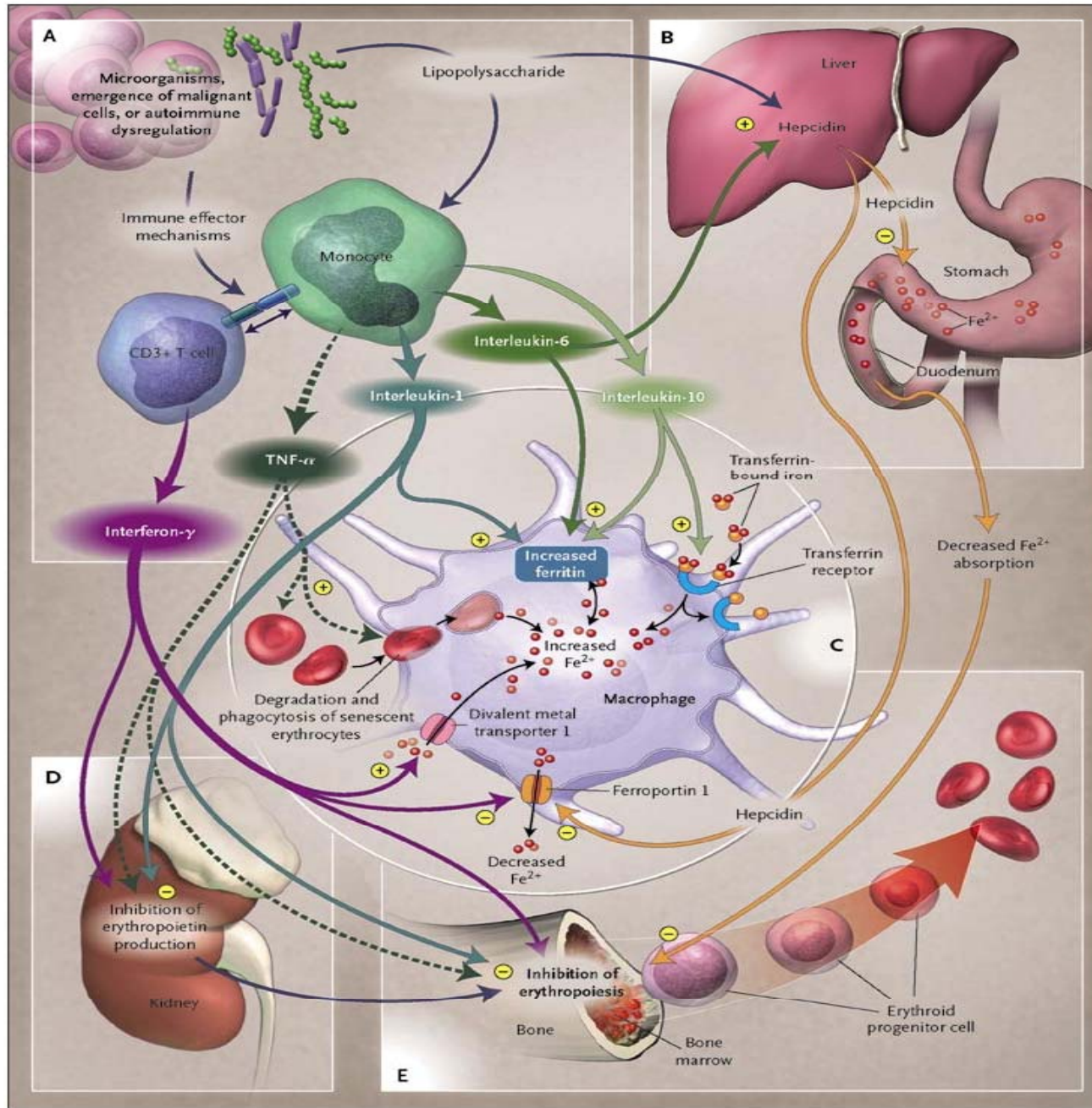
- **Dysregulation of Iron Homeostasis**
- **Impaired Proliferation of Erythroid Progenitor Cells**
- **Blunted Erythropoietin Response**

**Pathophysiological Mechanisms
Underlying Anemia of Chronic
Disease**

Weiss and Goodnough. NEJM Mar 10, 2005

The role of HEPCIDIN in chronic anemia





Pathophysiological Mechanisms Underlying Anemia of Chronic Disease.

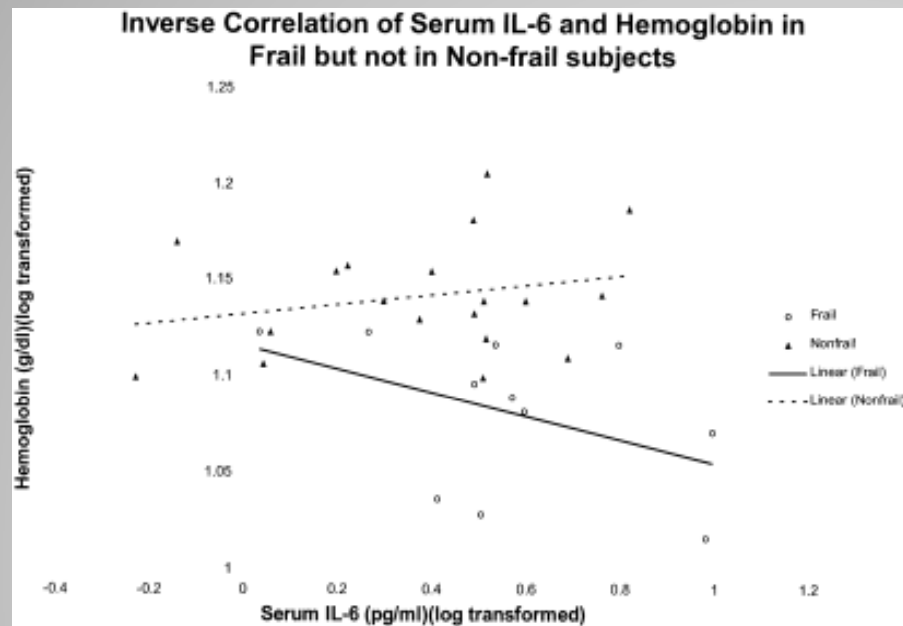
Weiss and Goodnough. NEJM Mar 10, 2005

- Bleeding episodes
- Vitamin deficiencies (e.g., of cobalamin and folic acid)
- Hypersplenism
- Autoimmune hemolysis
- Renal dysfunction
- Radio- and chemotherapeutic interventions

Factors that aggravate anemia of chronic inflammation

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

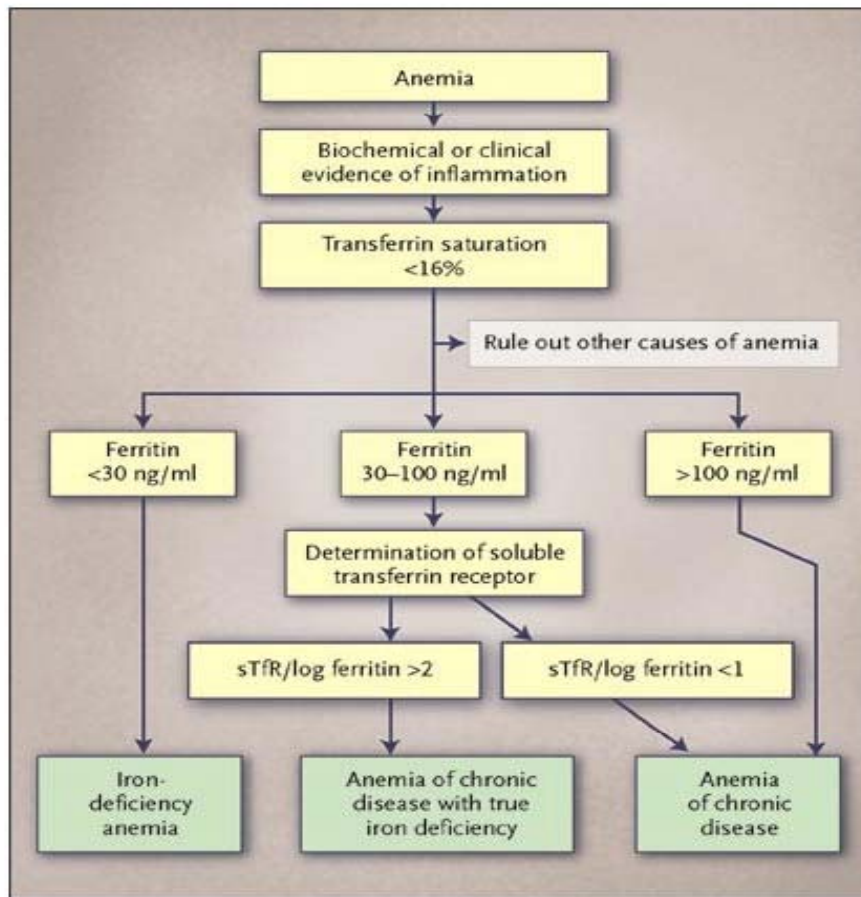
- Frail subjects have evidence of inflammation and lower Hb (12.1 vs 13.9)and Hct levels

- 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



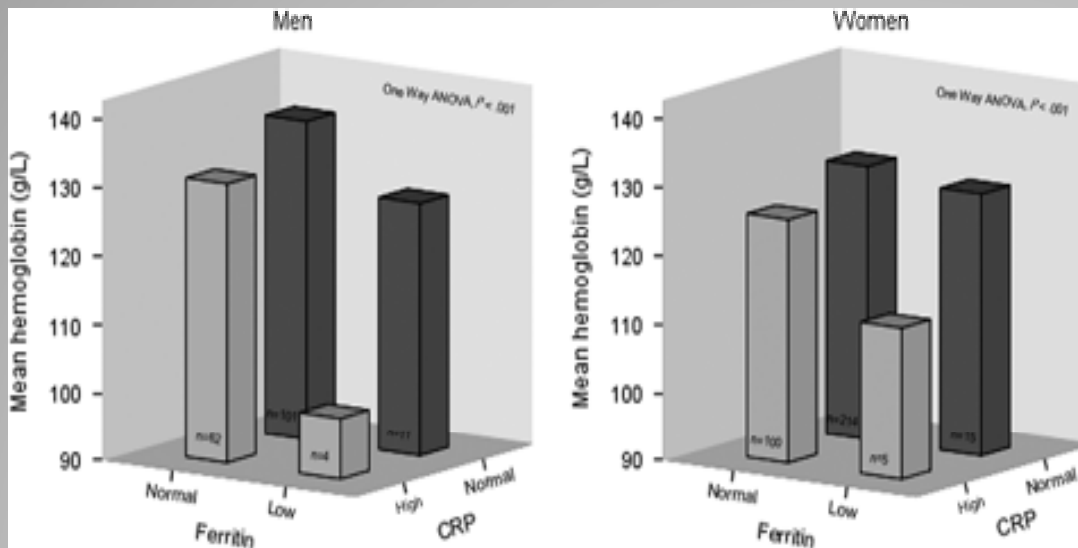
Algorithm for the Differential Diagnosis among Iron-Deficiency Anemia, Anemia of Chronic Disease, and Anemia of Chronic Disease with Iron Deficiency. Weiss and Goodnough. NEJM Mar 10, 2005

Blood Test	ACI	IDA	ACI + IDA
Iron	↓	↓	↓
TIBC	↓	↑	LN or ↓↑
% Transferrin saturation	↓ or N	↓	↓
Ferritin	↑ or N	↓	↓ or N
Soluble transferrin receptor	N	↑	↑ or N

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



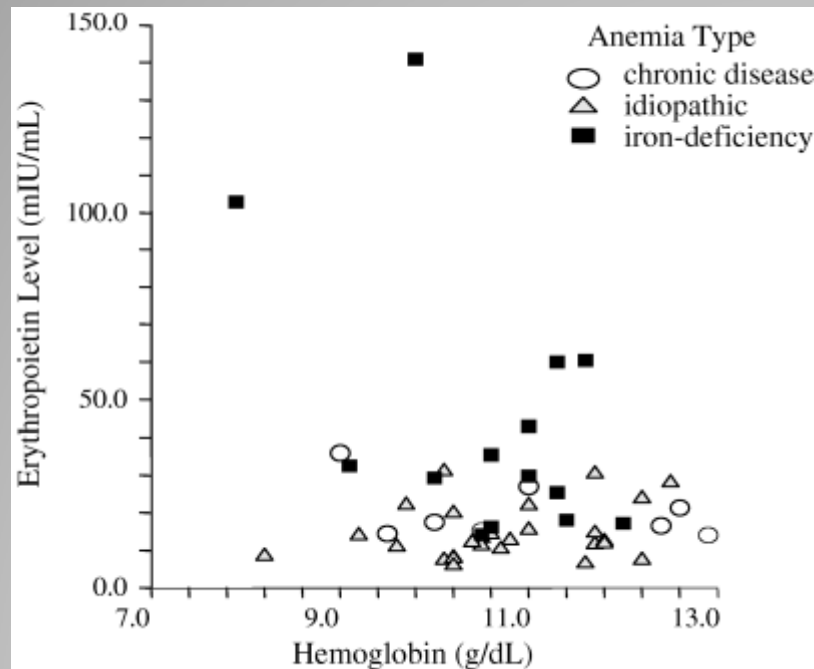
N=512 85 yr olds
34.8% male

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

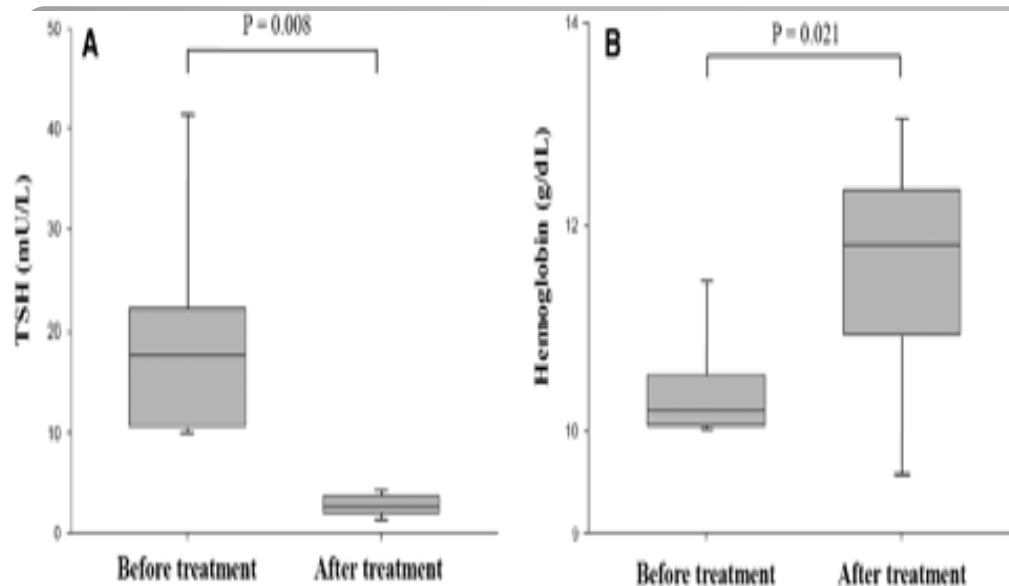
The predictive use of low ferritin in older persons with anemia, with and without inflammation; Leiden 85-plus study JAGS Aug 2010



- 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.

Treatment	Anemia of Chronic Disease	Anemia of Chronic Disease with True Iron Deficiency
Treatment of underlying disease	Yes	Yes
Transfusions*	Yes	Yes
Iron supplementation	No	Yes†
Erythropoietic agents	Yes‡	Yes, in patients who do not have a response to iron therapy

* 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.

QUESTIONS AND PANEL DISCUSSION