



# **Anemia Associated With Inflammatory Bowel Disease (IBD)**

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# National Anemia Action Council

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# NAAC Mission



The National Anemia Action Council, Inc. (NAAC) is dedicated to raising the awareness of health care professionals and the public regarding the prevalence, symptoms, consequences, and treatment options of anemia.

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# NAAC's Online Resources for Medical Professionals



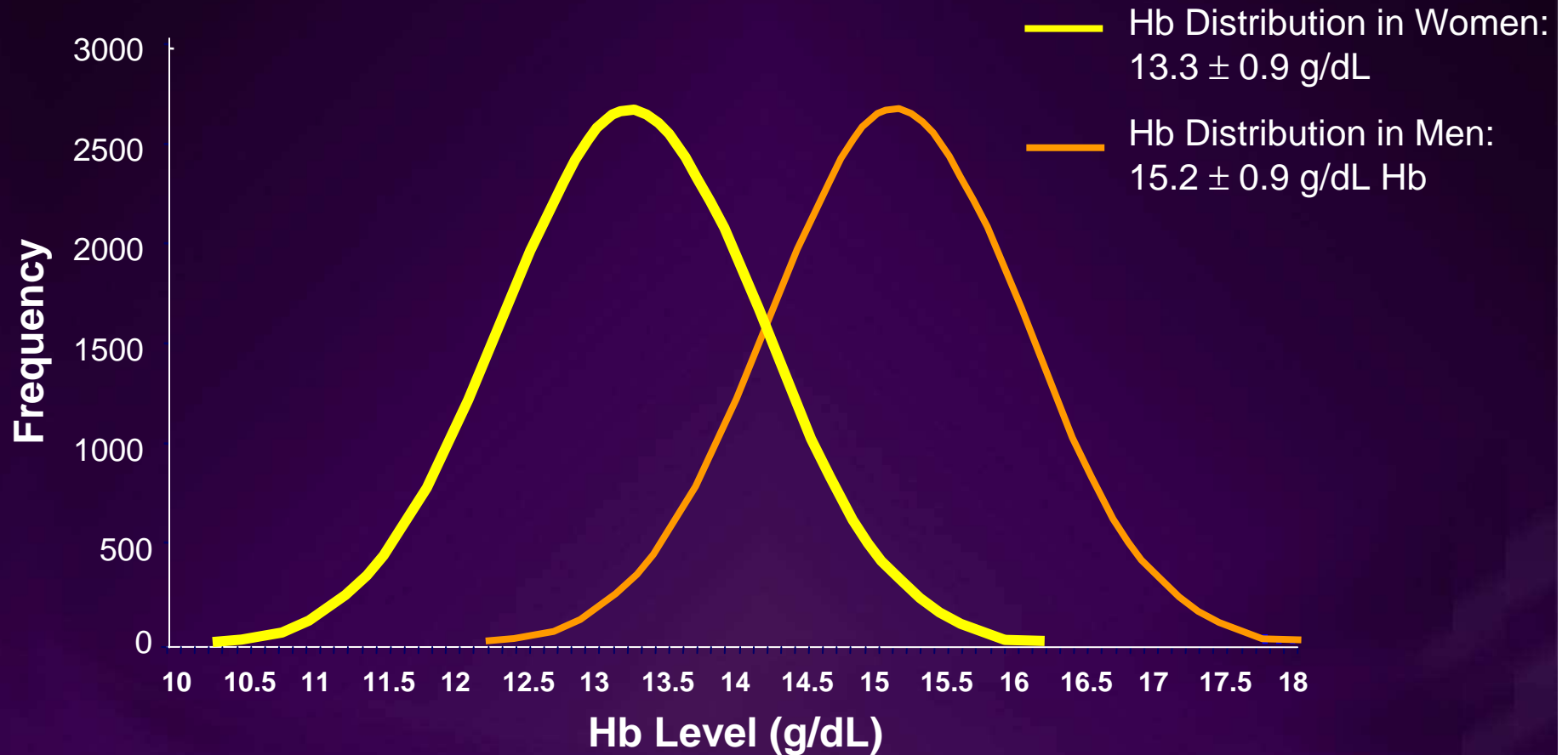
- Research Reviews - Recent clinical trials reviewed
- Ask the Expert - Your anemia questions answered
- Monograph - In-office handbook on anemia
- Feature Articles - Anemia related news and research
- Anemia Alert - Free monthly e-newsletter
- Slide Sets - Educational presentations about anemia
- We have materials for your patients too!

# Key Points



- Anemia affects many patients with IBD
- Multiple factors contribute to anemia in patients with IBD, including blood loss, inadequate nutrient intake/absorption, and the underlying inflammatory disease process
- Early evidence suggests that there is a relationship between anemia, disease severity, and quality of life in patients with IBD
- Erythropoietin therapy may be useful in treating anemia associated with Crohn's disease and ulcerative colitis

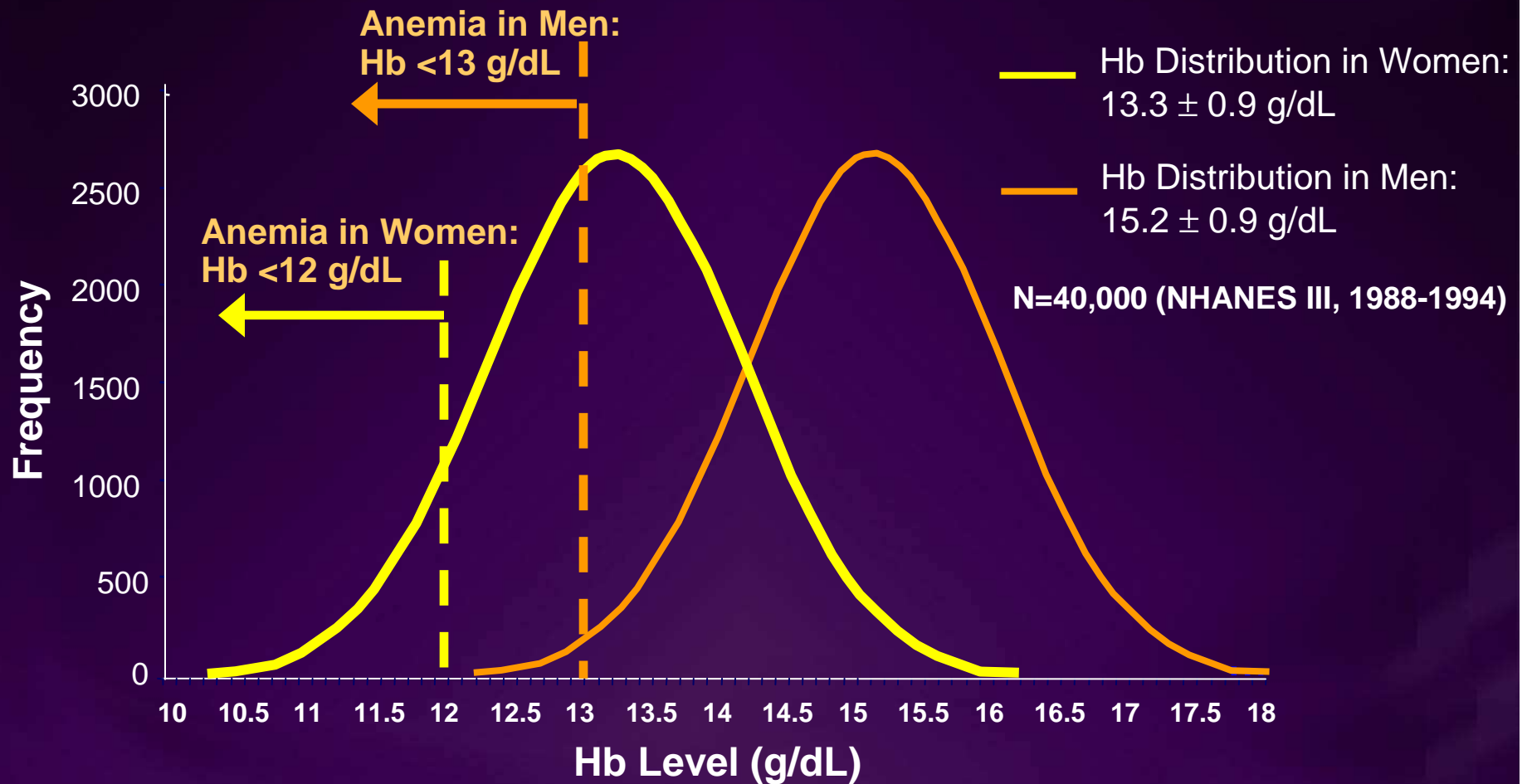
# Hemoglobin (Hb) Distribution in the General Population



**N=40,000 (NHANES III, 1988-1994)**

Dallman PR, et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

# WHO Definition of Anemia vs. Hb Distribution in General Population



1. World Health Organization. Geneva, Switzerland; 2001.

2. Dallman PR, et al. In: *Iron Nutrition in Health and Disease*. London, UK: John Libbey & Co; 1996:65-74.

# Laboratory Reference Ranges



Parameter	Male	Female
Hb (g/dL)	14.0 – 17.4	12.3 – 15.3
Hct (%)	41.5 – 50.4	36.0 – 45.0
RBC count ( $10^6/\mu\text{L}$ )	4.5 – 5.9	4.5 – 5.1
Reticulocyte count (% of RBC count)	0.5 – 2.5	
Mean corpuscular volume (fL)	80 – 96	
Mean corpuscular Hb (MCH) (pg)	27.5 – 33.2	
MCH concentration (g/dL)	33.4 – 35.5	

Hb = hemoglobin; Hct = hematocrit; RBC = red blood cell

Perkins S. In: Lee G et al, eds. *Wintrobe's Clinical Hematology (Vol. 2)*. 10th ed. Baltimore: Lippincott, Williams & Wilkins; 1998:2738.

# Anemia Signs and Symptoms



## Central nervous system

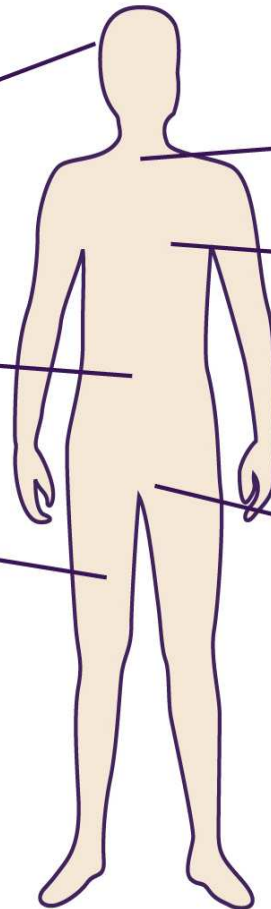
- Fatigue
- Depression
- Impaired cognitive function

## Gastrointestinal system

- Anorexia
- Nausea

## Vascular system

- Low skin temperature
- Pallor of skin, mucous membranes, and conjunctivae



## Immune system

- Impaired T-cell and macrophage function

## Cardiorespiratory system

- Exertional dyspnea
- Tachycardia, palpitations
- Cardiac enlargement, hypertrophy
- Increased pulse pressure, systolic ejection murmur
- Risk of cardiac failure

## Genital Tract

- Menstrual problems
- Loss of libido

Ludwig H, et al. *Semin Oncol.* 1998;25(suppl 7):2-6.

# The Two Main Types of IBD



Ulcerative colitis (UC) and Crohn's disease (CD) behave similarly but have distinctive characteristics.<sup>1</sup> In 10% to 15% of cases, no definitive diagnosis is possible.<sup>2</sup>

Parameter	UC	CD
Extent of disease	Colon	Any part of GI tract
Layers of intestine involved	Mucosa only	All
Inflammation continuous?	Usually	Healthy "skip areas" often spared between patches of diseased bowel

1. Crohn's & Colitis Foundation of America.

2. Chutkan RK. *Prim Care*. 2001;28:539-556.

# Natural History

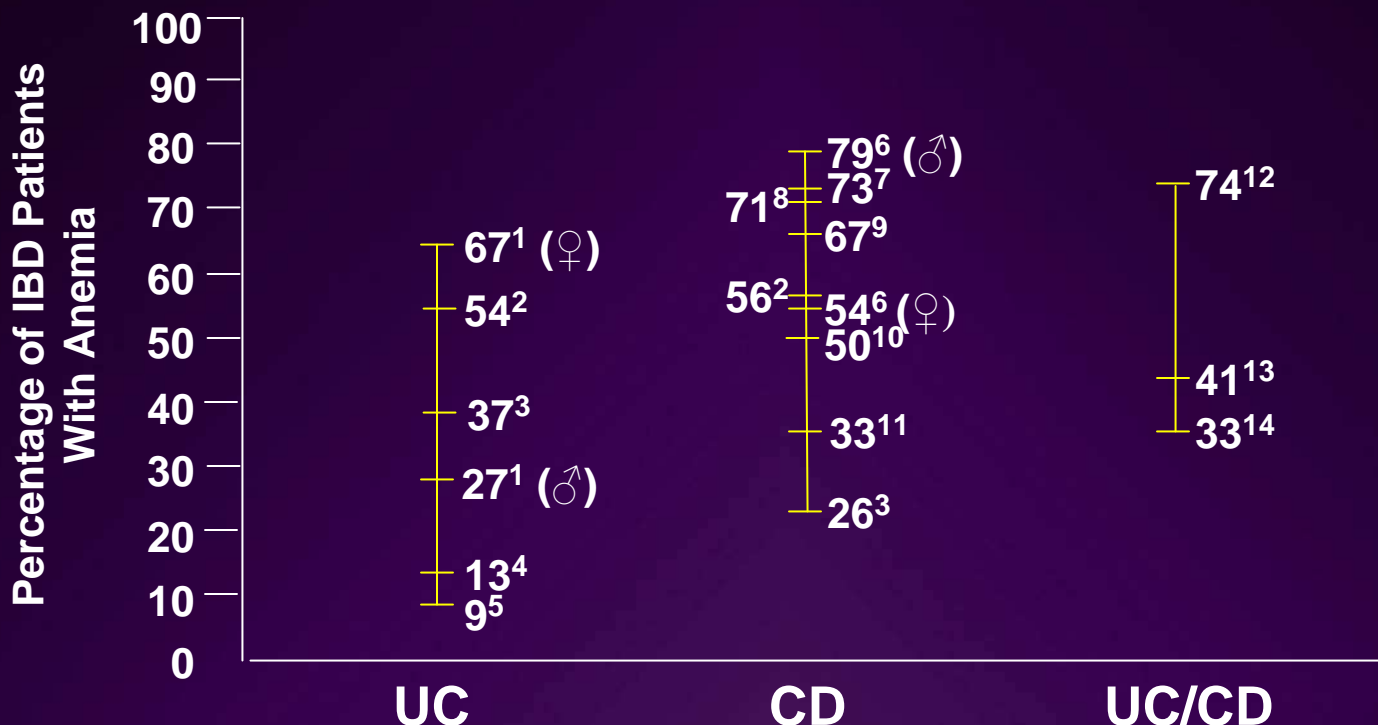


Parameter	UC	CD
Severity of disease	Correlates with extent of disease <sup>1</sup>	Does not correlate with extent of disease <sup>1</sup>
Course	Chronic, intermittent <sup>1</sup>	Erratic; recurrence likely after surgery <sup>1</sup>
Mortality risk	Modestly increased, especially the first few years after diagnosis <sup>2</sup>	Modestly increased, especially the first few years after diagnosis <sup>2</sup>

1. Andres P, et al. *Inflamm Bowel Dis*. 1999;28:255-281.

2. Ekblom A, et al. *Gastroenterology*. 1992;103:954-960.

# Prevalence of Anemia Varies Among IBD Populations Studied



1. Niv Y, et al. *Am J Gastroenterol.* 1990;85:1580-1583.
2. Reilly J, et al. *Am J Surg.* 1976;131:192-200.
3. Schreiber S, et al. *N Engl J Med.* 1996;334:619-623.
4. Walker A, et al. *Am J Gastroenterol.* 1997;92:816-820.
5. Niv Y, et al. *J Clin Gastroenterol.* 1991;13:98-101.
6. Dyer N, et al. *Q J Med.* 1972;41:419-436.
7. Beeken W. *Pediatrics.* 1973;52:69-74.

8. Greenstein A, et al. *Am J Gastroenterol.* 1975;63:40-48.
9. Beeken W. *Arch Intern Med.* 1975;135:686-690.
10. Burbige E, et al. *Pediatrics.* 1975;55:866-871.
11. Gasché C, et al. *Dig Dis Sci.* 1994;39:1930-1934.
12. Werlin S, et al. *Gastroenterology.* 1977;73:828-832.
13. Revel-Vilk S, et al. *Eur J Pediatr.* 2000;159:585-589.
14. Horina J, et al. *Gastroenterology.* 1993;104:1828-1831.

# Causes of IBD-Associated Anemia



- Blood loss
- Inadequate nutrient intake/absorption
- The underlying inflammatory disease process

1. Gasché C, et al. *Dig Dis Sci.* 1994;39:1930-1934.

2. Hugot J-P, et al. *Int J Colorect Dis.* 1999;14:2-9.

# Two Mechanisms Dominate IBD-Associated Anemia



Predominant: iron deficiency<sup>1,2</sup>

- Affected 95% of UC patients in one study<sup>3</sup>
- Affected 81% of UC patients and 39% of CD patients in another study<sup>4</sup>

Second most common: chronic inflammation<sup>1,2</sup>

- Affects ~10% of IBD patients overall,<sup>5</sup> affects ~50% of CD patients<sup>1</sup>
- Often coexists with IDA, especially in CD<sup>1,2</sup>

1. Dohil R, et al. *J Pediatr*. 1998;132:155-159.

2. Gasché C, et al. *Am J Gastroenterol*. 2001;96:2382-2387.

3. Gasché C, et al. *Digestion*. 1999;60:262-267.

4. Driscoll RH, et al. *Med Clin North Am*. 1978;62:185-201.

5. Christodoulou D, et al. *Eur J Intern Med*. 2000;11:222-227.

# Iron Deficiency Anemia (IDA) in IBD Patients



- Chronic blood loss, often occult, is the predominant mechanism of IDA in IBD patients<sup>1-3</sup>
- Other mechanisms:
  - Iron malabsorption<sup>1-3</sup>
  - Small bowel resection<sup>3</sup>
  - Inadequate dietary intake of iron<sup>3</sup>
  - Chronic inflammation resulting in functional iron deficiency (inadequate transportation of iron from storage pools to bone marrow)<sup>3</sup>

1. Cronin C, et al. *Am J Gastroenterol*. 2001;96:2296-2298.

2. Gasché C. *Inflamm Bowel Dis*. 2000;6:142-150.

3. Oldenburg B, et al. *Aliment Pharmacol Ther*. 2001;15:429-438.

# Anemia of Chronic Disease (ACD) in IBD Patients



- In active IBD, the balance of cytokines favors proinflammatory cytokines (eg, IL-1 $\beta$ , IFN- $\gamma$ , TNF- $\alpha$ )<sup>1</sup>
- Effects of proinflammatory cytokines<sup>2-5</sup>:
  - Impair production of endogenous erythropoietin (EPO) in response to anemia
  - Induce resistance to EPO by erythroid progenitor cells
  - Cause hypoferremia

1. Oldenburg B, et al. *Aliment Pharmacol Ther.* 2001;15:429-438.

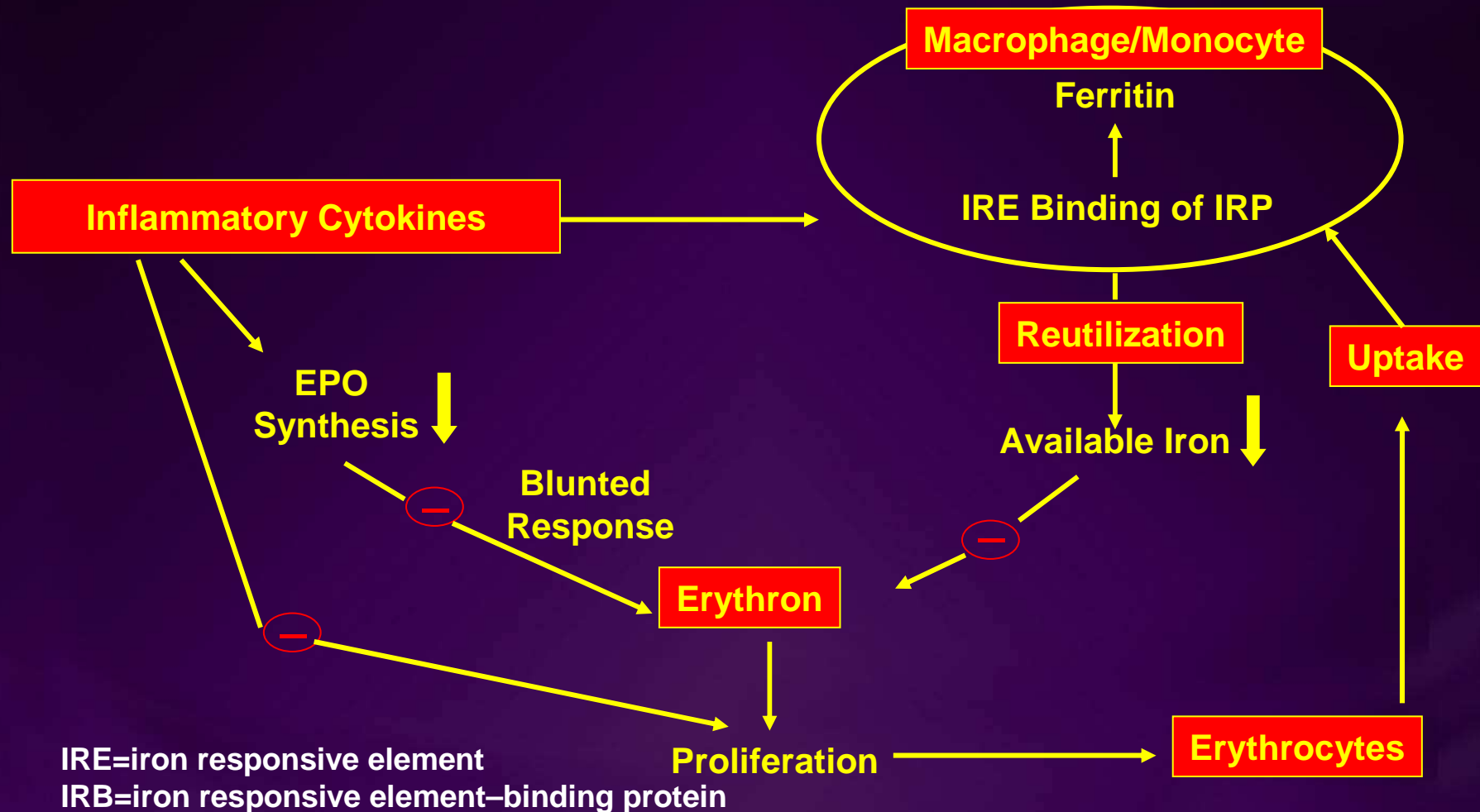
2. Schreiber S, et al. *N Engl J Med.* 1996;334:619-623.

3. Christodoulou D, et al. *Eur J Intern Med.* 2000;11:222-227.

4. Gasché C. *Inflamm Bowel Dis.* 2000;6:142-150.

5. Tilg H, et al. *J Immunol.* 2002;169:2204-2209.

# Pathogenesis of ACD in IBD



Adapted from Oldenburg B, et al. *Aliment Pharmacol Ther.* 2001;15:429-438.

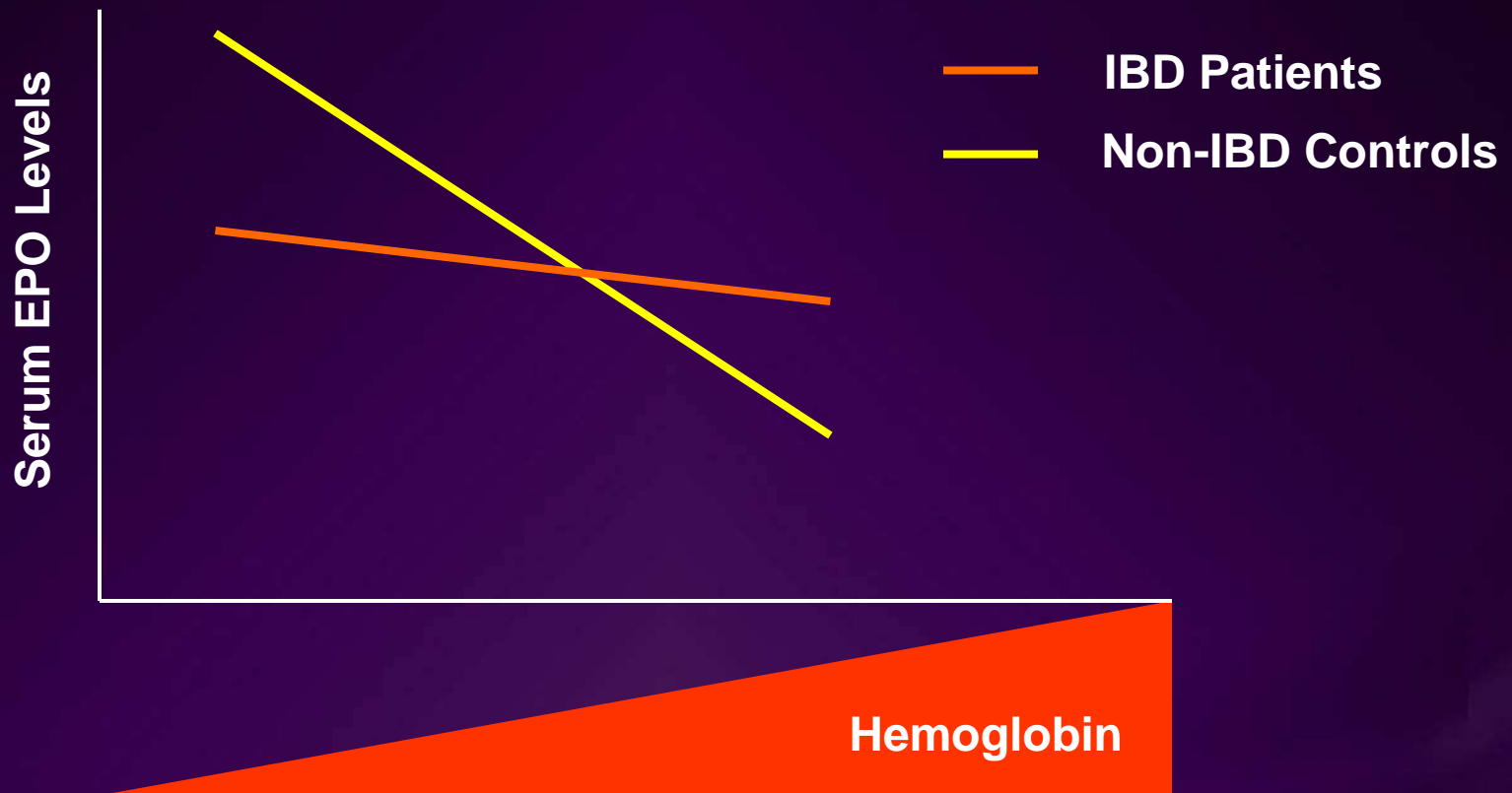
# Blunted EPO Production in IBD



Study	N	Finding
Horina et al., 1993	85 IBD	EPO $\leq$ 75 mU/mL except in 3 patients
Gasché et al., 1994	49 CD	Inadequate EPO for degree of anemia
Schreiber et al., 1996	18 anemic with IBD 18 anemic w/o IBD	EPO lower in anemic IBD patients than in anemic patients without IBD

1. Horina J, et al. *Gastroenterology*. 1993;104:1828-1831.
2. Gasché C, et al. *Dig Dis Sci*. 1994;39:1930-1934.
3. Schreiber S, et al. *N Engl J Med*. 1996;334:619-623.

# Anemic IBD Patients Have Blunted EPO Response

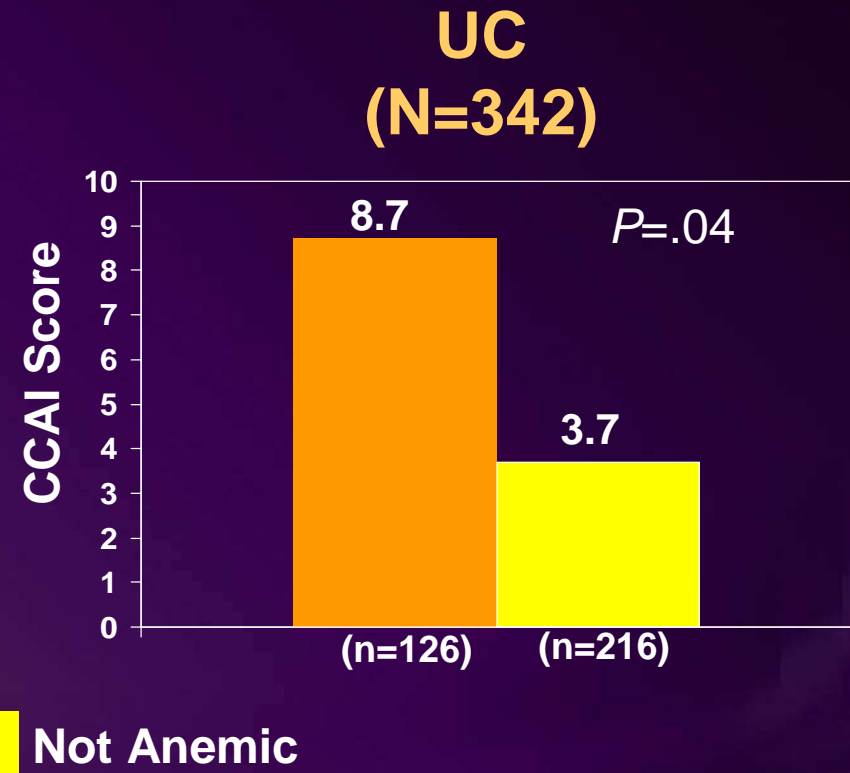
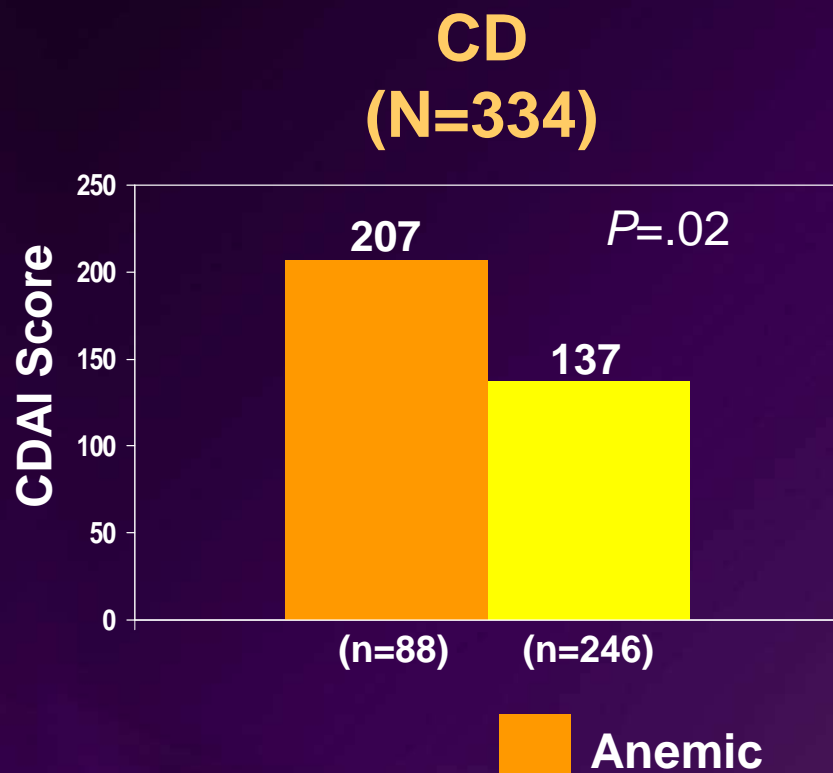


Schreiber S, et al. *N Engl J Med.* 1996;334:619-623.



# **Clinical Consequences of Anemia in Patients With IBD**

# Increased Morbidity: Anemia Correlates With Disease Severity



Schreiber S, et al. *N Engl J Med.* 1996;334:619-623.

# Increased Mortality



## Comorbidities associated with death<sup>1</sup>

- Iron deficiency anemia (IDA)
- Anemia, unspecified

Cucino C, et al. *Inflamm Bowel Dis*. 2001;7:250-255.



# Treatment of IBD-Associated Anemia

# Options for Treating IBD-Associated Anemia



- Iron
  - Oral
  - IV
- Corticosteroids or immune-modifying drugs to treat the underlying inflammation
- Allogeneic blood transfusion
- Erythropoietic stimulating proteins to overcome blunted EPO production
  - Recombinant human erythropoietin (rHuEPO)
    - eg, epoetin alfa, epoetin beta, epoetin omega
  - Darbepoetin alfa

# Iron Supplementation



- Iron is the first-line therapy for IBD-associated anemia<sup>1-3</sup>
- Compared with IV iron, oral iron is not as well incorporated into RBCs and takes longer to form Hb<sup>4</sup>
- For severe iron deficiency or malabsorption, IV iron is mandatory<sup>1</sup>
- 75% of anemic IBD patients respond to IV iron<sup>5,6</sup>

1. Christodoulou D, et al. *Eur J Intern Med.* 2000;11:222-227.

2. Dohil R, et al. *J Pediatr.* 1998;132:155-159.

3. Cronin C, et al. *Am J Gastroenterol.* 2001;96: 2296-2998.

4. Mamula P, et al. *J Pediatr Gastroenterol Nutr.* 2002;34:286-290.

5. Gasché C, et al. *Ann Intern Med.* 1997;126:782-787.

6. Gasché C, et al. *Digestion.* 1999;60:262-267.

# Antiinflammatory Therapy Treats ACD



- Corticosteroids
  - Prednisone, prednisolone, budesonide<sup>1,2</sup>
- Immunosuppressants
  - Conventional (azathioprine/6-mercaptopurine, methotrexate<sup>1</sup>)
  - Alternative (mycophenolate, tacrolimus, thalidomide<sup>3,4</sup>)
- Biological agents
  - Infliximab, CDP-571<sup>2,4</sup>
  - IL-10, IL-11<sup>3,5</sup>
  - Natalizumab<sup>5,6</sup>

1. Crohn's & Colitis Foundation of America.

2. Plevy SE. *Am J Gastroenterol*. 2002;97:1607-1617.

3. Forbes A. *Eur J Gastroenterol Hepatol*. 2003;15:245-248.

4. Sandborn WJ. *Best Pract Res Clin Gastroenterol*. 2003;17:105-117.

5. Shand A, et al. *Int J Colorectal Dis*. 2003;18(1):1-11.

6. Sandborn WJ, et al. *Gastroenterology*. 2002;122:1592-1608.

# Some Risks of Allogeneic Blood Transfusion<sup>1</sup>



Blood Transfusion Risk	Estimated Frequency per Actual Unit
<b><i>VIRUS</i></b>	
Hepatitis B	1/60,000-1/200,000
Hepatitis C	1/800,000-1/1.6 x 10 <sup>6</sup>
HIV	1/1.4-2.4 x 10 <sup>6</sup>
<b><i>BACTERIA</i></b>	
Red cells	1/500,000
Platelets	1/2000
<b><i>ACUTE HEMOLYTIC REACTIONS</i></b>	1/250,000-1,000,000
<b><i>DELAYED HEMOLYTIC REACTIONS</i></b>	1/1000
<b><i>TRANSFUSION-RELATED ACUTE LUNG INJURY</i></b>	1/8000
<b><i>ABO CLERICAL ERROR<sup>2</sup></i></b>	1/16,000

1. Modified with permission from Goodnough LT, et al. *N Engl J Med.* 1999;340:438-447.

2. Krombach J, et al. *Anesth Anal.* 2002;94:154-156.

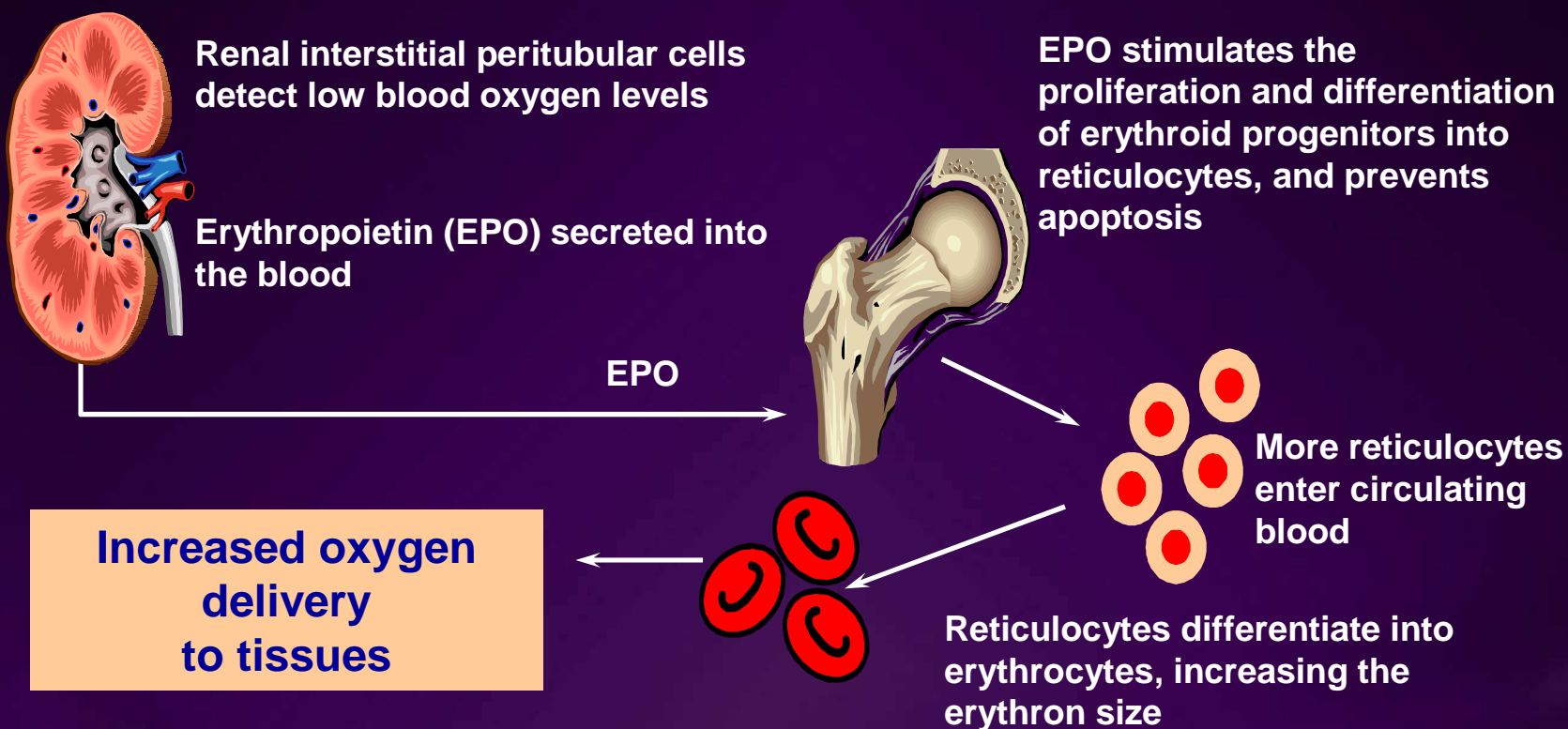
# Allogeneic Blood Transfusion Current Guidance



Except when the patient's symptoms require immediate enhancement of oxygen-carrying capacity, red-cell containing components should not be used to treat anemia that can be corrected with specific medications such as iron, vitamin B<sub>12</sub>, folic acid, or recombinant erythropoietin.

American Association of Blood Banks, America's Blood Centers, and the American Red Cross

# Erythropoietin Regulates Red Blood Cell Production



1. Bunn H. In: Isselbacher K, et al, eds. *Harrison's Principles and Practice of Internal Medicine*. 13th ed. New York, NY: McGraw-Hill; 1994:1717–1721.
2. Dessypris E. In: Lee G, et al, eds. *Wintrobe's Clinical Hematology (Vol. 1)*. Baltimore: Lippincott, Williams & Wilkins; 1998:169–192.

# rHuEPO Increases Hb in Anemic IBD Patients



**Study population** 34 patients (15 UC, 19 CD) with Hb  $\leq$ 10 g/dL despite 6 weeks of oral iron

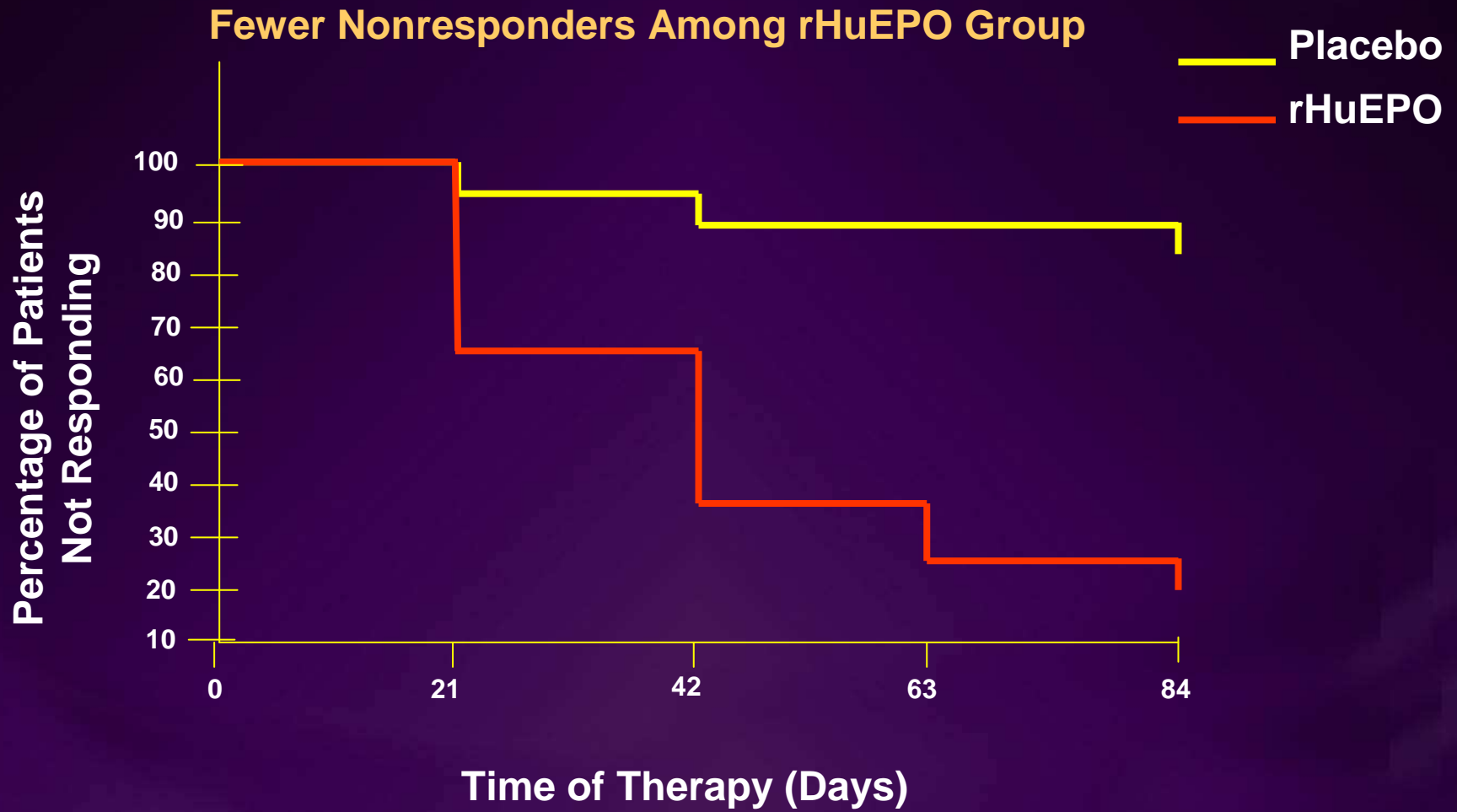
**Study design** Double-blind, randomized, controlled trial (rHuEPO or placebo) + oral iron for 12 weeks

**Definition of response** Increase in Hb by  $>1$  g/dL

**Findings** 82% of rHuEPO group responded vs. 24% of placebo group ( $P=.002$ )

Schreiber S, et al. *N Engl J Med.* 1996;334:619-623.

# Effect of rHuEPO on Hb in Anemic IBD Patients



Adapted from Schreiber S, et al. *N Engl J Med.* 1996;334:619-623.

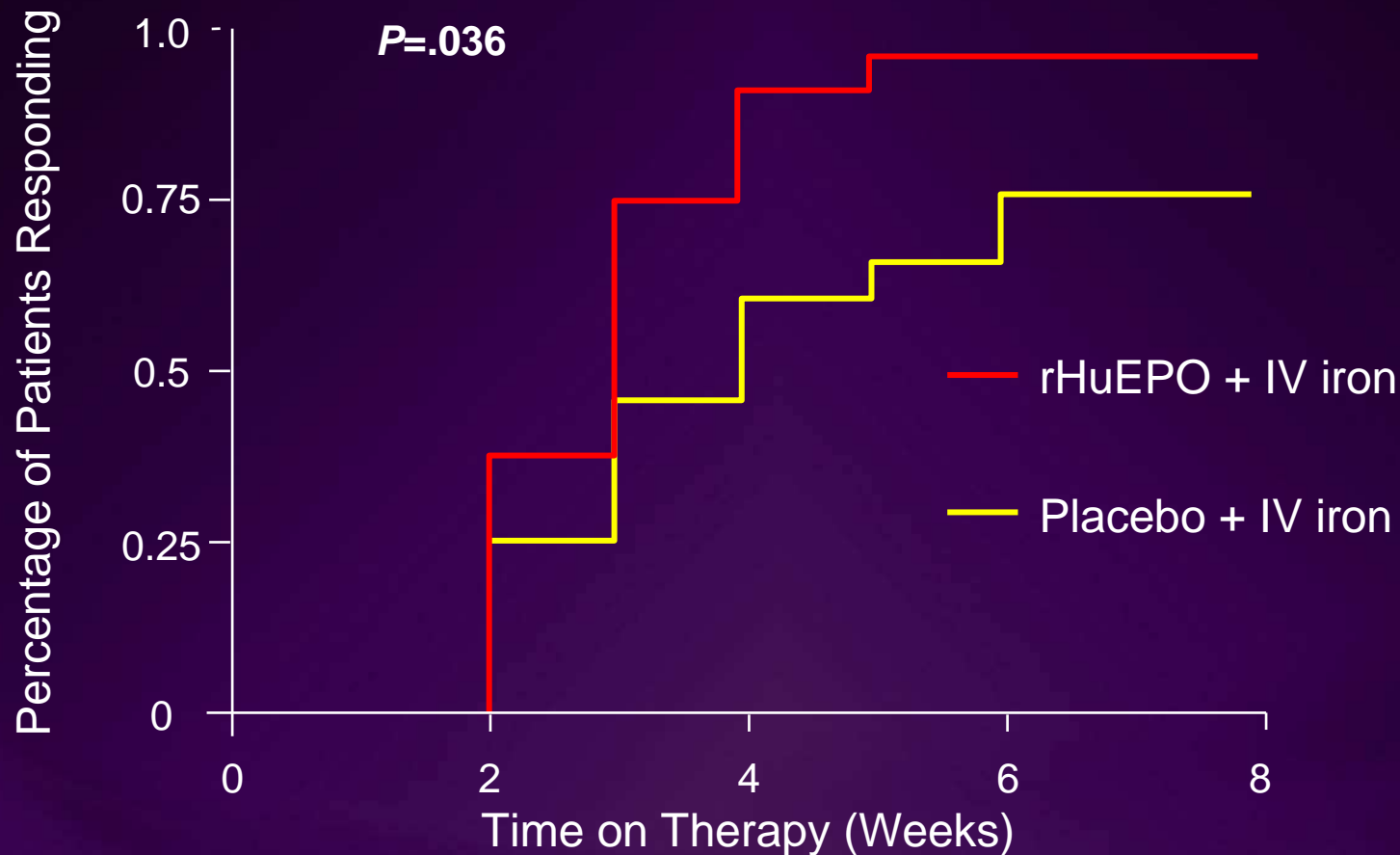
# rHuEPO Increases Hb in Anemic CD Patients



<b>Study population</b>	40 CD patients with Hb $\leq$ 10.5 g/dL, nonresponsive or intolerant to oral iron
<b>Study design</b>	<b>Phase 1, double-blind, randomized, controlled trial</b> (rHuEPO or placebo) + IV iron for 8 wk <b>Phase 2, open:</b> IV iron continued for 8 wk; rHuEPO added/doubled if no response in Phase 1
<b>Definition of response</b>	Increase in Hb by $\geq$ 2g/dL
<b>Findings</b>	<b>Phase 1:</b> 75% of iron-only group and 95% of rHuEPO group responded ( $P=.20$ ); cumulative response rate greater in rHuEPO group ( $P=.036$ ) <b>Phase 2:</b> All previous nonresponders responded

Gasché C, et al. *Ann Intern Med.* 1997;126:782-787.

# Effect of rHuEPO on Hb in Anemic CD Patients



Adapted from Gasché C, et al. *Ann Intern Med.* 1997;126:782-787.

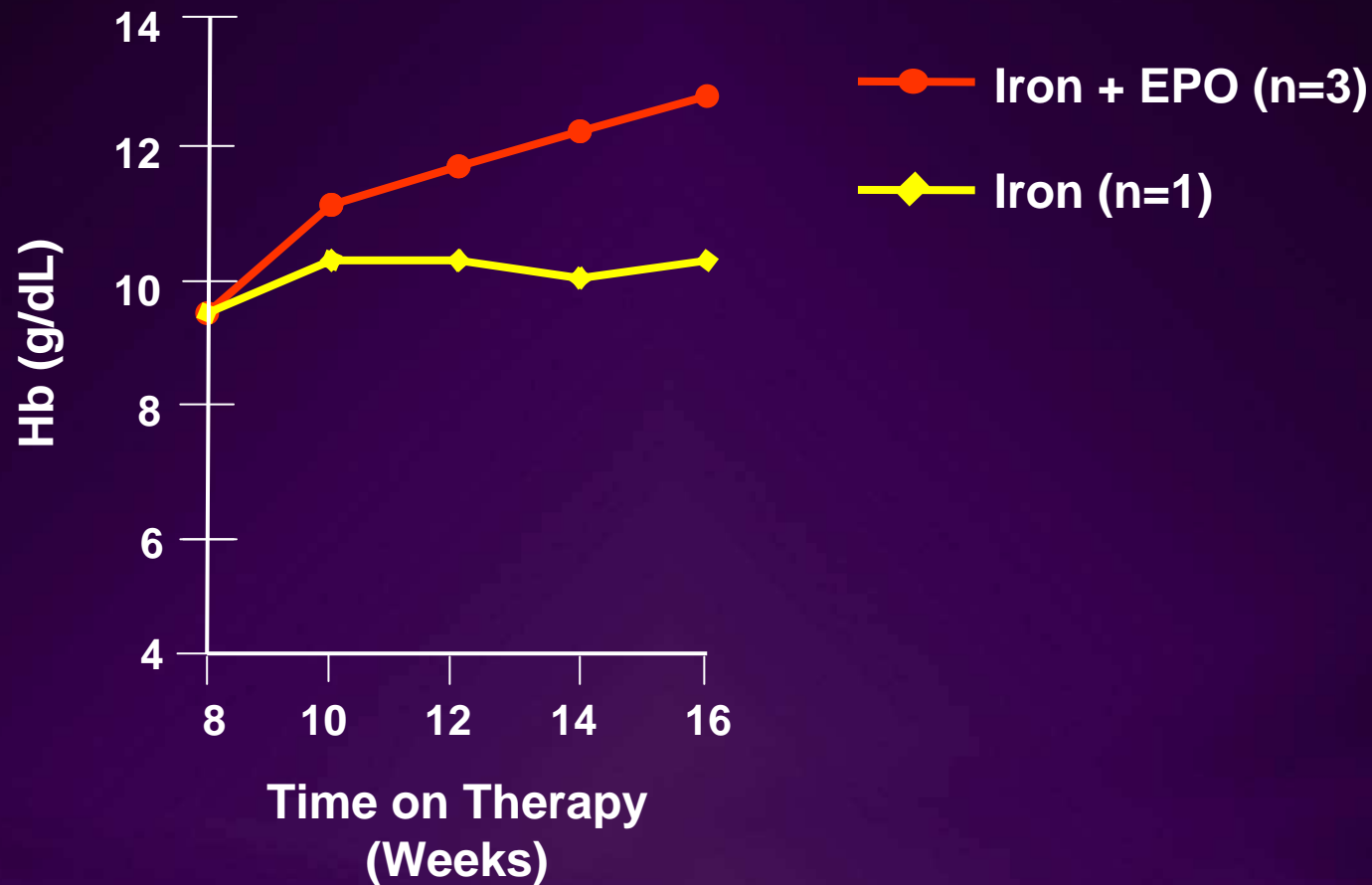
# rHuEPO Increases Hb in Anemic UC Patients



<b>Study population</b>	20 UC patients with Hb $\leq 10.5$ g/dL, nonresponsive or intolerant to oral iron
<b>Study design</b>	<b>Phase 1, open:</b> IV iron for 8 wk <b>Phase 2, open:</b> rHuEPO added for nonresponders
<b>Definition of response</b>	Full response: Hb $> 10.5$ g/dL Partial response: Hb $\leq 10.5$ g/dL But Hb increase $< 2$ g/dL = nonresponse
<b>Findings</b>	<b>Phase 1:</b> 75% full response (mean change $4.5 \pm 1.5$ g/dL); 5% partial response <b>Phase 2:</b> In 2 of 3 nonresponders, Hb increased $\geq 2$ g/dL

Gasché C, et al. *Digestion*. 1999;60:262-267.

# Effect of rHuEPO on Hb in Anemic UC Patients



Adapted from Gasché C, et al. *Digestion*. 1999;60:262-267.

# rHuEPO May Increase Hb in Anemic Children With CD



**Study population** 4 CD patients, 2.6 to 17 years old, with ACD (Hb  $\geq 2.5$  SD below mean for sex and age and nonresponse to oral iron)

**Study design** Pilot open-label study  
rHuEPO 150 U/kg 3 $\times$ /wk for up to 12 wk

**Definition of response** Increase in Hb by  $\geq 2$  g/dL, or increase to the appropriate mean

**Findings** The 17-year-old was noncompliant. The others responded, mean Hb increase = 2.93 g/dL. Transient injection-site pain was the only AE. The mean time for Hb correction was 9.5 wk.

Dohil R, et al. *J Pediatr.* 1998;132:155-159.

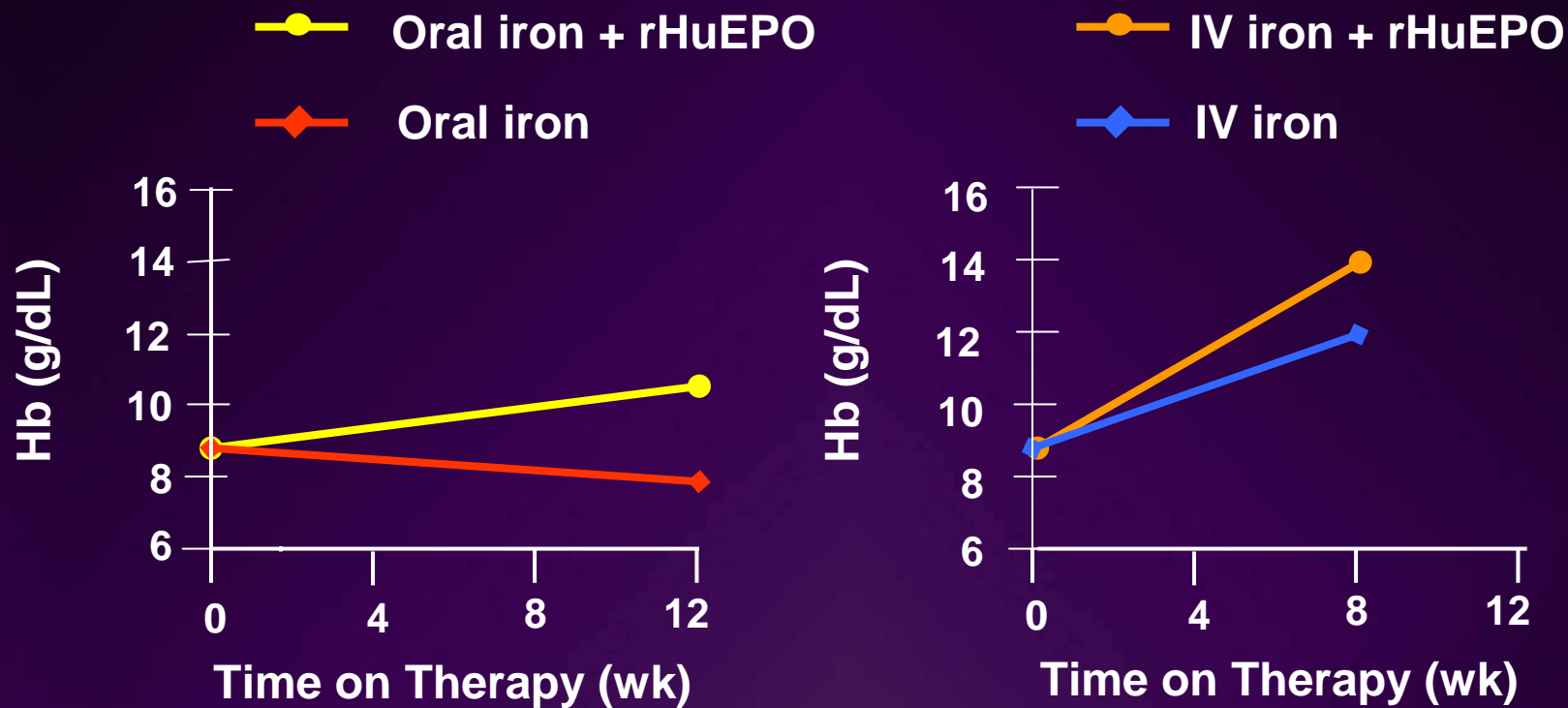
# IV Iron May Be Better Than Oral Iron as a Supplement to rHuEPO



- Two different double-blind, randomized studies tested the efficacy of rHuEPO in IBD-associated anemia:
  - One study used oral iron
  - The other study used IV iron
- In the two studies, the baseline Hb levels and total rHuEPO dosages were comparable
- Results showed that IV iron is more likely than oral iron to help rHuEPO stimulate erythropoiesis quickly

Gasché C. *Inflamm Bowel Dis.* 2000;6:142-150.

# IV Iron May Be Better Than Oral Iron as a Supplement to rHuEPO (cont.)



Gasché C. *Inflamm Bowel Dis.* 2000;6:142-150.

# Recommendations for Treating IBD-Associated Anemia



- Oral iron is often satisfactory for Hb >10.5 g/dL<sup>1</sup>
- IV iron is a reasonable first-choice therapy<sup>2,3</sup>
- IV iron is mandatory for severe IDA or iron malabsorption<sup>4</sup>
- The addition of rHuEPO to IV iron should be reserved for symptomatic patients who:
  - Are resistant to IV iron alone<sup>5-7</sup>
  - Do not respond to aggressive antiinflammatory treatment<sup>5,6</sup>
  - Might otherwise require transfusion<sup>6</sup>

1. Gasché C. *Inflamm Bowel Dis*. 2000;6:142-150.

2. Gasché C, et al. *Ann Intern Med*. 1997;126:782-787.

3. Gasché C, et al. *Digestion*. 1999;60:262-267.

4. Christodoulou D, et al. *Eur J Intern Med*. 2000;11:222-227.

5. Sandborn WJ. *Gastroenterology*. 1997;112:660-661.

6. Cronin CC, et al. *Am J Gastroenterol*. 2001;96:2296-2998.

7. Gasché C, et al. *Am J Gastroenterol*. 2001;96:2382-2387.

# Summary



- Anemia is prevalent in patients with UC or CD
- Multiple factors contribute to IBD-associated anemia, but blood loss is predominant, followed by overproduction of proinflammatory cytokines
- Early evidence suggests that there are relationships between IBD-associated anemia and disease severity, risk of death, and quality of life
- The addition of rHuEPO is useful for anemic IBD patients who do not respond to IV iron alone

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