Anemia in the Critically Ill

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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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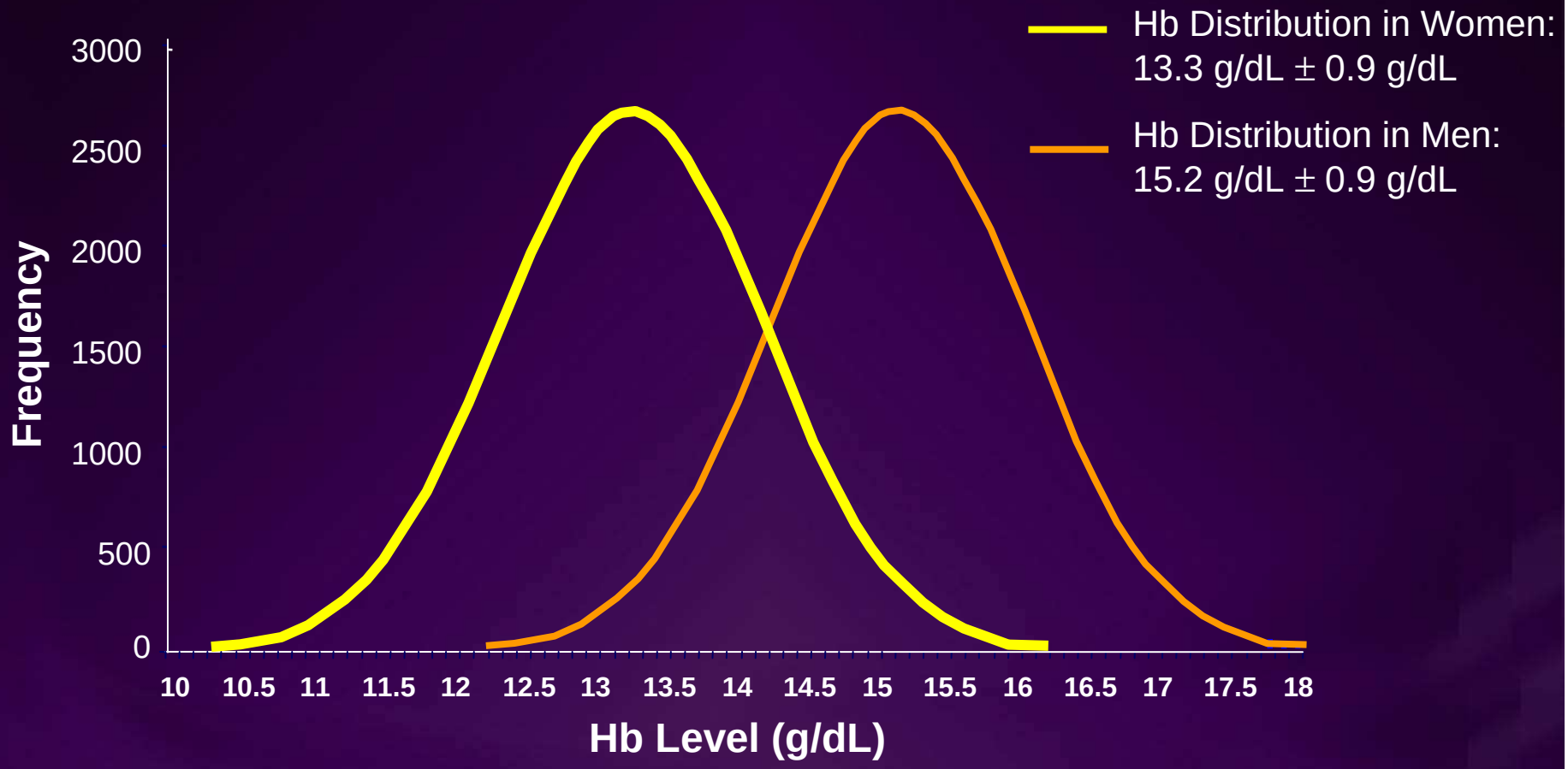
NAAC's Online Resources for Medical Professionals

- 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 is prevalent in critically ill patients
- Most common anemia in the critically ill is secondary to inflammation
- Transfusion in the critically ill has been associated with reduced survival and increased morbidity
- Anemia in the critically ill responds well to erythropoietin therapy, reducing the need for allogenic blood transfusion (ABT)
- Optimal erythropoietin dosing and administrations, and outcome measures must be established

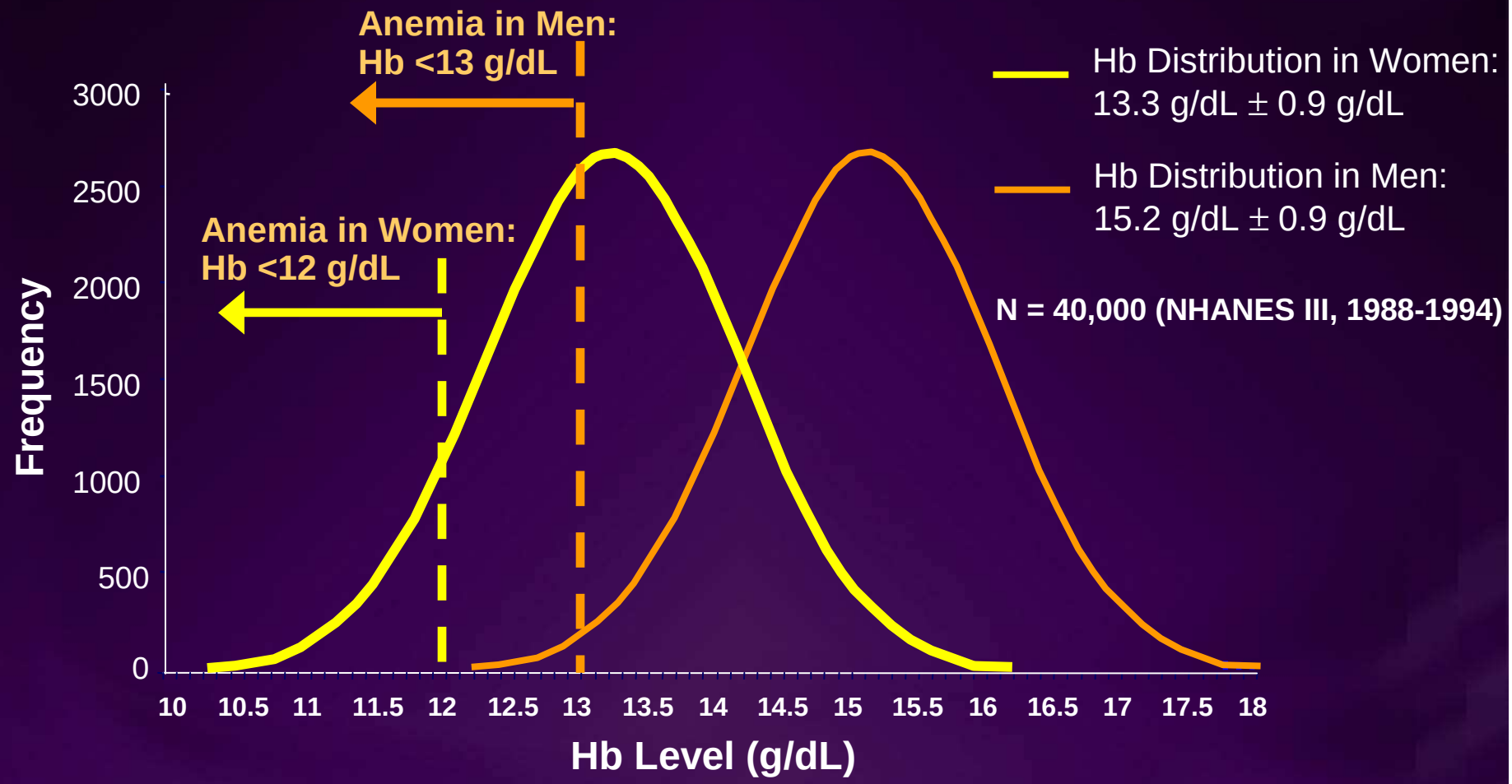
Hemoglobin (Hb) Distribution in the General Population



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.

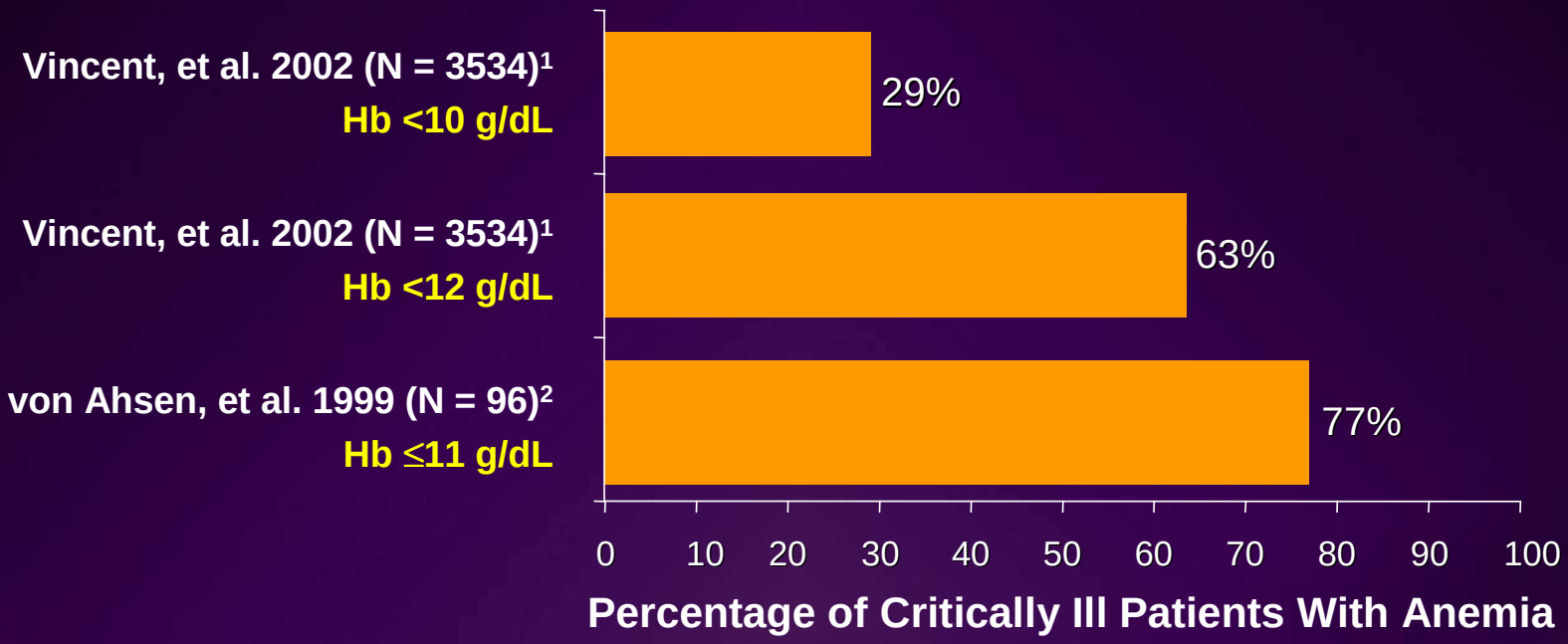
Laboratory Reference Ranges

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/µL)	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, Md: Lippincott, Williams & Wilkins; 1998:2738.

Prevalence of Anemia in Critically Ill Patients



1. Vincent JL, et al. *JAMA.* 2002;288:1499-1507.
2. von Ahsen N, et al. *Crit Care Med*. 1999;27:2630-2639.

Etiology of Anemia in the Critically Ill

- Blood loss (phlebotomies, occult GI bleeding, surgical technique)[1,2]
- Ineffective erythropoiesis (blunted erythropoietin [EPO] production, blunted response to EPO)[1-3]
- Nutritional deficiencies[3]
- Chronic kidney disease[3]
- Inflammation, sepsis[3-4]
- Immune-associated iron deficiencies[3]

1. von Ahsen N, et al. *Crit Care Med.* 1999;27:2630-2639.
2. Darveau M, et al. *Ann Pharmacother.* 2002;36:1068-1074.
3. van Iperen CE, et al. *Crit Care Med.* 2000;28:2773-2778.
4. Vincent J. *JAMA.* 2002;288:1499-1507.

Anemia of Chronic Disease

Certain chronic infections and inflammatory diseases cause several changes in the hematopoietic system.

- Slightly shortened red blood cell life span
- Sequestration of iron in inflammatory cells called macrophages
- Decreased iron availability for red blood cell production

In the presence of these effects a low to moderate grade anemia develops. Symptoms may go unnoticed in the face of the primary disease.

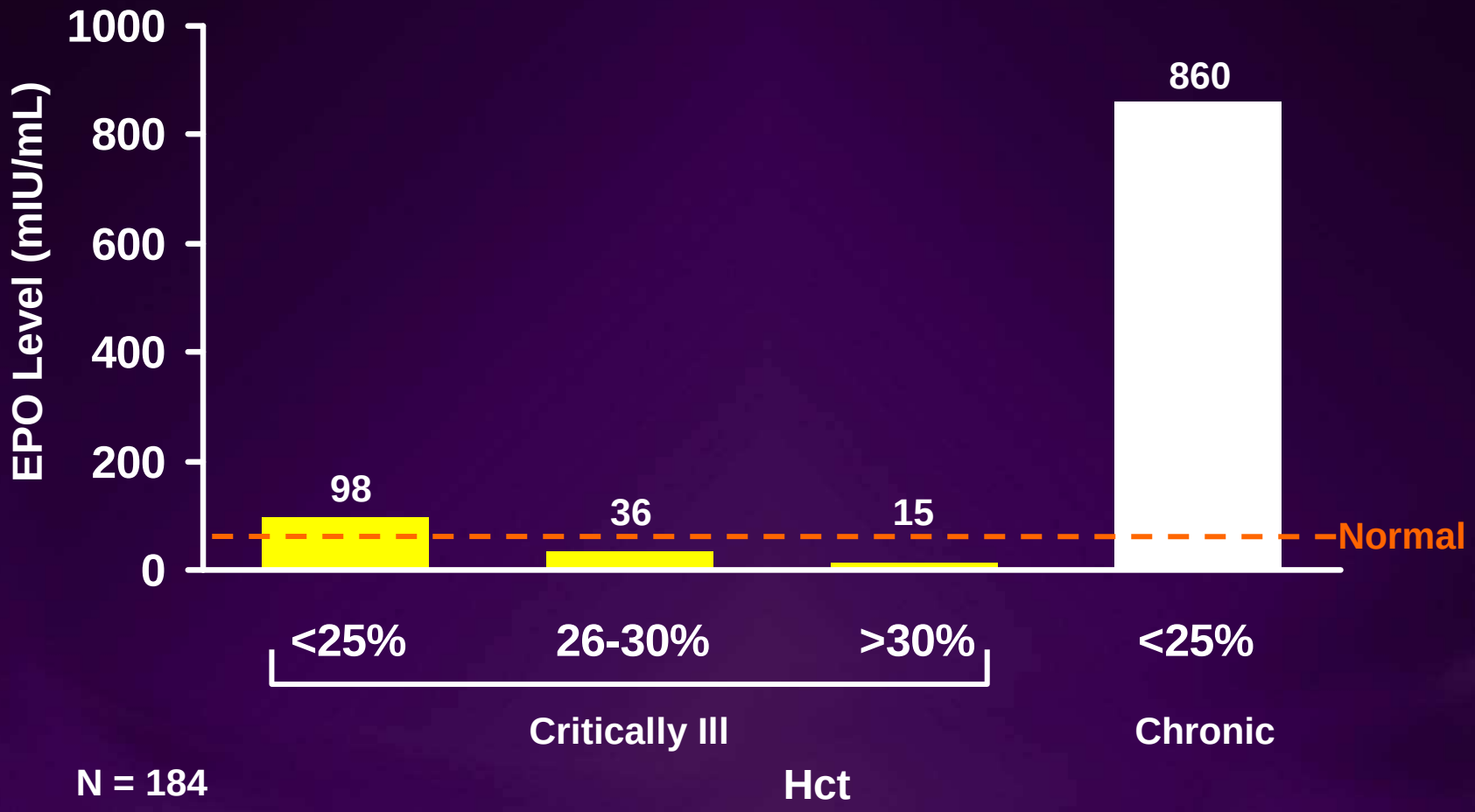
NIH Medline Definition

Anemia in the Critically Ill

- Linked to high levels of inflammatory cytokines[1]
- Mechanisms:
  - EPO response is blunted[1,2]
  - Cytokines directly inhibit RBC formation[1]
  - Increased iron sequestration blunts erythropoietin production[3]

1. von Ahsen N, et al. *Crit Care Med*. 1999;27:2630-2639.
2. Rodriguez RM, et al. *J Crit Care.* 2001;16:36-41.
3. Spivak, JL. Oncology. 2002(Suppl 10);16:25-33.

Relationship Between Erythropoietin Level and Hematocrit in the Critically Ill

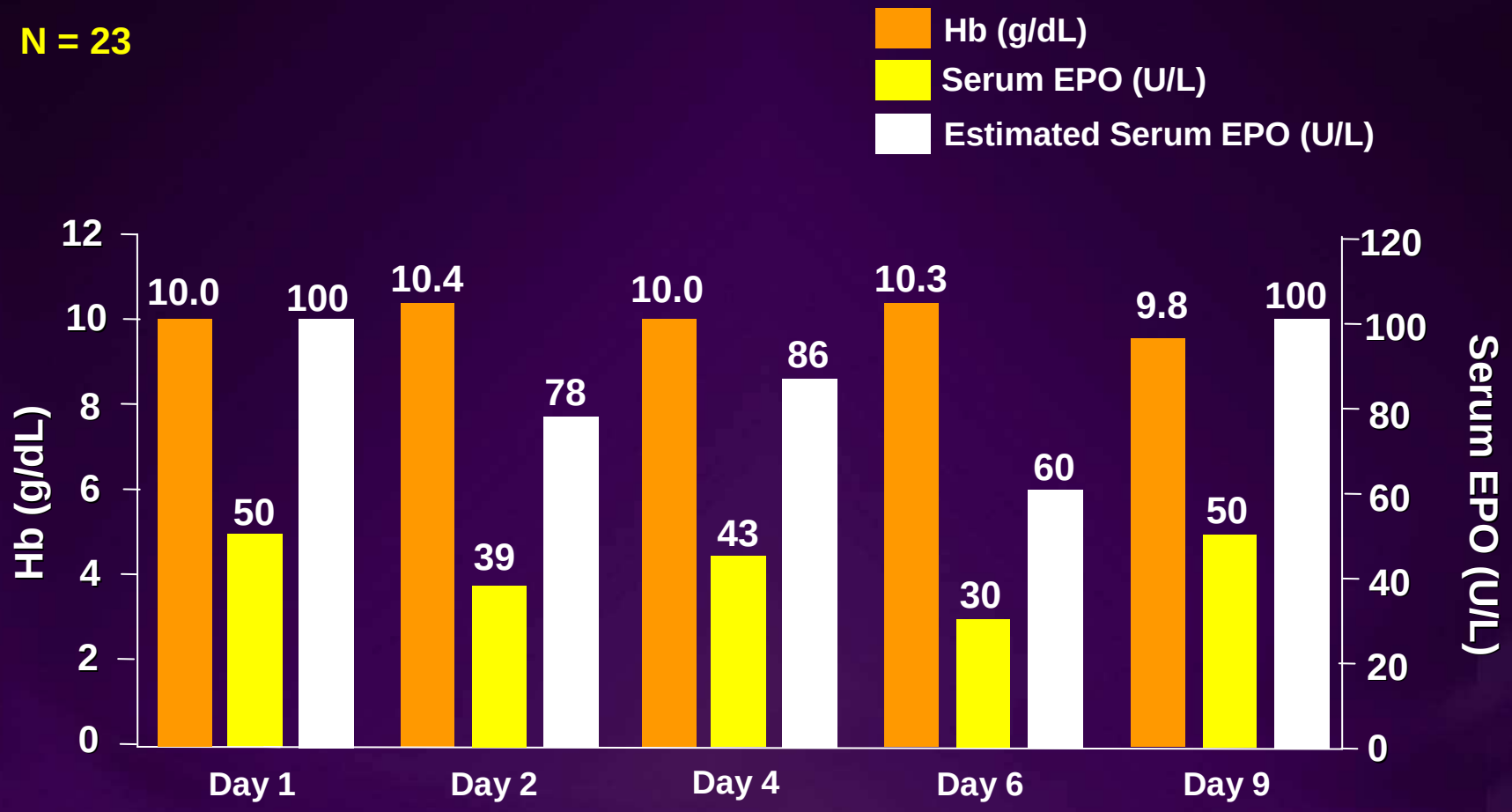


N = 184

Rodriguez RM, et al. *J Crit Care.* 2001;16:36-41.

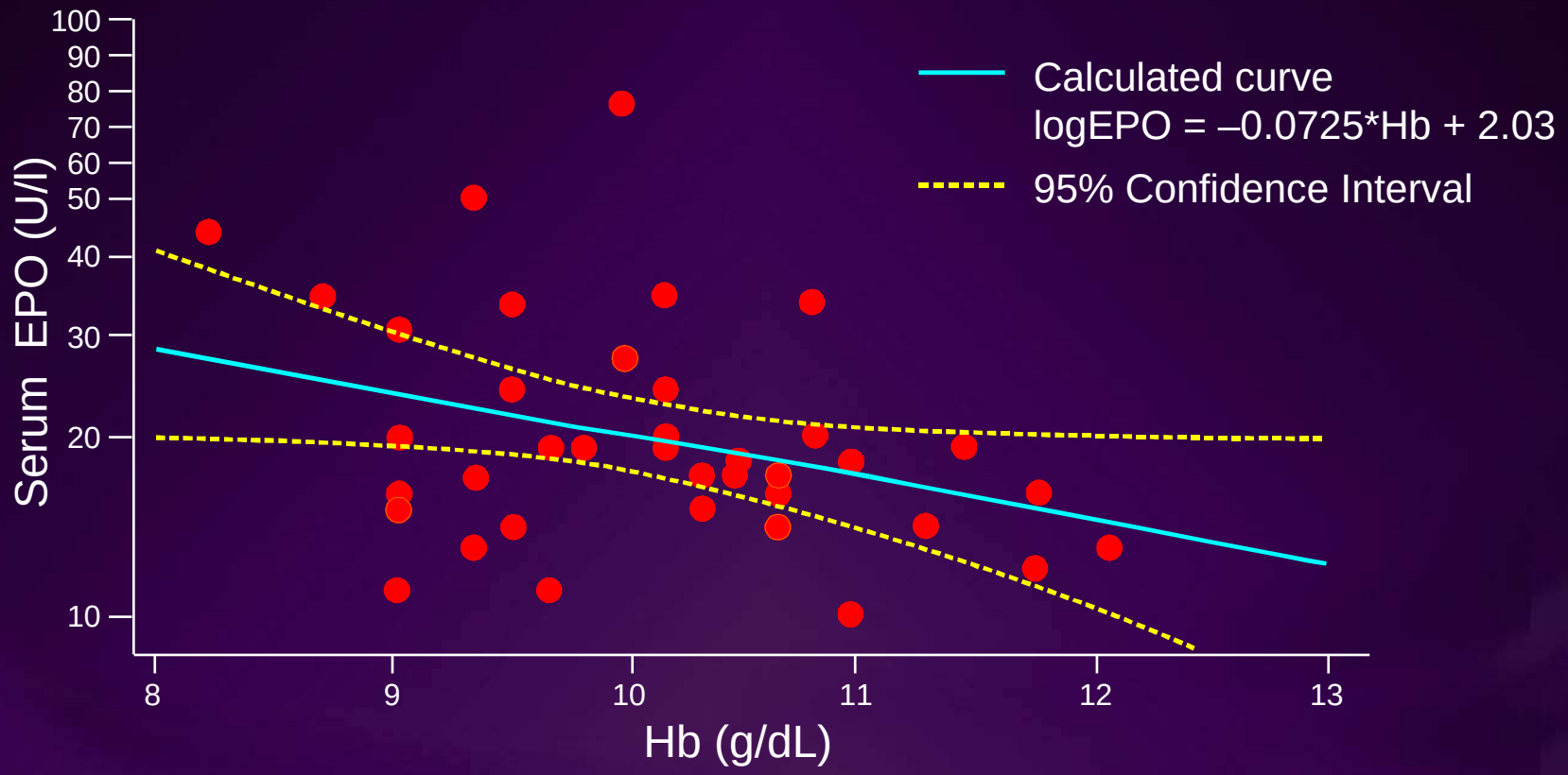
Slide courtesy of Aryeh Shander, MD.

Blunted Erythropoietic Response to Anemia in Multiply Traumatized Patients



Adapted from Hobisch-Hagen P, et al. *Crit Care Med.* 2001;29:743-747.
Slide courtesy of Aryeh Shander, MD.

Blunted EPO Response in Critically Ill Patients



van Iperen CE, et al. *Crit Care Med*. 2000;28:2773-2778.

Possible Increase in Mortality/Morbidity in ICU Patients with Anemia

Data suggest possible link between anemia and the following outcomes:

- Increased mortality in critically ill patients with ischemic heart disease[1]
- Increased risk of delirium[2]

1. Hébert PC, et al. *Am J Respir Crit Care Med.* 1997;155:1618-1623.
2. Aldemir M, et al. *Crit Care.* 2001;5:265-270.

Treatment Options in Anemia Management

- Detection/prevention
- Tolerance of acute anemia (increased threshold for transfusion)
- Erythropoietic stimulating proteins
- Blood transfusion
- Oxygen-carrying solutions (blood substitutes)

Detection/Prevention

- Organize blood draws to avoid unnecessary phlebotomy[1]
- Eliminate arterial line blood discard[2]
- Reduce phlebotomy by eliminating standing blood orders when possible[2]
- Consider pediatric collection tubes for adults[1]

1. McPherson RA. *Clin Leadersh Manag Rev.* 2001;15:3-10.
2. Corwin HL, et al. *Chest.* 1995;108:767-771.

Hemoglobin Thresholds for Allogeneic Blood Transfusion: Published Guidelines

Organization	Year	Trigger Hb (g/dL)
NIH Consensus Conference[1]	1988	8
American College of Physicians[2]	1992	7
American Society of Anesthesiologists[3]	1996	6
Canadian Medical Association[4]	1997	Insufficient evidence
Association of Anaesthetists of Great Britain[5]	2001	8 (a)
Scottish Intercollegiate Guidelines Network[6]	2001	7 (b)

(a) Applies to patients with significant cardiorespiratory disease
(b) 9 g/dL for patients with CVD or likely covert CVD

1. National Institutes of Health. *JAMA.* 1988;260:2700-2703.
2. American College of Physicians. *Ann Intern Med.* 1992;116:403-406.
3. American Society of Anesthesiologists. *Anesthesiology.* 1996;84:732-747.
4. Canadian Medical Association. *Can Med Assoc J.* 1997;156(suppl 11):S1-S24.
5. Association of Anaesthetists of Great Britain & Ireland. *Blood Transfusion and the Anaesthetist: Red Cell Transfusion*. 2001.
6. Scottish Intercollegiate Guidelines Network. 2001.

Multicenter Study Evaluates Hemoglobin Threshold for ICU Patients

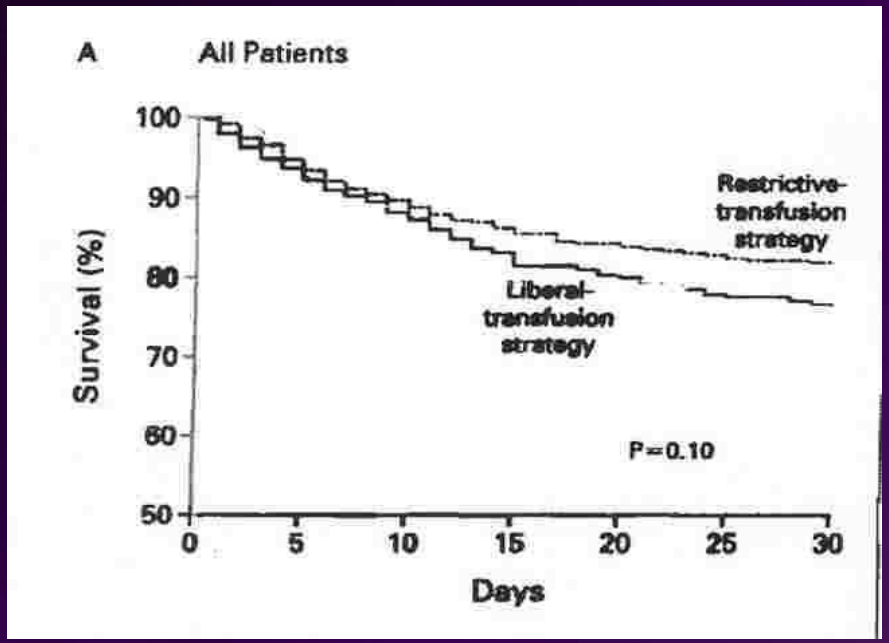
Transfusion Requirements in Critical Care (TRICC) Study

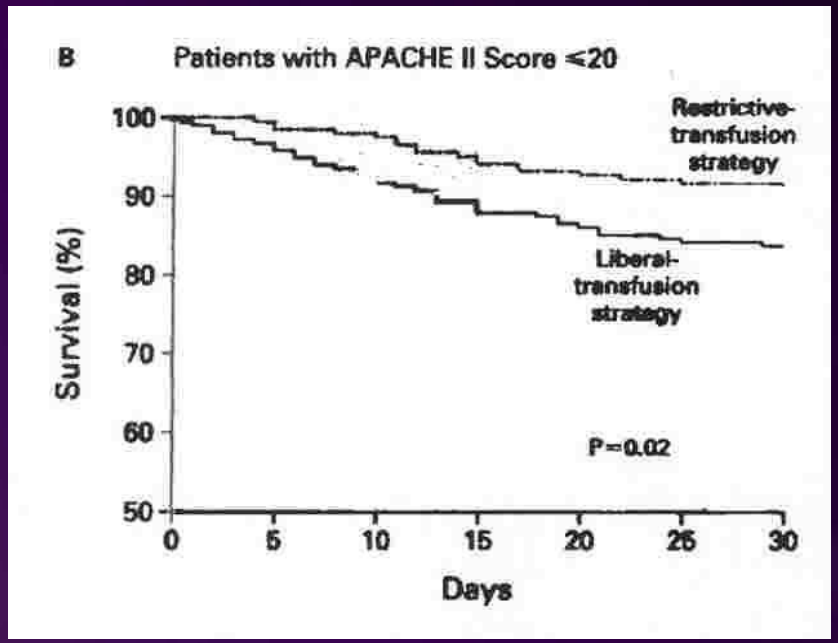
- Multicenter, randomized, controlled study of 838 normovolemic patients[1]
- First study adequately powered to evaluate ICU transfusion triggers[2]
- Compared 2 strategies regarding Hb threshold:[1]
  - Restrictive (transfuse at 7 g/dL, maintain at 7 g/dL-9 g/dL)
  - Liberal (transfuse at 10 g/dL, maintain at 10 g/dL-12 g/dL)

1. Hébert PC, et al. *N Engl J Med.* 1999;340:409-417.
2. Hébert PC, et al. *JAMA.* 2002;288:1525-1526.

Transfusion to Higher Hb Does Not Benefit ICU Patients

Results of the TRICC Trial





Hébert PC, et al. *N Engl J Med.* 1999;340:409-417.
Slide courtesy of Aryeh Shander, MD.

Patients who are Critically Ill with Heart Disease: Transfusion Threshold Safety Studies

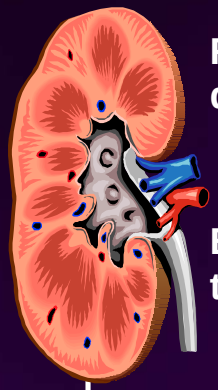
Study	N	Findings
Hébert, et al *Chest*, 2001	713 on mechanical ventilation	The liberal transfusion strategy did not decrease the duration of ventilation compared with the restrictive strategy
Hébert, et al *Crit Care Med*, 2001	357 with CVD	Mortality rates were similar with the two transfusion strategies In the subgroup of 257 patients with severe ischemic heart disease (IHD), the restrictive strategy was associated with lower absolute survival rates than the liberal strategy

1. Hébert PC, et al. *Chest.* 2001;119:1850-1857.
2. Hébert PC, et al. *Crit Care Med.* 2001;29:227-234.

Erythropoietic Stimulating Proteins

- Peptide hormones and their derivatives, manufactured by recombinant DNA technology, which stimulate the production of red blood cells
  - Recombinant human erythropoietin (rHuEPO)
    - eg, epoetin alfa, epoetin beta, epoetin omega
  - Darbepoetin alfa

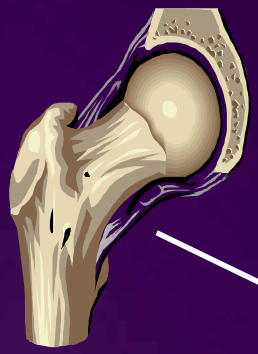
Erythropoietin Regulates Red Blood Cell Production



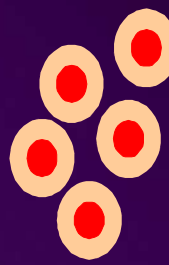
Renal interstitial peritubular cells detect low blood oxygen levels

Erythropoietin (EPO) secreted into the blood

EPO



EPO stimulates the proliferation and differentiation of erythroid progenitors into reticulocytes, and prevents apoptosis



More reticulocytes enter circulating blood

Reticulocytes differentiate into erythrocytes, increasing the erythron size

Increased oxygen delivery to tissues

1. Dessypris E. In: Lee G, et al, eds. *Wintrobe's Clinical Hematology (Vol. 1)*. Baltimore, Md: Lippincott, Williams & Wilkins; 1998:169-192.
2. 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.

rHuEPO Stimulates Erythropoiesis in ICU Patients

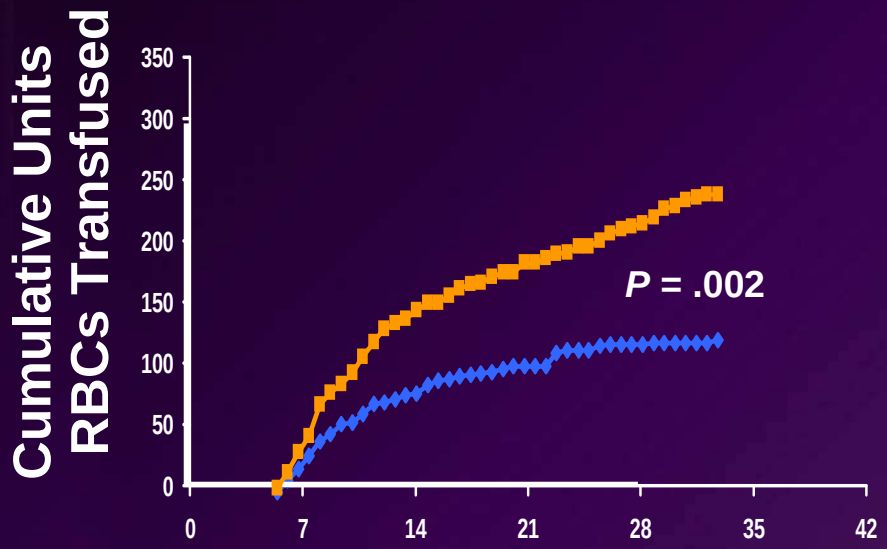
Study	N	Outcome
Gabriel, et al, 1998	19	In the rHuEPO group, reticulocyte count improved significantly compared with baseline ($P < .006$) and placebo ($P < .04$)
Corwin, et al, 1999	160	Final Hct was significantly greater with rHuEPO than with placebo ($P < .01$)
van Iperen, et al, 2000	36	EPO level, reticulocyte count, and serum transferrin receptor significantly increased in the rHuEPO group over baseline ($P < .05$)
Corwin, et al, 2002	1302	Increase in Hb was significantly greater with rHuEPO than with placebo ($P < .001$)

1. Gabriel A, et al. *J Trauma.* 1998;44:361-367.
2. Corwin HL, et al. *Crit Care Med.* 1999;27:2346-2350.
3. van Iperen CE, et al. *Crit Care Med.* 2000;28:2773-2778.
4. Corwin HL, et al. *JAMA.* 2002;288:2827-2835.

rHuEPO Reduces Requirement for Red Blood Cell Transfusions

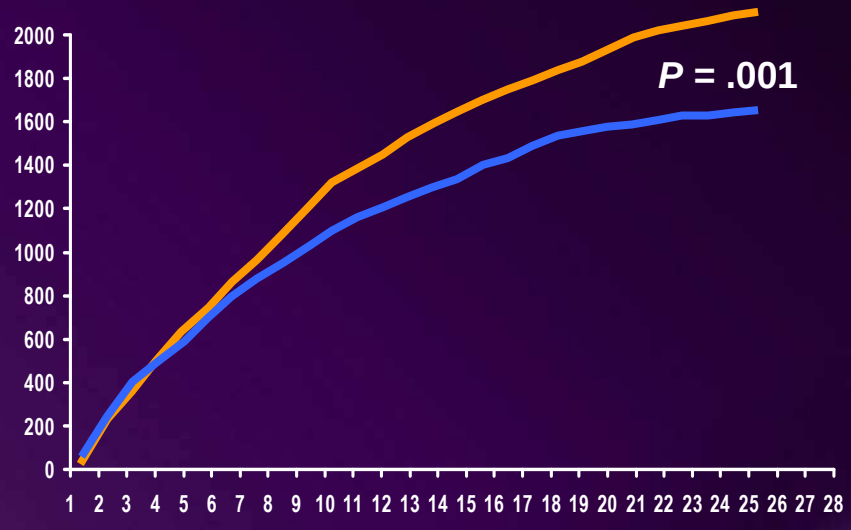
Placebo — Epoetin alfa

1999 Study (N = 160)



45% reduction in RBC units transfused (*P* < .002)

2002 Study (N = 1302)



19% reduction in RBC units transfused per day alive (*P* = .04)

1. Corwin HL, et al. *Crit Care Med*. 1999;27:2346-2350.
2. Corwin HL, et al. *JAMA*. 2002;288:2827-2835.

Issues Under Investigation Regarding rHuEPO for ICU Patients

- Are morbidity and mortality better outcome measures than reduction of the need for ABT?[1]
- Is high-dose rHuEPO cost effective?[2,3]
- What is the optimal dosage of rHuEPO?[2,3]
- Is IV iron safe for critically ill patients?[3]
- How does rHuEPO affect nonerythroid cells?[3]
- Effect of rHuEPO on neuronal, muscle, and other tissues?

1. Carson J. *JAMA.* 2002;288:2884-2886.
2. Darveau M, et al. *Ann Pharmacother.* 2002;36:1068-1074.
3. Eckardt K-U. *Nephrol Dial Transplant.* 2002;17(suppl 5):48-55.

Oxygen-Carrying Solutions

- Still investigational
- Two types:
  - Hemoglobin-based oxygen carriers (HBOC)
  - Perfluorocarbon emulsions
- Some may not require refrigeration[1]
- Could be used with or without acute normovolemic hemodilution (ANH)[1]
- Could be used as bridge to EPO therapy[2]

1. Goodnough LT, et al. *Lancet.* 2003;361:161-169.
2. Gannon CJ, et al. *Crit Care Med.* 2002;30:1893-1895.

Transfusion

Transfusion Prevalence in the ICU

- Studies report varying percentages of ICU patients receiving transfusions:
  - Groeger, et al: 4% to 27% transfused each day[1]
  - Littenberg, et al: 47% transfused during any stay[2]
  - Von Ahsen, et al: 39% transfused within 3-week length of stay[3]
  - Corwin, et al: 85% of patients staying in ICU >1 week were transfused with ≥1 unit of RBCs (mean 9.5 ±0.8 units)[4]

1. Groeger JS, et al. *Crit Care Med.* 1993;21:279-291.
2. Littenberg B, et al. *Immunohematology*. 1995;11:8894.
3. von Ahsen N, et al. *Crit Care Med*. 1999;27:2630-2639.
4. Corwin HL, et al. *Chest.* 1995;108:767-771.

Slide courtesy of Aryeh Shander, MD.

Allogeneic Blood Transfusion Current Guidance

Red-cell containing components should not be used to treat anemia that can be corrected with specific medications such as iron, vitamin B_{12}, folic acid, or recombinant erythropoietin, except when the patient's symptoms require immediate enhancement of oxygen-carrying capacity.

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

Some Risks of Allogeneic Blood Transfusion[1]

Blood Transfusion Risk	No. Deaths per Million Units	Estimated Frequency per Unit
VIRUS		
Hepatitis B		1/60,000-1/200,000
Hepatitis C	0.5-17	1/800,000-1/1.6 x 10^6
HIV	0.5-5	1/1.4-2.4 x 10^6
BACTERIA		
Red cells		1/500,000
Platelets		1/2000
ACUTE HEMOLYTIC REACTIONS	0.67	1/250,000-1,000,000
DELAYED HEMOLYTIC REACTIONS		1/1000
TRANSFUSION-RELATED ACUTE LUNG INJURY		1/8000
ABO CLERICAL ERROR[2]		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.

Immune Effects of Blood

- Immunologic effects of autologous/allogeneic blood transfusion:
  - Decreased T-cell proliferation
  - Decreased $CD3^+$, $CD4^+$, $CD8^+$ T cells
  - Increased soluble cytokine receptor
    - sTNF-R, sIL-2R
  - Increased serum neopterin
  - Increased cell-mediated lympholysis
  - Increased TNF-α
  - Increased suppressor T-cell activity
  - Reduced natural killer cell activity

1. McAlister FA, et al. *Br J Surg.* 1998;85:171-178.
2. Innerhofer P, et al. *Transfusion.* 1999;39:1089-1096.

Slide courtesy of Aryeh Shander, MD.

Survival of Donor Leukocytes in Transfusion Recipients

- Persistence of donor leukocytes in trauma patients for up to 1.5 years after an ABT
- "Survival of donor leukocyte subpopulations in immunocompetent transfusion recipients: frequent long-term microchimerism in severe trauma patients"
  - 2×10^9 WBCs in one unit of packed RBCs
  - 1×10^8 WBCs – centrifuged, buffy coat depleted
  - $1–5 \times 10^6$ WBCs – leukocyte filter, leukocyte-depleted

Lee T-H, et al. *Blood.* 1999;93:3127–3139.
Slide courtesy of Aryeh Shander, MD.

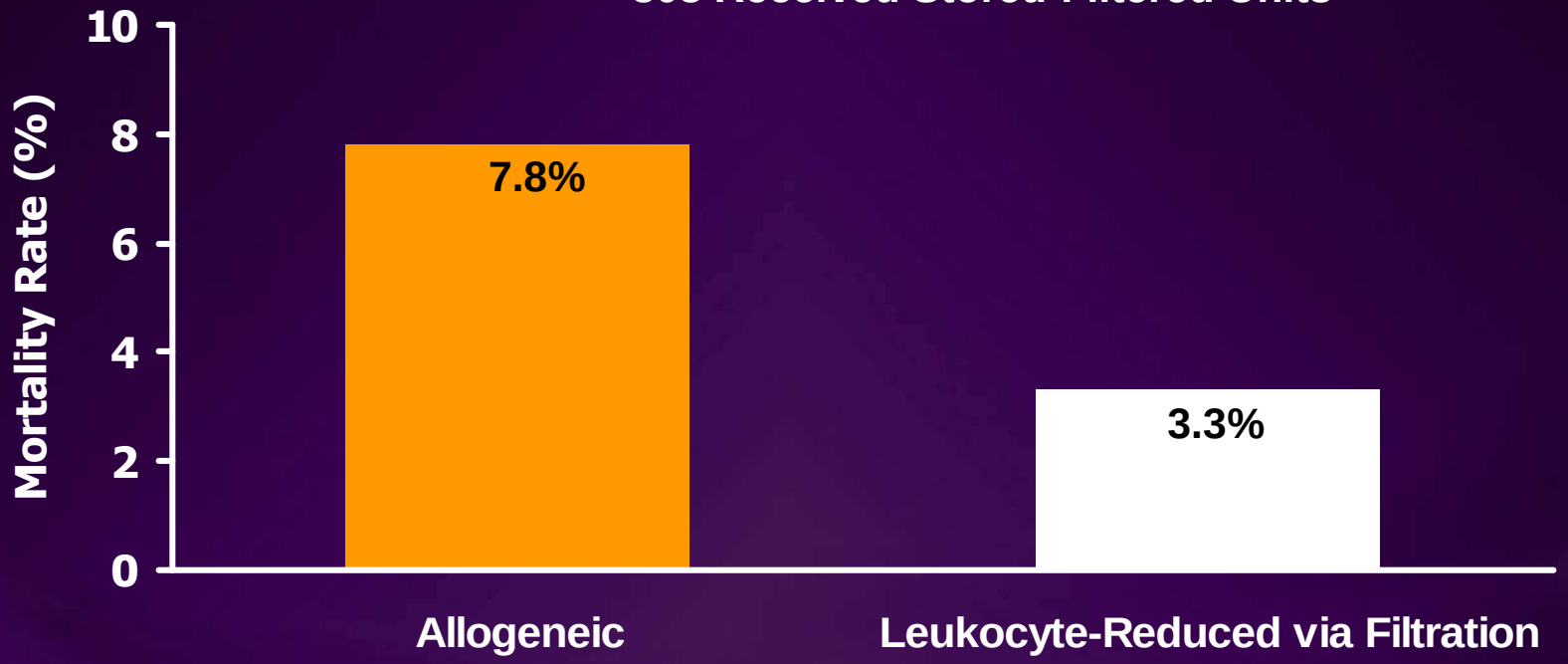
Leukocyte Depletion

- Prevalent belief that leukocyte depletion alleviates immune modulation[1,2]
  - Despite conclusive evidence, leukocyte depletion practice is mandatory in Europe
- A recent randomized, controlled study shows no clinical difference between leukocycte-reduced and nonleukocycte–reduced RBC transfusions[3]
  - Is there truly no difference or was there inadequate leukocyte depletion?

1. Jensen LS, et al. *Lancet.* 1996;348:841-845.
2. van de Watering LMG, et al. *Circulation.* 1998;97:562-568.
3. Dzik WH, et al. *Transfusion*. 2002;42:1114-1122.
Slide courtesy of Aryeh Shander, MD.

Mortality Rates Are Lower When Leukocyte-Reduced Blood Is Used

N = 914
306 Received Packed Cells Without Buffy Coat
305 Received Fresh-Filtered Units
303 Received Stored-Filtered Units



van de Watering LMG, et al. *Circulation.* 1998;97:562-568.
Slide courtesy of Aryeh Shander, MD.

A Prospective, Randomized Clinical Trial of Universal Leukocyte Reduction

	Control Group	Leukocyte-Reduced Group
Number of In-Hospital Deaths	121 (8.5%)	122 (9.0%)
Mean Length of Stay From First Transfusion	10.6 days ±14.5 days	10.3 days ±13.7 days
Mean Total Hospital Cost	$29.8K ±$33.2K	$29.0K ±$34.0K
Mean Length of Nonprophylactic Antibiotic Use After Transfusion	5.1 days	4.5 days

N = 2780; no demographic differences between groups

Dzik WH, et al. *Transfusion*. 2002. 42:1114-1122.
Slide courtesy of Aryeh Shander, MD.

Transfusion: Problems With Oxygen Delivery

- Storage of RBCs can lead to:[1,2]
  - Impaired ability of RBCs to distribute oxygen
  - Microcirculatory occlusion
- Greater age of blood has been linked to increased risk of death,[2] pneumonia,[2] and splanchnic ischemia[3]
- In patients with sepsis, transfusion does not appear to increase oxygen uptake[3-5]

1. Corwin HL, et al. *Crit Care Med.* 1999;27:2346-2350.
2. Carson J. *JAMA.* 2002;288:2884-2886.
3. Marik P, et al. *JAMA.* 1993;269:3024-3029.
4. Lorente JA, et al. *Crit Care Med.* 1993;21:1312-1317.
5. Gramm J, et al. *Shock.* 1996;5:190-193.

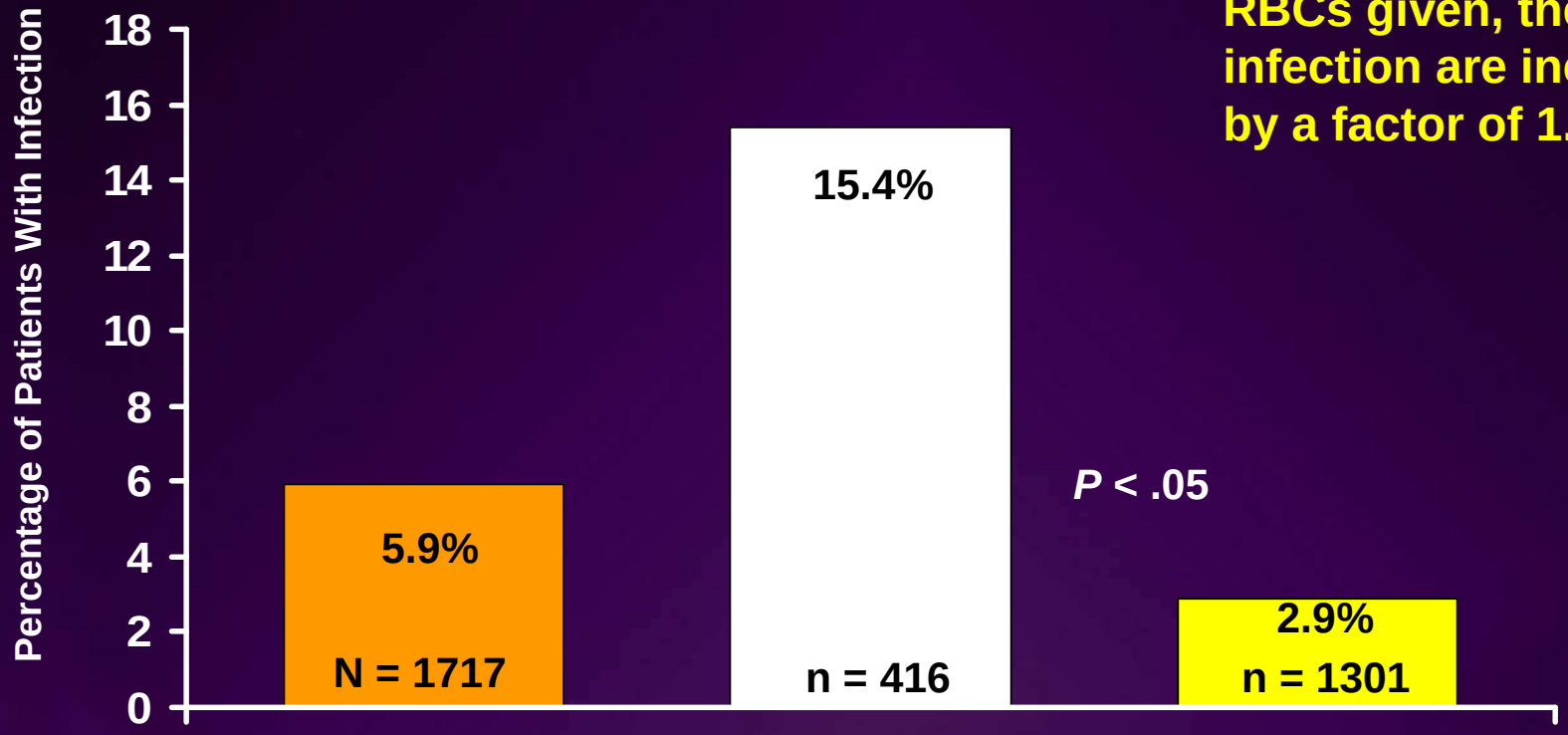
Potential Risks Associated With Transfusion

- Transfused patients have
  - Longer ICU stays
  - Higher mortality
    - Risk of death increased by factor of 1.4 in transfused patients
  - Diminished organ function
  - Increased risk of infection

1. Vincent JL, et al. *JAMA*. 2002;288:1499-1507.
2. Taylor RW, et al. *Crit Care Med*. 2002;30:2249-2254.

Nosocomial Infection Rates in Critically Ill Patients

For each unit of packed RBCs given, the odds of infection are increased by a factor of 1.5

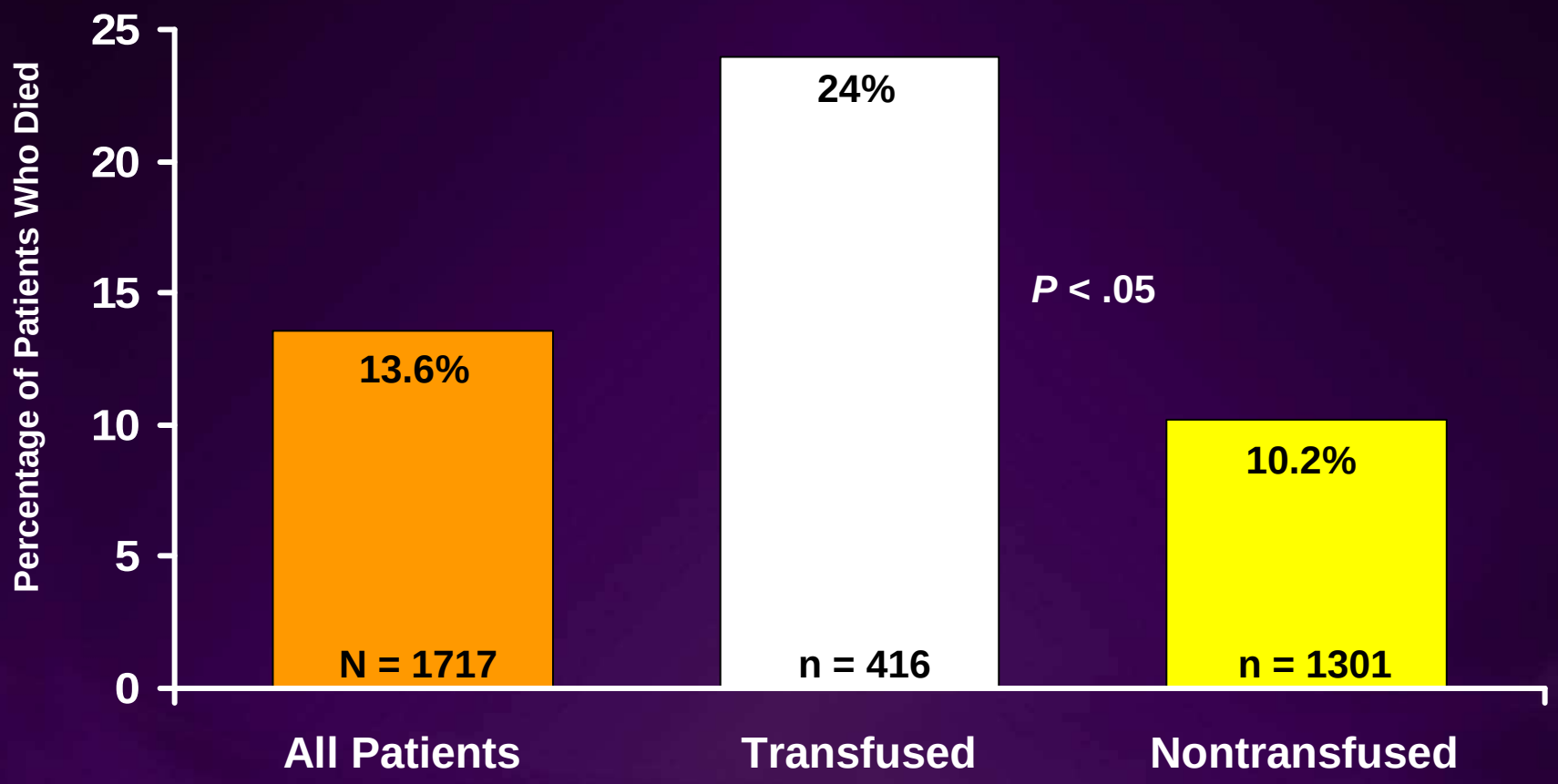


Adjusted for severity of illness using MPM-0 scores, age, gender (Project IMPACT).

Taylor RW, et al. *Crit Care Med*. 2002;30:2249-2254.

Slide courtesy of Aryeh Shander, MD.

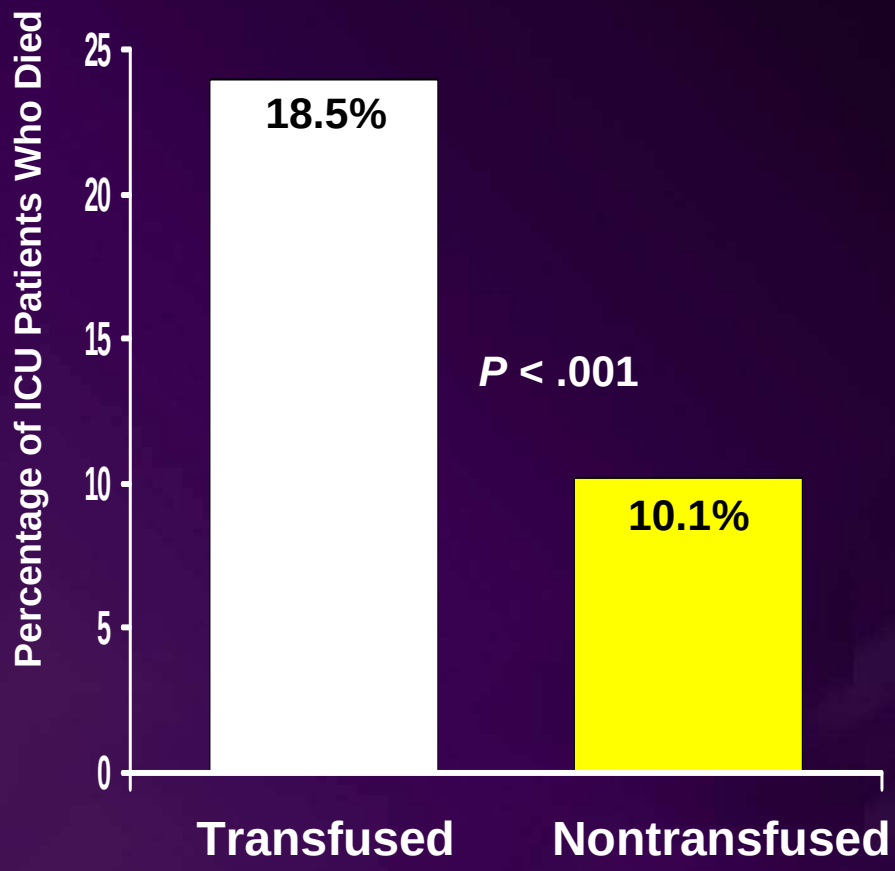
Mortality Rates in Critically Ill Patients



Taylor RW, et al. *Crit Care Med*. 2002;30:2249-2254.
Slide courtesy of Aryeh Shander, MD.

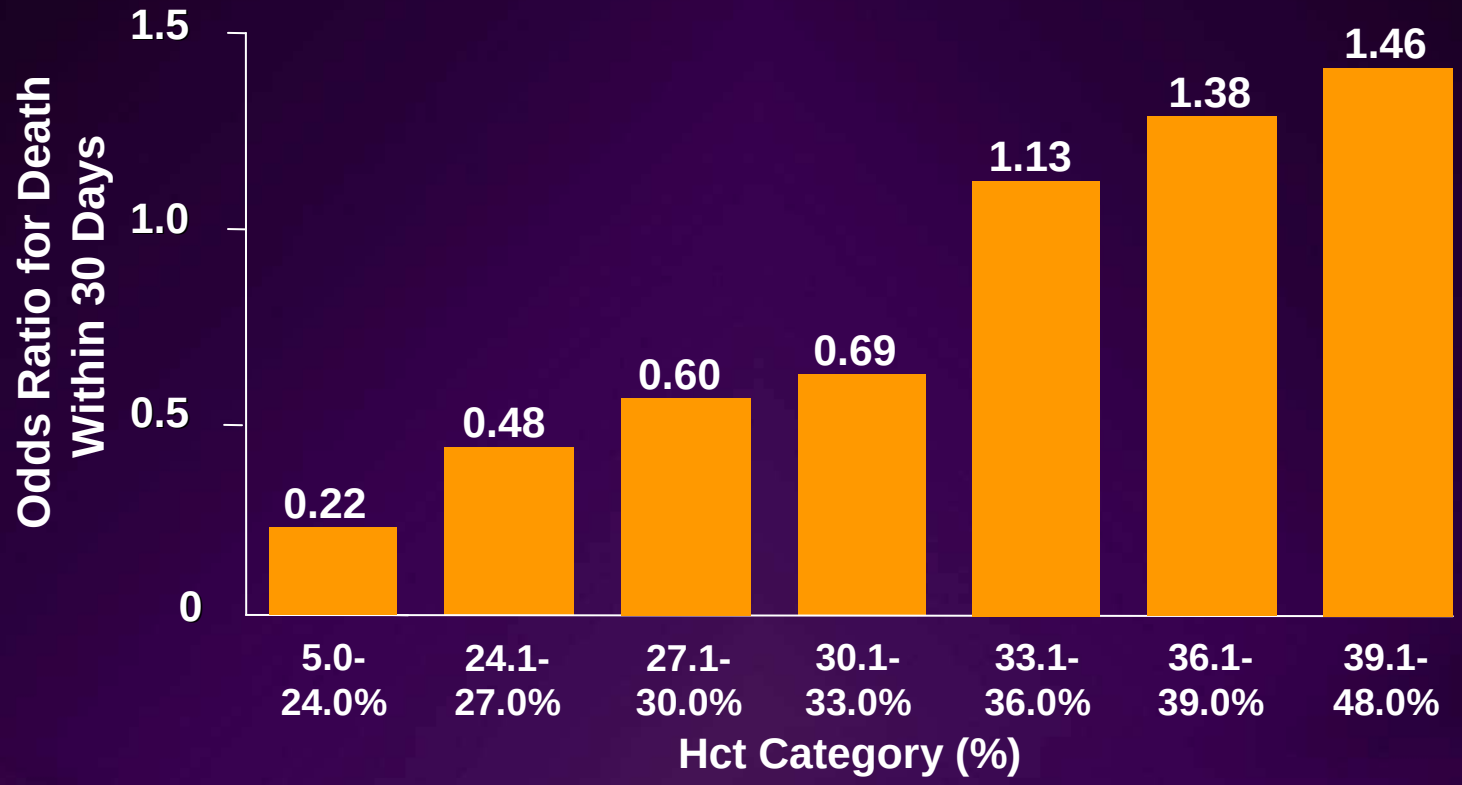
Mortality Rates in Transfused Critically Ill Patients

- Transfusion rate was 37% among ICU patients
- Hb as transfusion trigger was similar (8.4 g/dL) in all groups of patients (bleeding versus nonbleeding)
- Mortality associated with transfusion was independent of severity of illness and Hb level



Vincent JL, et al. *JAMA*. 2002;288:1499-1507.

Transfusion Associated With Lower 30-Day Mortality in Elderly AMI Patients With Severe Anemia



AMI = Acute Myocardial Infarction

N = 78,974 Medicare recipients ≥65 years of age

Wu W-C, et al. *N Eng J Med.* 2001;345:1230-1236.

Summary

- Anemia is highly prevalent in critically ill patients
- Transfusion in the ICU has been linked to reduced survival and increased morbidity
- Anemia in the ICU is often induced by inflammation and responds well to rHuEPO, reducing the need for ABT
- Optimal dosing of rHuEPO, frequency of administration, and outcome measures need to be established
- Additional anemia treatment modalities are on the horizon

Please send feedback on this slide set to info@anemia.org