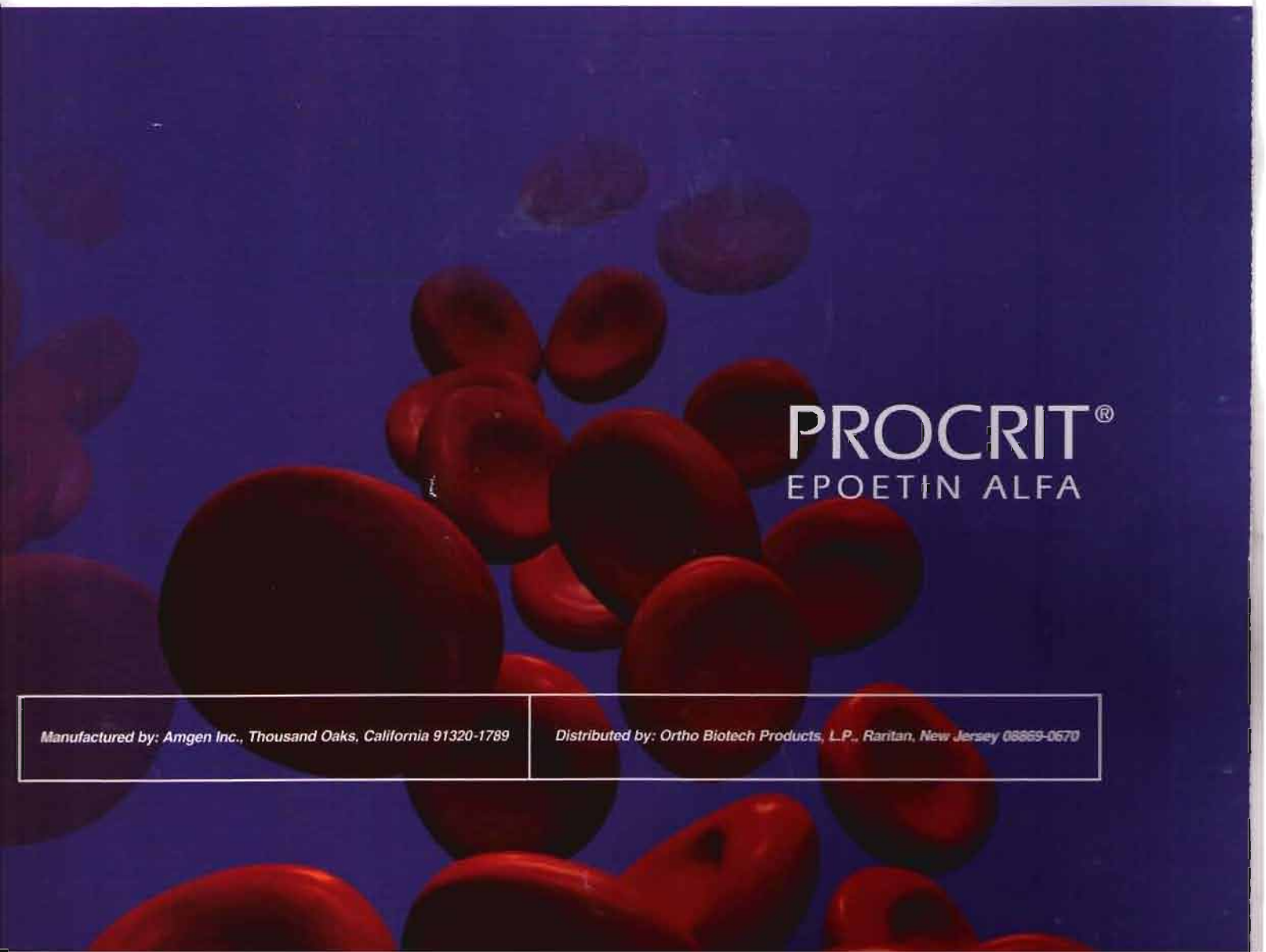
Critical Decisions

in Managing Anemia



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Tissue Hypoxia in Critical and Chronic Illness

Tissue Hypoxia: Prevalence and Impact

- Prevalent in critically ill patients[1,2]
- Common in many chronic diseases, including diabetes,[3] chronic kidney disease,[4] and chronic liver disease[5]
- Important cofactor in morbidity and mortality[6]
- Often difficult to detect using standard measures for assessing systemic oxygenation[7]

Consequences of Tissue Hypoxia: Emerging Research

New research links tissue hypoxia with:

- The development of multiple organ dysfunction[7,8]
- The pathogenesis of hemorrhagic and septic shock[1]
- Physiologic changes in the pulmonary vasculature that result in pulmonary hypertension[9]
- The development of right ventricular hypertrophy in patients with COPD[10] and left ventricular hypertrophy in patients with chronic renal failure[11]
- The risk of developing tachyarrhythmias in surgical intensive care patients[12]
- Poor neurological outcome in patients with severe head injury[13,14]
- Impeded wound healing[15]
- The initiation and progression of chronic renal disease[4,16]
- The initiation of visual and vascular dysfunction in diabetic retinopathy[17]
- Reduced efficacy of radiation therapy in head and neck cancer patients[18]
- Increased expression of vascular endothelial growth factor, a marker for angiogenesis, in patients with prostate cancer[19]

Age of Blood

Storage Changes Blood

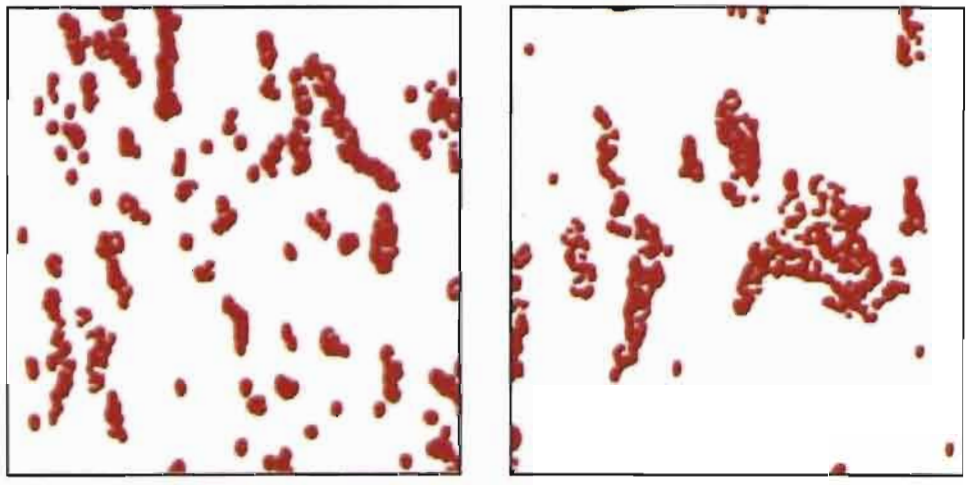
Negative impact of storage on blood characteristics:

- Storage of blood at 25° to 30°C causes a significant loss of 2,3-DPG.[1] Under common storage conditions, red blood cells (RBCs) begin to lose 2,3-DPG within the first week of storage, and the loss is complete by week 2[2]
- When stored, erythrocytes become less deformable and blood viscosity is modified[3]

Consequences of Blood Storage

- Loss of 2,3-DPG decreases the RBC's ability to transport and release oxygen[1]
- Poorly deformable RBCs may cause microcirculatory occlusion, possibly leading to tissue ischemia in some organs[4]
- Storage of RBCs may significantly impair the viability of transfused RBCs[5]
- The transfusion of stored RBCs may increase aggregability in vivo[6]

Micrographs of RBC aggregates.[6]



Fresh blood **Blood stored 35 days**

Reproduced with permission from Hovav et al. *Transfusion.* 1999;39:277-281.

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Transfusion Risks

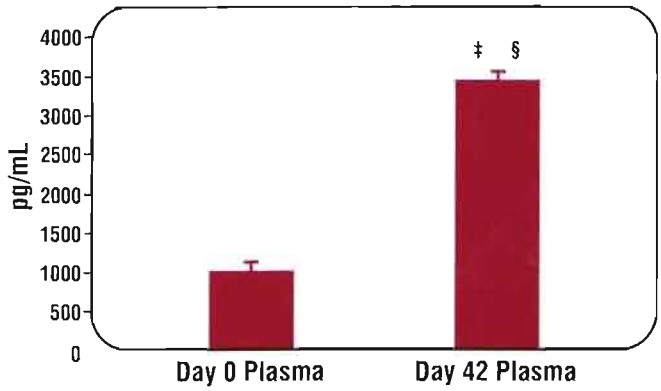
Allogeneic Blood Transfusion May Be Associated With Increased Mortality

- Liberal use of transfusion* may be associated with higher in-hospital mortality rates[1]
- A higher mortality rate was found among HIV-infected patients who had received transfusions[2]

Allogeneic Red Blood Cell Transfusion May Be Associated With:

- **The release of inflammatory cytokines.** Plasma from packed red blood cells (PRBCs) stored for 42 days[†] selectively primes neutrophils (PMN) to release interleukin-8 (IL-8) and secretory phospholipase A_2, which may be one of the mechanisms responsible for the development of multiple organ failure (MOF)[3]

PMN IL-8 release.



Healthy donor PMNs were incubated with 20% PRBC plasma in cell culture medium for 24 hours and the release of IL-8 was measured. Day 0 plasma did not stimulate IL-8 release, whereas, plasma from day 42 PRBC stimulated significant IL-8 release.

- A **marked drop in natural killer cells**,[4] reducing the body's ability to fight infection, which may persist for years[5]
- Repeated transfusions can lead to more pronounced and prolonged **immunosuppression**[6]
- The development of **MOF**. A relationship has been demonstrated between blood transfusion and subsequent development of MOF, ***independent*** of other risk factors. Most patients at risk for MOF need hemoglobin (Hb) loading to meet oxygen demands[7]
- A higher rate of **hospital-acquired infection, more days on antibiotics,** and **longer hospital stays**[4]

* Liberal transfusion strategy: Hb of 10 g/dL was used as a transfusion trigger in this group.
† PRBCs stored for 42 days are considered transfusable under American Association of Blood Banks guidelines.
‡ $P<.05$ from day 0.
§ $P<.05$ from cell culture medium.

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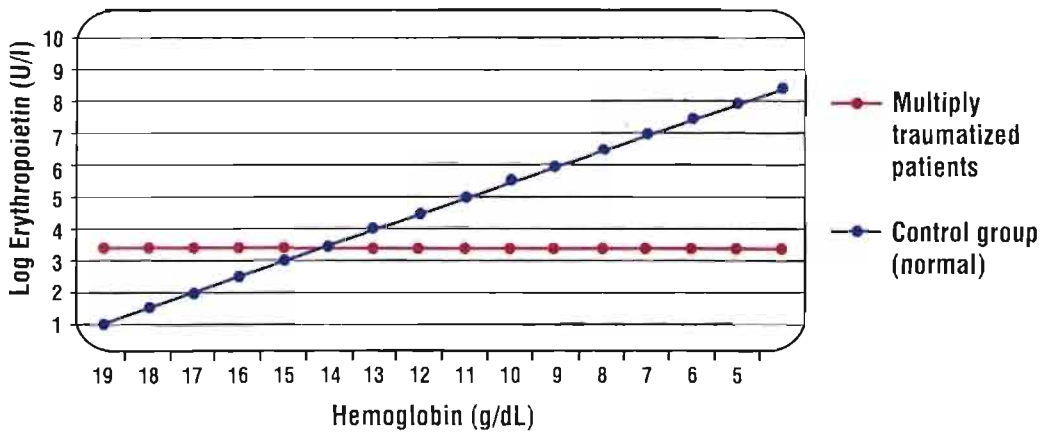
Impact of Anemia

Anemia in Critically Ill Patients

- Critically ill patients fail to produce adequate erythropoietin in response to anemia[1]
- Frequent phlebotomy in the ICU also contributes to anemia[2,3]
- Critical illness confounds patients' ability to tolerate anemia[4]
- Critical illness is often unstable and is associated with heightened metabolic demands that make intolerance of anemia difficult to predict[4]
- Clinical monitoring of hemoglobin (Hb) levels is needed to prevent outcomes such as angina, high-output congestive heart failure, and tissue hypoxia/ischemia[4]

Serum erythropoietin levels do not rise appropriately in critically ill, anemic patients.[5]



Serum erythropoietin and degree of anemia in multiply traumatized patients (n=23) compared to control (normal) patients (n=63). Adapted with permission from Hobisch-Hagen et al. *Crit Care Med.* 2001;29:743-747.

Critically ill patients may experience an inflammatory response, due to either an underlying chronic disease or an acute event, which can cause anemia through 4 mechanisms.

Inflammatory cytokines:

- Directly inhibit expression of the erythropoietin gene[6]
- Are myelosuppressive[7,8]
- Inhibit red blood cell (RBC) survival[9] and accelerate RBC clearance[10]
- Inhibit release of iron stores from reticuloendothelial cells[7]