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Anemia in the critically ill

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The US National Center for Health Statistics, a division of the US Department of Health and Human Services, estimated in 1996 that 3.4 million Americans were living with anemia. Anemia is present in a substantial number of patients with a variety of chronic and serious diseases, including chronic kidney disease, cancer, diabetes, cardiovascular disease, HIV/AIDS, rheumatoid arthritis, and inflammatory bowel disease. Anemia is the primary cause of red blood cell transfusions. Anemia can be both acute (eg, hemorrhage) and chronic (eg, anemia of chronic disease), and it is especially prevalent and even expected in critical care settings. This article describes the underlying physiology of anemia and the various ways by which red blood cell production can be affected by ongoing disease processes [1–3].

In critically ill patients, the body's erythropoietic response to anemia is blunted as a consequence of diminished iron availability and the direct inhibitory effects of inflammatory cytokines. [1]

A descriptive analysis of adult intensive care units (ICUs) in the United States found that approximately 3500 transfusions are given daily to ICU patients [4], which translate to approximately 1.25 million transfusions per year in United States ICUs. Daily ICU bed census for gastrointestinal (GI) hemorrhage has been estimated to be 3%, or 1.1 patients per ICU per day throughout the United States [4]. The estimates for burns (4%), renal insufficiency (2.1%), sepsis (4%), and trauma (3.4%) add to the complex mix of intensive care patients and may result in anemic patients [4]. A large epidemiological study in European ICUs recently validated the common occurrence of anemia in critically ill patients and reported than lower hemoglobin levels were associated with longer ICU length of stray and in-hospital mortality [5]. Furthermore, this study reported that in patients with ICU length of stay greater than 7 days, 73% received a blood transfusion

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and had a mean overall pretransfusion hemoglobin level of 8.4%, thus highlighting the incidence and severity of anemia in critically ill patients [5].

It is estimated that there are 10 million people in the United States with cancer. Of these, 1.3 million cancer patients are anemic with hemoglobin levels less than 12 mg/dL [6]. Many of these patients will be admitted to the ICU for postoperative management or critical illness (eg, pneumonia).

Erythropoiesis

Erythropoiesis is the development of mature red blood cells (RBCs, erythrocytes). Like all blood cells, RBCs begin as stem cells. The first cell that is recognizable as specifically leading down the RBC pathway is the proerythroblast. As development progresses, the nucleus becomes somewhat smaller, and the cytoplasm becomes more basophilic because of the presence of ribosomes. As the cell begins to produce hemoglobin, the cytoplasm attracts both basic and eosin stains, and is called a polychromatophilic erythroblast [7]. The cytoplasm eventually becomes more eosinophilic, and the cell is called an orthochromatic erythroblast. This orthochromatic erythroblast then extrudes its nucleus and enters the circulation as a reticulocyte. Reticulocytes contain small fragments and remnants of basophilic material such as mitochondria and other organelles. As reticulocytes lose these basophilic remnants (over 1 to 2 days), they become mature RBCs (Fig. 1) [8].

The life span of a normal RBC is approximately 120 days, and the supply is renewed continually. Old and damaged RBCs are removed from the circulation primarily by the spleen, and the cell components (ie, iron from hemoglobin) are

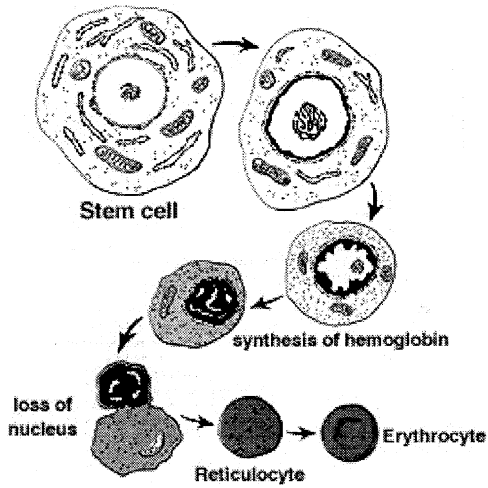

Fig. 1. Erythropoiesis. (*From* Belair J, Mackey MC, Mahaffy JM. Age-structured and two-delay models for erythropoiesis. Math Biosci 1995;128(1–2):317–46; with permission.)

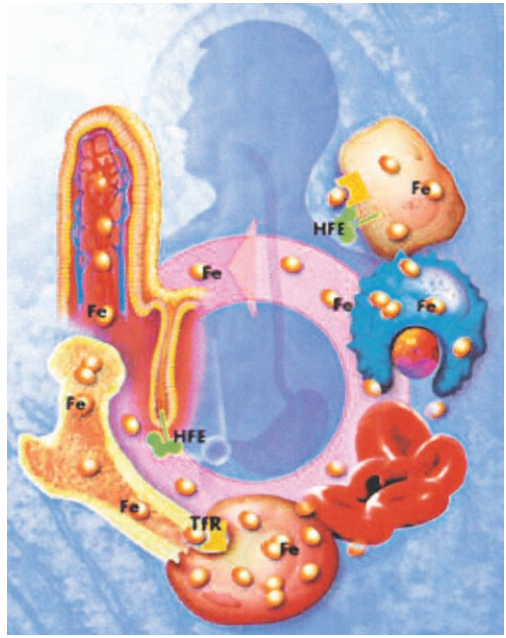

Fig. 2. Iron cycle. Fe, iron; TfR, transferrin. (Courtesy of Steven Lustig, Biodesign.)

recycled to form new RBCs (Fig. 2). Erythropoiesis requires a normal supply of substrates (ie, vitamins [folate and B12]), nutrients, and essential minerals (iron). The normal adult bone marrow produces 2.5 billion RBCs, 22.5 billion platelets, and 1 billion white blood cells (WBCs) for every kilogram of body weight per day [8].

In people, erythropoiesis occurs almost exclusively in the red bone marrow. The red bone marrows of essentially all bones produce RBCs from birth to about 5 years of age. Between the ages of 5 to 20, the long bones slowly lose their ability to produce RBCs. Above the age of 20, most RBCs are produced primarily in the marrow of the vertebrae, the sternum, the ribs, and the pelvis. The control of erythropoiesis is multi-factorial, and the bone marrow can respond to a need for increases in RBCs by releasing reticulocytes into blood and developing a sustained increase in red cell synthesis.

The kidney plays a central role in RBC production in the adult (Fig. 3). In the adult, the kidneys detect low levels of oxygen in the blood and release erythropoietin, a glycoprotein hormone produced primarily by cells of the peritubular capillary endothelium of the kidney, which circulates to the red bone marrow and stimulates the marrow to begin RBC production by an incompletely understood mechanism.

RBC production changes during gestation of the fetus. Erythropoietin synthesis initially occurs in cells that reside in the fetal liver, with production

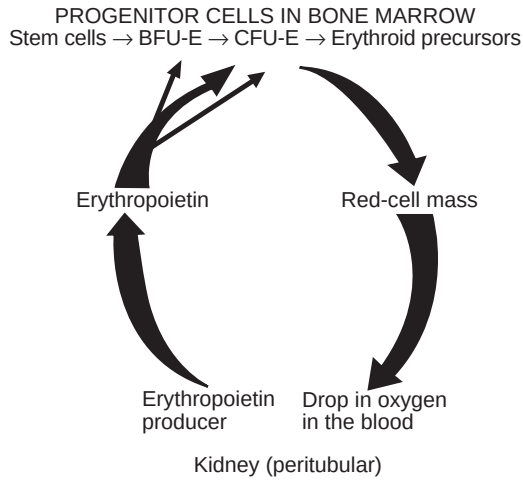

Fig. 3. Production of erythropoietin by the kidney in response to reduced oxygen levels. BFU-E, burst forming units–erythroid; CFU-E, colony forming units–erythroid. (*Adapted from* Erslev J. Erythropoietin. N Engl J Med 1991;324:1339–44; with permission.)

gradually shifting to the peritubular cells of the kidney. By the end of gestation, however, the liver remains a major source of erythropoietin [9].

Although erythropoietin is not the only erythropoietic growth factor in the fetus, it is the most important, and it is synthesized in response to both anemia and hypoxia. The degree of anemia and hypoxia required to stimulate erythropoietin production is far higher for the fetal liver than for the fetal kidney [9]. As a result, new RBC production in the extremely premature infant (whose liver remains the major site of erythropoietin production) is blunted despite potentially marked anemia [9].

Inflammation and anemia

The normal range of serum erythropoietin concentrations in healthy individuals is 5 to 30 IU/L [10]. Current thinking is that the primary mechanism for the production of erythropoietin is the reduction of oxygen supply to the kidney. A sudden drop in hemoglobin, especially in an otherwise healthy individual, causes an exponential increase in the production of erythropoietin, which can be measured in the circulation within minutes of the initial insult [10–12]. This normal response of the body to a decrease in oxygen supply is altered or blunted in critically ill patients with multiple organ dysfunction syndrome (MODS) or sepsis [12]. When cytokines and other inflammatory mediators are elevated, as in MODS and sepsis, erythropoietin secretion is blunted. Rogiers et al found that endogenous levels of erythropoietin in ambulatory patients with anemia were eight times higher than ICU patients with anemia and sepsis with the same level of hemoglobin [12].

An increase in proinflammatory cytokines on arrival to the ICU and during the ICU stay has been correlated with poor outcomes in critically ill patients [13,14]. Anemia has been proposed as a link between these elevated cytokines and poor outcomes. Several potential mechanisms linking cytokines and anemia have been proposed. Proinflammatory cytokines may induce bone marrow suppression of erythropoiesis and erythropoietin secretion; they also may exacerbate intestinal or other bleeding and disrupt iron metabolism [11,12,15].

Evidence suggests that the proinflammatory cytokines interleukin-1 (IL-1), tumor necrosis factor (TNF-α) and interferon (IFN-α) have significant suppressive effects on erythropoiesis and are probably central in the pathogenesis of anemia in patients with either chronic (eg, end-stage renal disease [ESRD] or rheumatoid arthritis [RA]) or acute inflammation (eg, trauma, surgery, or cardiopulmonary bypass [CPB]). In vivo studies have shown IL-1β, IL-1α, and TNF-α to exhibit a potent inhibition of hypoxia-induced erythropoietin production by as much as 89% [16]. Deficient erythropoiesis, as seen in chronic inflammatory disease states, may explain why critically ill patients with MODS or sepsis, in whom cytokines and other inflammatory mediators are elevated, develop anemia in this setting despite the absence of active bleeding [1,11,12,17,18].

Proinflammatory cytokines also may exacerbate intestinal or other bleeding disorders through vasodilatation and increased permeability of the intestinal wall. For example, a recent study demonstrated significant intestinal blood loss in animals with IL-6-induced anemia [19]. Furthermore, a direct relationship between cytokines and altered iron metabolism, a common cause of anemia, has been described in chronic [20] and acute [21] inflammation. It has been hypothesized that the release of cytokines during inflammatory states leads to an increase in iron uptake and retention by activated macrophages, resulting in an altered iron metabolism [22].

Macrophages are responsible for catabolism of RBCs taken up by the liver and spleen and the release of iron to the circulation for subsequent binding by transferrin. The iron then is transported to the red marrow, where it is reincorporated into hemoglobin in RBC precursors.

Most cells acquire iron for metabolic use from transferrin, by way of the transferrin–transferrin receptor endocyotic route. Expression of this receptor is regulated by iron requirements, and in most non-RBCs expression is linked to cell proliferation [23]. Thus iron uptake from transferrin in nonproliferating cells tends to be low [24].

Macrophages involved in RBC catabolism take up large amounts of iron by means of phagocytosis. This process is not regulated by cellular iron status in the same way as uptake from transferrin, and the steps involved in this intracellular routing of iron are unclear. RBCs, however, are broken down in a phagolysosome, where iron first must be released from hemoglobin by heme oxygenase [25].

The macrophage continues to be under intense investigation and may be the link to understanding disorders of iron metabolism. Infectious and inflammatory

diseases commonly result in reduced serum iron (hypoferremia), which can lead to anemia. Inflammation alters macrophage iron homeostasis, resulting in increased iron retention and reduced iron release, thus giving rise to the hypoferremia and anemia, although in anemia, defects in erythropoiesis also are involved [26].

The body's response to anemia, increased production of erythropoietin, can be restricted by iron deficiency. Therefore, iron supplementation often is required to maintain adequate iron stores. In most critically ill patients, oral iron is problematic because of dysfunction in the intestinal absorption and transport of iron that is inadequate to meet the erythropoietin driven demands [27]. Additionally, iron supplementation has been associated with malaise, heat, vomiting, loin pain, and rarely life-threatening anaphylactoid reactions [28]. Potential long-term safety issues such as iron overload, infection, cardiovascular and thrombotic risk, and iron's vascular oxidative properties are of concern. With low-dose supplementation, however, iron may not pose a risk to the critically ill patient. To date, the literature is limited on these subjects [28].

Iron-deficiency anemia

The most common cause of anemia is iron deficiency. In iron deficiency, there is a decrease in the amount of iron available for metabolic processes. Iron deficiency occurs when more than 10% of RBCs show hypochromasia (a decrease in the hemoglobin in the red cell so that they appear pale in color). Iron is stored most often in the body in the hemoglobin. About 30% of iron also is stored as ferritin and hemosiderin in the bone marrow, spleen, and liver. Patients with iron deficiency have been shown to have a longer ICU length of stay and a longer time to discharge than those critically ill patients without an iron deficiency [29]. Furthermore, the severity of hypochromasia has been correlated with the duration of both hospital and ICU length of stay [29].

Iron-deficiency anemia may be caused by diets low in iron, increased iron requirement, and increased RBC production requirements such as when the body is going through changes such as growth spurts in children and adolescents, or during pregnancy and lactation. GI tract abnormalities can cause malabsorption of iron. This is common after some forms of GI surgeries and can result in iron-deficiency anemia. Loss of blood because of GI bleeding, menstrual bleeding, or injury also can cause a decrease of iron and result in iron-deficiency anemia.

Hemolytic anemia

Hemolytic anemia is a disorder in which the RBCs are destroyed (hemolysis) faster than the bone marrow can produce them. There are two types of hemolytic anemia: intrinsic and extrinsic. Intrinsic hemolytic anemia is the destruction of the RBCs because of a defect within the RBCs themselves. Intrinsic hemolytic anemias often are inherited, such as sickle cell anemia and thalassemia. These

conditions produce RBCs that do not live as long as normal RBCs. In extrinsic hemolytic anemia, RBCs are produced healthy but are damaged later. This damaged RBC, a spherocyte, is highly susceptible to further interactions with the reticuloendothelial system's phagocytic cells in the spleen, liver, or bone marrow. The spleen's unique filtering system efficiently removes the damaged RBCs from circulation [7].

The causes of extrinsic hemolytic anemia, also called autoimmune hemolytic anemia, can be infections, such as hepatitis and cytomegalovirus (CMV), Epstein–Barr virus (EBV), typhoid fever, *Escherichia coli,* or medications such as penicillin, antimalarial medications, sulfa medications, or acetaminophen. Leukemia or lymphoma, autoimmune disorders such as systemic lupus erythematosus (SLE, or lupus), rheumatoid arthritis, Wiskott–Aldrich syndrome, ulcerative colitis, and various tumors types also can cause extrinsic hemolytic anemia [1,7,8,30–32].

Some types of extrinsic hemolytic anemia are temporary and resolve over several months. Other types can become chronic with periods of remissions and recurrence. These forms of anemia are referred to as chronic disease anemia (CDA).

Bleeding-related anemia

Bleeding events in medicine and surgery often cause many patients to become anemic. Patients may become anemic after surgery, in the ICU, and during septic insults. Surgical blood loss is an important determining factor in a patient's postoperative hematocrit and hemoglobin (Hb) concentration. Many patients who do not experience significant blood loss, however, still experience significant reductions in Hb concentrations following surgery. These reductions cannot be explained by intraoperative dilution alone [21]. In fact, 6 weeks after total hip replacement, Hb levels are still below preoperative levels [33]. Inflammatory cytokines may play an important role in this phenomenon.

The decision to transfuse patients historically has been made to promote hemostasis or improve the oxygen carrying capacity of blood. This practice is not supported by clinical or experimental evidence, however. RBC transfusion may not cause an increase in oxygen delivery [34]. Furthermore the rise in oxygen carrying capacity observed following transfusion is counterbalanced by a decrease in blood flow because of a higher blood viscosity [35]. Even with an increase in oxygen delivery, transfusion often is not associated with an increase in oxygen uptake [35]. Therefore it is not surprising that numerous studies have not found RBC transfusion to improve outcome in critically ill patients [5,36–38]. Additionally, it has been shown that in trauma patients, other than those at risk of exsanguination, RBC transfusion does not improve outcome and may be deleterious [39,40].

A recent randomized blinded clinical trial has demonstrated that in patients at increased risk of major (greater than 1000 mL) blood loss, a single injection of

recombinant factor VIIa reduced perioperative blood loss and eliminated the need for transfusion [41]. This finding may add to the limited options available for preventing bleeding-related anemia.

Anemia and renal failure

The association of chronic renal failure and anemia has been recognized since the early 19th century. The anemia of renal failure usually is characterized by normochromic and normocytic blood cells. There is usually hypoplasia of the erythroid precursors in the bone marrow. The anemia aggravates as the renal function further declines, and the hematocrit may reach levels as low as 20% or 15%.

Anemia in renal failure can be explained partially by a decreased production of erythroid precursors and increased destruction of erythrocytes. Many studies have shown an inverse correlation between the red cell survival and serum blood urea nitrogen concentration [32,42–44]. This could be demonstrated by the classical study where RBCs from uremic individuals showed a normal life span when injected in normal individuals. The inverse (shortened red cell life span) could be demonstrated when erythrocytes from normal individuals were injected in uremic patients [31]. The most convincing demonstration that specific toxins (not necessarily urea) were responsible for the shortened red cell survival in renal failure was obtained with the introduction of dialysis. Dialysis improved, to a limited extent, the anemia in chronic renal failure patients, although this finding could not be ascribed to prolonged red cell survival. Rather, a better use of iron (not increased serum levels) and red cell production seemed to be the most important factors. Patients undergoing dialysis showed diminished transfusion requirements after initiation of a dialysis program. Dialysis itself can be responsible for the increased destruction of RBCs. Hemodialysis can worsen the anemia, however, because of procedure-associated blood losses and the mild effect on oxygen-transporting function [45].

Despite the mechanisms described previously, the most important determinant of anemia in chronic renal failure is the failure of red cell production caused by decreased levels of circulating erythropoietin. In uremic patients, the normal response to hypoxemia (increased secretion of erythropoietin) is blunted partially. These individuals show increased levels of the glycoprotein after hemorrhage or hypoxic crisis, although the levels are not even close to those of a normal nonuremic patient. Therefore, the stimulus to erythropoiesis is not sufficient in uremic patients.

Anemia in cancer patients

Anemia is a common complication of malignancy, occurring in over 50% of patients [46]. Anemia in cancer patients is multi-factorial and may occur as either

Table 1
Anemia and cancer: direct effects of neoplasm

Blood loss: acute/chronic	Gastrointestinal malignancies
	Head and neck cancer
	Genitourinary cancers
	Cervical cancers
Intratumor bleeding	Sarcomas
	Ovarian cancer
	Adrenocortical tumors
	Liver cancer
Erythrophagocytosis-induced anemia	Histiocytic lymphomas
	Other histiocytic neoplasms
Bone marrow replacement	Leukemia
	Lymphomas
	Myelomas
	Carcinomas of the breast and prostate

a direct effect of the cancer, as a result of the cancer treatment, or because of chemical factors produced by the cancer. Recent data have suggested that anemia may be related to poorer outcomes following chemotherapy [47].

The factors contributing to anemia that are caused by the effects of the cancer itself are summarized in Table 1. Cancers that invade the marrow (ie, breast and prostate) produce a fibrotic reaction that increases marrow fibrosis, resulting in the alteration of marrow space and the sinusoidal matrix, which affect the release of reticulocytes and can produce immature reticulocytes being released from the marrow. Known substances from tumors that cause anemia are shown in Table 2 [48]. The deposits of amyloid can be great enough to displace bone marrow, and the development of antibodies lead to an immune response known to suppress the production of erythropoietin and can lead to immune hemolytic anemia. Microangiopathic hemolytic anemia can lead to organ failure and may be a result of certain procoagulants known to be secreted by some solid tumors [48].

The regimen and type of chemotherapy or radiation and the type and stage of malignancy and complications such as sepsis, pneumonia, and other infections contribute to the development of anemia in cancer patients [49]. These cytotoxic agents have a number of adverse effects on hematopoiesis (Table 3).

An additional mechanism by which anemia affects clinical outcomes is related to the degree of tumor oxygenation, since hypoxia has an adverse effect on the

Table 2
Anemia and cancer: known products of cancer

Substance	Mechanism	Neoplasm
Amyloid	Marrow replacement	Plasma cell dyscrasia
Antibodies	Immune hemolytic anemia	Adenocarcinoma
		Lymphoma
Procoagulant proteins	Microangiopathic hemolytic anemia	Gastrointestinal neoplasms
		Prostate cancer

Table 3
Anemia and cancer: chemotherapeutic-induced

Stem cell death (long-term myelosupression)
Committed progenitor cell death (short-term myelosupression)
Delay in cell cycling of hematopoietic precursors (ie, iron)
Reduced levels of erythropietin (reduced response also)
Long-term myelodisplasia

radiosensitivity of cells [50,51]. The association between anemia and tumor hypoxia is not understood fully. It has been established, however, that low hemoglobin levels independently predict cancer recurrence and survival [52]. Still, it is not clear if low hemoglobin levels predict poor outcome because they indicate advanced disease or because they indicate poor tumor oxygenation [52]. Current opinion recognizes anemia as a main contributor to tumor hypoxia [52].

Physiological response and tolerance of anemia

Oxygen (O_2) is carried in blood in two distinct forms: bound to hemoglobin within the RBC and dissolved in the plasma. The actual oxygen content of arterial blood (CaO_2) is determined by the concentration of Hb in the blood, the arterial oxygen saturation of Hb (SaO_2), the oxygen binding capacity of Hb, the arterial oxygen partial pressure (PaO_2), and the oxygen solubility of plasma. These variables are interrelated and can be expressed in the following equation:

$$\begin{aligned} CaCo_2 = &(Hb \times SaO_2 \times Hb\ O_2 \text{binding capacity}) \\ &+ (PaO_2 \times \text{ plasma } O_2 \text{ solubility}) \end{aligned}$$

Adult hemoglobin consists of four protein chains, each carrying one heme group. One mole of Hb is able to bind to a maximum of 4 mol of O_2. O_2 binding capacity per gram of Hb is 1.39 mL g^{-1}. The relationship between PaO_2 and Hb oxygen saturation is shown in Fig. 3. The steep part of this curve (PO_2 20 to 40 mm Hg) facilitates oxygen release from hemoglobin. Tissue PO_2 values of different organs are shown in Figs. 4 and 5 and lie on this steep part of the curve (see Fig. 4), facilitating oxygen release from hemoglobin.

Recent evidence suggests that in addition to O_2 binding, release, and CO_2 removal, Hb mediates the alternating uptake and delivery of nitric oxide (NO) [53]. This mechanism provides insight into the physiological matching of blood flow with tissue O_2 delivery. Although controversial, McMahon et al recently verified that NO alternately can be captured and released by RBCs [54]. These data suggest the capture of NO bioactivity in highly oxygenated tissue (resulting in vasoconstriction) and release in ischemic tissue (resulting in vasodilation) [53].

The body's response and adaptation to hypoxia influence the pathophysiology of anemia and tissue ischemia. Studies on the regulation of the genes that encode erythropoietin have provided a mechanism of O_2 sensing and signal transduction

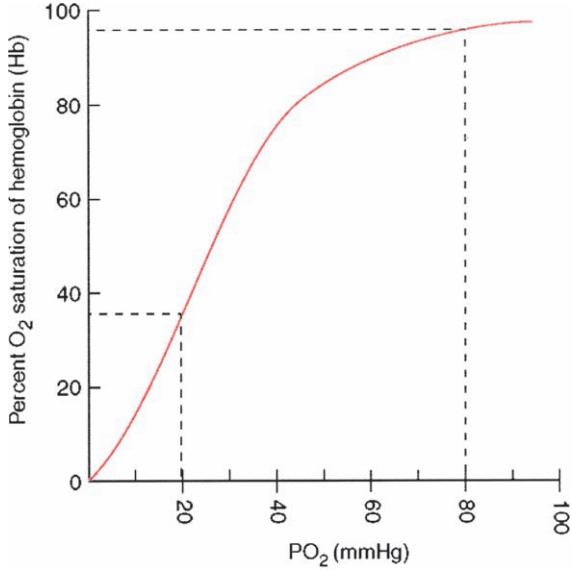

Fig. 4. Hemoglobin dissociation curve.

that leads to the activation of hypoxia inducible factor-1 (HIF-1) [55]. HIF-1 controls O_2 delivery (by means of angiogenesis) and metabolic adaptation to hypoxia (by means of glycolysis) by regulating genes that are activated by low oxygen levels [56]. These then encode proteins essential in acute hypoxia (ie, regulating glucose uptake and metabolism) and for chronic hypoxic conditions (ie, angiogenesis and erythropoiesis) [57].

Mild anemia is compensated by a shift in the in $Hb-O_2$ dissociation curve. The impact of more severe anemia may be modulated physiologically by an increase in cardiac output that will increase tissue perfusion, a decrease in peripheral vascular resistance, and decreases in whole blood viscosity [58,59].

Microcirculatory blood flow is governed by perfusion pressure, vessel radius, vessel length, and blood viscosity. Autoregulation of regional blood flow is controlled by neural and metabolic factors that influence vascular resistance by modifying perfusion pressure and vasomotor reactivity. Under normal physiologic conditions, blood viscosity plays a passive role in affecting microcirculatory flow. Changes in blood viscosity, however, have been known to affect blood flow. Anemia not only decreases the oxygen content of blood, but also decreases blood viscosity, promoting an increase in regional blood flow. Moreover, this increase in blood flow augments the perfused capillary area by increases in filling pressures and microvasculature vasodilation [60], resulting in an increase in O_2 uptake and regional and total body O_2 extraction by the tissue beds [60]. The effects of blood transfusion on O_2 uptake is not as optimal as increasing blood

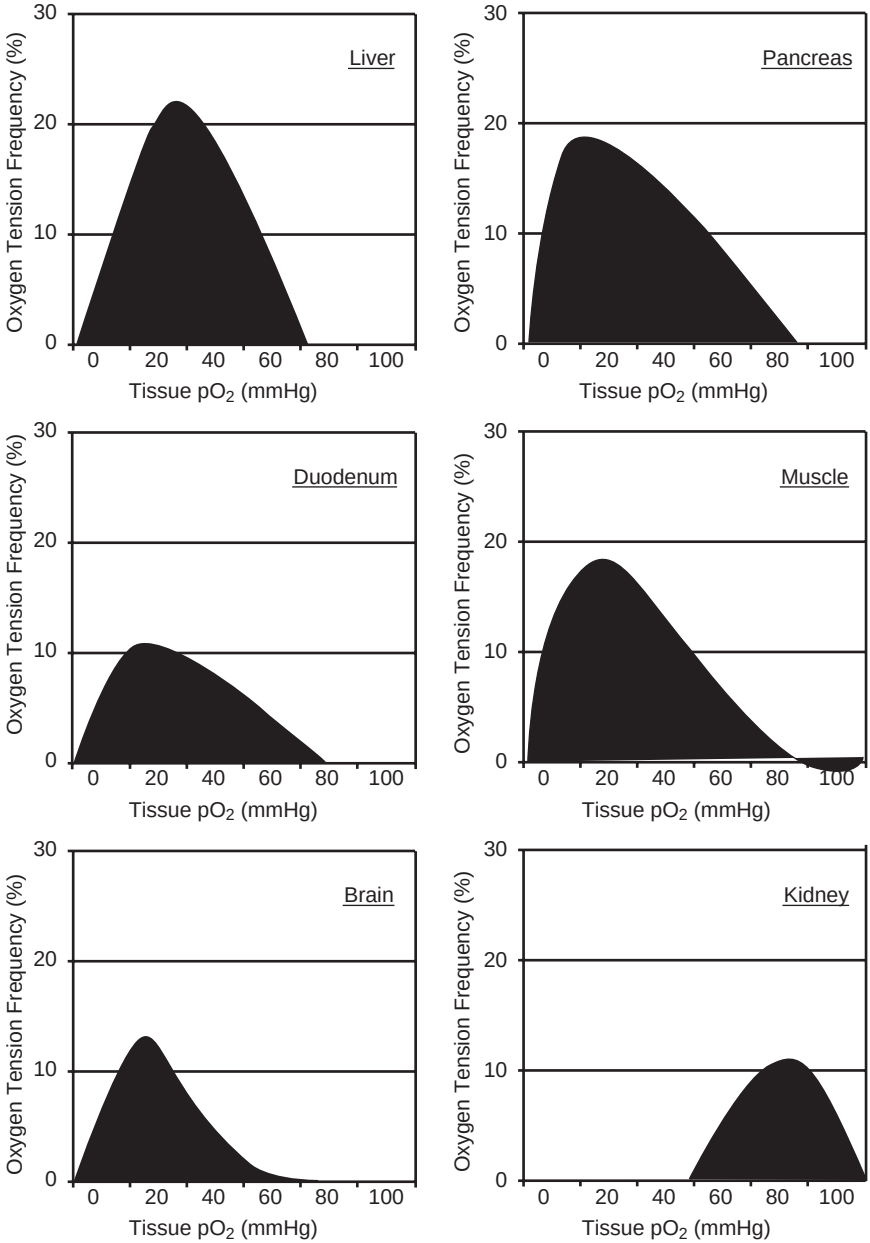

Fig. 5. Frequency distribution of oxygen tensions in different organs measured with oxygen-sensitive electrodes. (*From* Messmer K, Gornandt L, Sinagowitz E, Sunder-Plassmann L, Jesch F, Kessler M. Local oxygen tension in tissue of different organs during limited normovolemic hemodilution. Bibl Anat 1973;12:327–32; with permission.)

flow, because the rise in hematocrit increases blood viscosity, which alters regional microvascular blood flow (ie, perfusion) [60]. Therefore, in anemic patients, tissue perfusion may be compromised, not as a result of low hemoglobin levels, but as a result of hypovolemia.

The viscosity of blood relies almost entirely on the concentration of red cells; therefore any conditions lowering this concentration will lower the viscosity of blood. In severe anemia, the blood viscosity may fall to as low as 1.5 times that of water rather than the normal value of 3 times the viscosity of water, and transfusion may not be the solution. Plasma expanders or hemodiluents have been shown previously to affect blood viscosity under normothermic conditions, and they can increase perfusion to end organs.

In normal animals undergoing acute hemodilution, cardiovascular function is maintained until the Hb reaches between 3 and 5 g/dL; ischemic changes then begin to appear on endocardial ECG leads (ie, ST-segment changes) [61,62]. Animals with experimentally created 50% to 80% coronary stenosis, however, develop ischemic changes at Hb concentrations of 7 to 10 g/dL [63].

Transfusion

Evidence indicates that allogeneic blood transfusion allows for the development of immune down-regulation. Allogeneic blood transfusion has been shown to enhance the survival of renal allografts [64] and may increase the recurrence rate of resected malignancies [65] and activate infections associated with CMV [66] and HIV [37].

The mechanism of this immunomodulation remains unclear. Animal and human data suggest that these immune effects are most likely caused by or mediated by transfused allogeneic WBCs [67–69]. The United Kingdom, Ireland, Portugal, Canada, and France recently mandated WBC reduction of all transfused cellular blood, primarily based on the hypothesis (the United Kingdom and Ireland also cite the theoretical risk of Creutzfeldt–Jakob Disease transmission) that this practice would enhance overall transfusion safety [70]. A strong contingent from the academic blood banks of the United States have strongly opposed the US Food and Drug Administration's (FDA's) intent to mandate universal WBC reduction in the United States [71].

Recent randomized clinical trials have had conflicting results. One study found no difference in the incidence of postoperative infection between recipients of WBC-reduced and buffy-coat-reduced RBCs with the use of prestorage WBC reduction by filtration [72]. van de Watering et al found the use of WBC-reduced RBCs decreased the incidence of postoperative infections by 30% compared with patients receiving buffy-coat-reduced RBCs. This study found no difference in the incidence of postoperative infection between the recipients of RBCs that were WBC-reduced by filtration before or after storage [73].

The recently described relationship between WBC-reduced allogeneic blood transfusion and increased postoperative mortality from causes other than infec-

tion [73] and evidence suggesting a restrictive strategy for RBC transfusion may be superior to a liberal strategy when evaluating mortality in critically ill patients [36] furthers the debate of whether to implement universal WBC reduction.

Red blood cell storage

During preservation, allogeneic RBCs undergo functional and structural changes and biochemical alterations collectively referred to as the storage or cold lesion. Numerous authors have shown that RBCs older than 7 days begin to have a decrease in RBC deformability and shape abnormalities, acidosis, and a decrease in blood clotting, and these abnormalities progress up to the end of the storage period [74].

Several retrospective studies support the possible adverse effects of transfusion with older RBCs. Purdy et al associated mortality with the age of blood transfused in septic ICU patients [75]. Vamvakas found an association between the length of storage of RBCs and postoperative pneumonia [38], while others have associated storage times with increases in ICU length of stay [76].

The transfusion of aged blood may alter regional and microcirculatory blood flow and oxygen use [77,78]. The changes observed in RBCs during storage, decreased deformability and increased oxygen affinity, may result in decreased splanchnic blood flow and oxygen use. This may lead to increased gut permeability and the translocation of bacterial products into the circulation, resulting in the exacerbation of sepsis or multiple organ failure [35,75].

Hemodilution and critical hematocrit

The intentional dilution of blood volume often is referred to as acute normovolemic hemodilution (ANH) anemia. Acute normovolemic hemodilution is a technique in which whole blood is removed from a patient while the circulating blood volume is maintained with acellular fluid. Blood is collected by means of central lines with simultaneous infusion of crystalloid or colloid solutions. Collected blood is reinfused after major blood loss has ceased, or sooner if indicated. Blood units are reinfused in the reverse order of collection.

Acute normovolemic hemodilution can be performed in patients undergoing surgical procedures or at the bedside in the ICU. This technique provides fresh, whole blood for transfusion and avoids the waste of blood associated with the collection and storage of predonated blood.

Under conditions of ANH, the increased plasma compartment becomes an important source of oxygen delivered to the tissues. Oxygenation is maintained by increased cardiac output and increased oxygen extraction by the tissues, when these compensatory mechanisms fail to match the oxygen needs of the tissues the critical hematocrit is said to have been reached. The critical hematocrit has been a source of debate for many years. A theoretical model was developed describing

the relation between hematocrit, myocardial O_2 demand, and the required coronary blood flow during progressive hemodilution [79]. Using this model, the determinants of critical hematocrit and the limits of ANH can be calculated based on the limits of coronary vasodilator reserve. For a normal systemic oxygen consumption of 120 $mL/min^{-1}/m^{-2}$ a critical degree of hemodilution is achieved at a hematocrit of 14% and Hb content of 4.7 g/dL, respectively. Hyperoxia with an arterial PO_2 of 400 mm Hg will shift the critical hematocrit to 12%. An increase of systemic O_2 consumption by a factor of three (460 $mL/min^{-1}/m^{-2}$), which might be typical for a patient during the postoperative recovery phase, increases the critical hematocrit to 21% [79]. In patients with coronary artery disease (CAD), however, critical hematocrit levels might be much higher, as previously described. Therefore, many have concluded that a fixed critical hematocrit as a transfusion trigger is not appropriate in most patients. Rather, the indication for blood transfusions must appreciate the specific circumstances of the individual patient, such as expected blood loss and required O_2 transport capacity reserves, hemodynamic stability, CAD, and systemic oxygen consumption.

Summary

The anemia of critical illness is a distinct clinical entity with characteristics similar to that of chronic disease anemia. Several solutions to the processes of anemia, such as blunted erythropoietin production and erythropoietin response and abnormalities in iron metabolism have been developed.

The transfusion of RBCs provides immediate correction of low hemoglobin levels, which may be of value in patients with life-threatening anemia. Avoidance of RBC and blood component transfusion, however, is becoming increasingly important as data of adverse clinical outcomes in critically ill patients become clearer. Although the optimal hemoglobin in critically ill patients is not determined, this organ system has a generous reserve. Short-term compensated anemia is tolerated well, while exogenous erythropoietin allows patients to achieve higher hemoglobin concentrations without exposure to transfused blood/blood components [80].

A recent randomized trial enrolled over 1300 critically ill patients to receive either 40,000 units of exogenous erythropoietin or placebo. These authors found that patients randomized to erythropoietin received significantly less allogeneic RBC transfusions and had significantly greater increases in hemoglobin [81]. Although no differences were found between groups in gross clinical outcomes (ie, death, renal failure, myocardial infarction), this study did not have the power to identify small differences in outcomes. This and other studies of exogenous erythropoietin therapy in critically ill patients [82,83] clearly demonstrate that the bone marrow in many of these patients will respond to the administration of erythropoietin despite their illness, suggesting a blunted production of erythropoietin rather than a blunted response to erythropoietin. Exogenous erythropoietin therefore represents a therapeutic option for treating anemia in critical illness.

Acute events in medicine and surgery often lead to many patients becoming anemic. Solutions to this process of anemia should be focused on preventing such events. Anemia after surgery represents an area for prevention. Blood conservation strategies can be performed with adequate results. Monk et al randomized 79 patients undergoing radical prostatectomy to preoperative autologous donation (PAD), preoperative exogenous erythropoietin therapy plus ANH immediately following induction of general anesthesia, and ANH alone. This study concluded that all three techniques resulted in similar hemostasis outcomes (eg, bleeding and transfusion rates), but ANH alone was the least expensive, and ANH plus exogenous erythropoietin and ANH alone resulted in a higher ICU hematocrit compared with PAD [84].

Regardless of these prophylactic strategies, patients still become anemic after surgery or during critical illness. This acute event anemia usually is treated with RBC transfusion; however, autologous blood recovery (cell salvage systems) has been shown to be effective in patients with acute bleeding-related anemia, and this may reduce patients' exposure to allogeneic blood in these patients.

There are no universally accepted treatment guidelines for managing anemia, and practice differs between clinicians, hospitals, regions, and countries. Transfusion medicine is evolving and incorporating many new pharmacological agents into the armamentarium of anemia and bleeding therapy [85,86]. Accumulating evidence suggests that anemia in critically ill patients is common and correlated with poor outcomes. The management of anemia can improve outcomes; however, the optimal management of anemia is not performed universally. New approaches, continued research, and an understanding of anemia may result in more consistent and improved outcomes for critically ill patients.

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