Anemia in the Surgical ICU

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Definition and Epidemiology of Anemia in the ICU

Definition of Anemia

The definition of anemia has attracted considerable interest, as several studies have shown that anemia is associated with poorer outcomes in a variety of patient populations, including the critically ill [1, 2]. Based on recommendation of an expert committee some four decades ago, the World Health Organization (WHO) has defined anemia in men and women as a hemoglobin (Hb) <13 g/dL and <12 g/dL, respectively [3, 4]. These general definitions have been applied in most settings, including critical care.

The WHO definition is a reflective of hemoglobin distribution in studied populations, and it has been challenged recently in a population study of 26,530 adults in the town of Tromso in Norway which found that the prevalence of anemia among women was two to three times higher if the WHO criteria were used rather than the constructed reference range of <11.4 g/dL for women. This study provided confirmatory evidence of the gradual decline in mean Hb with age and a postmenopausal decrease of mean Hb among women [5].

Some experts in the field have advocated for new lower limits of normal hemoglobin concentrations to use as reasonable benchmarks for anemia for clinicians to use today (Table 25.1) based on a number of observational studies [6]. But these new definitions have not yet been evaluated in critically ill patient population. A potential definition of severe anemia as <8 g/dL was advocated by a panel of experts convened by the National Institute of Aging in 2004 [7], but further validation studies are needed in general or critically ill populations.

Epidemiology of Anemia in the ICU

Anemia (Hb <13 g/dL) is a common finding among critically ill patients within the intensive care unit (ICU) setting. Studies have demonstrated that up to two-thirds of patients presenting to an ICU may be anemic upon admission, that almost 95 % have anemia by ICU day 3, and that this anemia can persist for up to 6 months in over 50 % of patients beyond discharge [1, 8–14].

In the Audit of the Transfusion in Intensive Care in Scotland (ATICS) study, admission Hb was the factor most strongly associated with the persistence of anemia to ICU discharge. Interestingly, the APACHE II score and ICU length of stay were not independently associated with anemia on ICU discharge [15]. In a study of 155 critically ill patients with an ICU length of stay of 30 days or longer (median 49 days), Hb decreased significantly from mean 11.1 ± 2.5 g/dL on ICU admission to 9.0 ± 1.1 g/dL on ICU day 21. The majority

Table 25.1 Proposed lower limits of normal hemoglobin concentration in adults [6]

Group, age	Hemoglobin, g/dL
White men, years	
20–59	13.7
60+	13.2
White women, years	
20–49	12.2
50+	12.2
Black men, years	
20–59	12.9
60+	12.7
Black women, years	
20–49	11.5
50+	11.5

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Table 25.2 Blood transfusion in the critically ill patients across studies

	N	Mean ICU admission Hb, g/dL	ICU transfusion rate	Mean pre-transfusion Hb, g/dL	Mean transfusions per patient, units
CRIT study, USA [8]	4892	11.0±2.4	44.1 %	8.6±1.7	4.6±4.9
ABC trial, Western Europe [13]	3534	11.3±2.3	37.0 %	8.4±1.3	4.8±5.2
TRICC investigators, Canada [18]	5298	9.9±2.2	25.0 %	8.6±1.3	4.6±6.7
North Thames Group, UK [20]	1247	–	53.4 %	–	5.7±5.2
ABA Multicenter Trials Group [19]	666	–	74.7 %	9.3±0.1	13.7±1.1
CRIT study, USA, trauma cohort [17]	576	11.1±2.4	55.4 %	8.9±1.8	5.8±5.5
ATICS study, Scotland, UK [15, 22]	1023	10.6±1.3	39.5 %	7.4–7.9	1.2–1.9
SOAP study, Europe [21]	3147	–	33.0 %	–	–
Prolonged acute mechanical ventilation [23]	4344	11.1±2.4	67.0 %	8.2±1.4	9.1±12.0

(62 %) of patients received a mean of 3.4±5.3 red blood cell (RBC) units at a mean Hb trigger of 7.7±0.9 g/dL after this period. Transfused patients had significantly greater acuity of illness, phlebotomy volumes, ICU length of stay and mortality, and a lower Hb than those who were not transfused. Small increases in phlebotomy (3.5 mL/day) were associated with a doubling in the odds of being transfused after ICU day 21 [16]. This anemia in critically ill and injured patients is associated with worse clinical outcomes [8, 17].

RBC transfusions are also common in critically ill patients (Table 25.2) [8, 13, 15, 17–23]. Another retrospective analysis of critically ill patients from 139 hospitals in the USA confirmed that anemia, and in particular declining Hb concentration, is associated with a higher likelihood of RBC transfusion (odds ratio [OR] 2.315, 95 % confidence interval [CI] 2.288–2.342) [24]. RBC transfusion is associated with risk and little evidence of benefit [25].

Pathophysiology

Oxygen Delivery and Consumption

Among the many functions of blood and circulatory system, perhaps the most critical and time-sensitive one is delivering oxygen to the tissues and organs throughout the body. While reaching every single cell residing in the furthest corners of body is a daunting challenge in itself, the bigger challenge is to maintain the supply consistent with the demand, which can be rapidly changing severalfold within minutes, while responding to many other changes such as the oxygen content and pressure in the respiratory tract and changes in hemoglobin (Hb) level, as is the case in anemia [26].

Once the oxygen makes its way down to the airways and crosses the alveoli, its effective delivery and distribution to the tissues will be dependent on harmonized collaboration of three key components: a far-reaching circulatory system, a tireless pump, and an effective carrier [27]. Blood carries oxygen mainly in two forms: bound to Hb within the red blood cells and dissolved in water. Each Hb molecule in adults is a tetramer of two alpha and two beta chains, with each individual chain hosting a heme molecule. The Hb-oxygen association is essentially a chemical reaction which involves the iron ions in the center of heme molecules. The rest of the Hb molecule – consisting of over 140 amino acids per chain – is responsible for supporting and modulating this central reaction. Each Hb molecule can bind one to four molecules of oxygen, which translates to about 1.39 mL oxygen per gram of Hb when fully saturated under physiological condition [28]. The value measured in practice is often slightly lower, down to around 1.31 mL, due to the presence of other forms and conformations of Hb [29]. In contrast, oxygen solubility in plasma is around 0.031 mL per liter per each 1 mmHg partial oxygen pressure (PO_2) [27, 28, 30]. The total oxygen content of blood (CaO_2) can be estimated using the equations below:

$$\text{Total Hb-bound oxygen} = \text{Hb concentration} \times \text{Oxygen saturation}\left(SO_2\right) \times \text{Hb oxygen binding capacity} \quad (25.1)$$

$$\text{Total water-dissolved oxygen} = PO_2 \times \text{water oxygen solubility} \quad (25.2)$$

And from 25.1 and 25.2 above:

$$CaO_2 = \text{Total Hb-bound oxygen} + \text{Total water-dissolved oxygen} \quad (25.3)$$

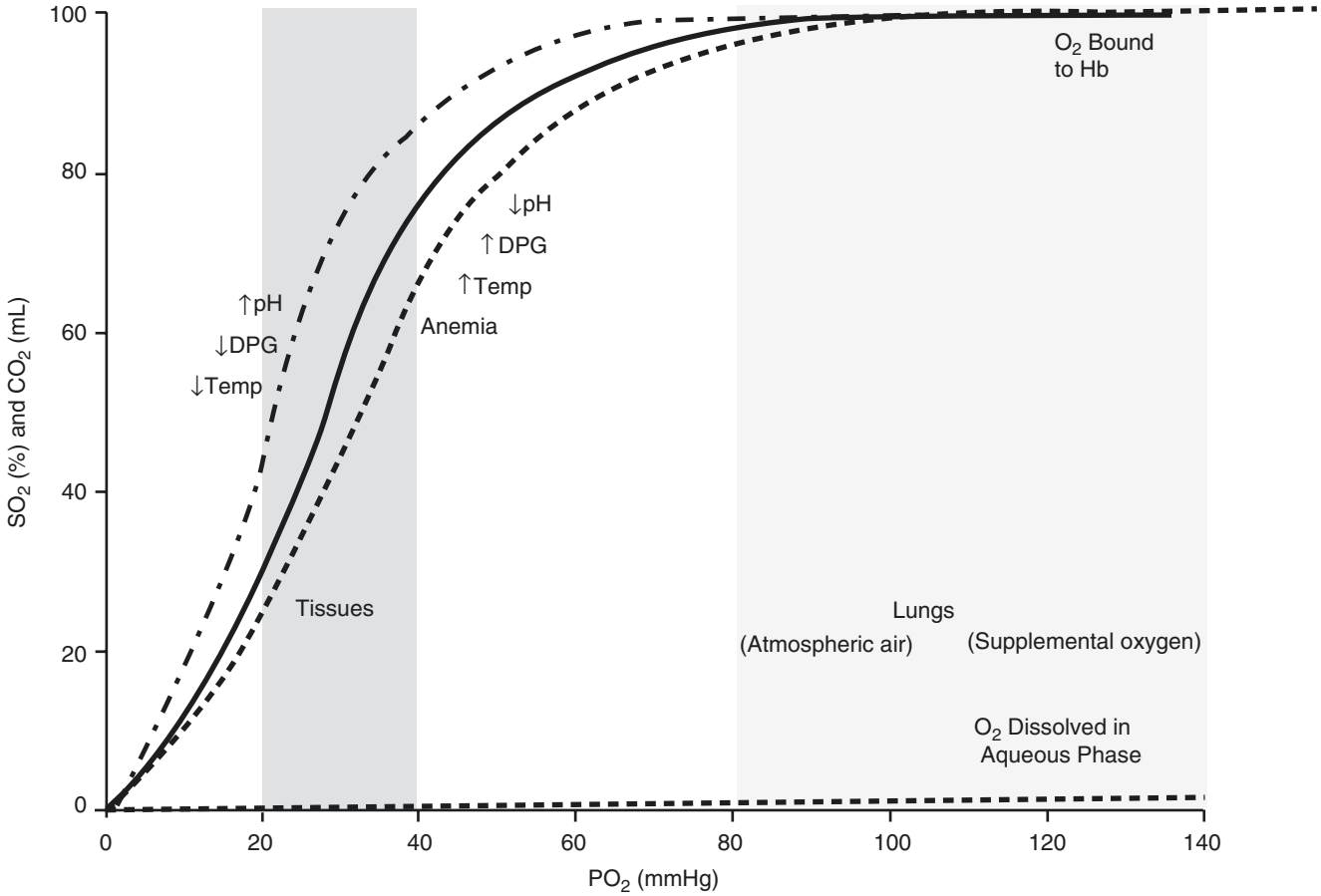

Fig. 25.1 Blood as an oxygen carrier. Relationship between partial pressure of oxygen (PO_2) and Hb-oxygen saturation/content as well as oxygen dissolved in the aqueous phase (plasma and cytoplasm of blood cells) is depicted. The vertical axis represents both the Hb-oxygen saturation (SO_2,%) and the Hb-bound and water-dissolved oxygen content (CO_2, mL) of a 150 mL hypothetical aqueous solution containing 75 g Hb at 37 °C. The *dashed gray lines* represent the shift to the left or right in Hb-oxygen dissociation curve as a result of changes in pH, 2,3-diphosphoglycerate (2,3-DPG), temperature, and anemia. *Dashed black line* represents the oxygen dissolved in the aqueous phase of blood

Considering that the Hb-oxygen-binding capacity is 1.39 mL/g, the calculated Hb-bound oxygen will be expressed in mL per L blood (if Hb concentration is expressed in g/L) or in mL per dL blood (if Hb concentration is expressed in g/dL). Oxygen saturation (SO_2) is usually expressed in %, but should be converted to decimal (e.g., 98 % saturation converted to 0.98). SO_2 in arterial blood (which is commonly denoted as SaO_2) is around 100 % (or 1 for use in the equation). Likewise, water oxygen solubility is about 0.031 mL per liter or 0.0031 mL per dL blood per each 1 mmHg of PO_2. Based on the above, 1 L of arterial blood with Hb concentration of 150 g/L (in which PaO_2 is around 100 mmHg and Hb molecules are fully saturated with oxygen, i.e., $SO_2 = 1$) can carry around 208.5 mL oxygen bound to Hb and around 3.1 mL oxygen dissolved in water. Thus, over 98 % of the oxygen carried by blood is normally bound to Hb [27, 28, 30].

One important aspect of oxygen transportation that is not accounted for in these simple equations is the Hb-oxygen association (or dissociation) curve. Unlike dissolving of oxygen in water which is directly related with PO_2 according to Henry's law (Eq. 25.2, Fig. 25.1), oxygen binding to Hb is dependent on availability of heme sites, which will reach a plateau sooner or later as all the oxygen-binding sites become occupied. Furthermore, Hb is a complex macromolecule that undergoes conformational changes in response to oxygen binding and the presence of other effectors. It has been long-recognized that Hb molecules generally exist in one of two conformational states – the T (tense) state and the R (relaxed) state, with the R state having a higher affinity for oxygen compared with T state [31].

Hb undergoes conformational changes as oxygen binds to the available heme site on each of the subunits, shifting from T state to R state and modulating the affinity of other available heme sites for oxygen. As a result, binding of oxygen is facilitated at higher PO_2 (e.g., at the alveolar capillary beds in the lung), while its release is facilities at lower PO_2 (e.g., at target tissues). This behavior is portrayed in the characteristic sigmoid Hb-oxygen association curve (Fig. 25.1). On the other hand, Hb molecules undergo allosteric regulation through interactions with other molecules and ions such as H^+ (pH) and 2,3-diphosphoglycerate (2,3-DPG) and

environmental parameters such as temperature, further modulating their affinity for oxygen in response to their vicinity. Increased temperature and levels of H^+ (lower pH) and 2,3-DPG – common at sites of increased oxygen consumption and/or low availability – decrease the affinity of Hb for oxygen and facilitate the release of oxygen, while release of oxygen from Hb molecules is inhibited in the presence of lower levels of H^+ (higher pH) and 2,3-DPG and lower temperature [30]. These changes result in shift of the Hb-oxygen association curve to the right and left, respectively (Fig. 25.1) [27, 30, 32].

The precise modulation of the affinity of Hb molecules for oxygen turns Hb into a highly efficient and specialized oxygen carrier that senses its surrounding and responds accordingly. As a result, Hb molecules react to scenarios of increased demand (e.g., physical activity or when fighting an infection) and reduced supply (e.g., anemia) by shifting the oxygen dissociation curve to the right (Fig. 25.1), off-loading their oxygen content easier and more readily when and where it is needed most [30, 32].

Besides modulation of Hb-oxygen affinity which affects how readily oxygen is released from Hb at any given PO_2, the real drive behind moving oxygen from the blood into the tissues is the PO_2 gradient: oxygen simply flows from higher PO_2 to lower PO_2 [33]. This gradient has been investigated in animal models as it spans from the arterioles (PO_2 around 80 mmHg), to the capillary (PO_2 around 60–30 mmHg), to the interstitial space (PO_2 around 30 mmHg) and eventually into the cells (PO_2 around 20 mmHg [34, 35], with the PO_2 gradient between the capillary and the interstitial space as the one driving the oxygen to be released from Hb molecules. This so-called transmural PO_2 gradient can be very small, as low as 1 mmHg/μm [36]. Nonetheless, given that Hb normally resides within the red blood cells (RBCs) in the blood and the blood is a non-Newtonian fluid [37], its rheological characteristics, namely, RBC nonsteady and heterogeneous flow, deformity and uneven distribution in microvasculature come into play as well. Recent models of moving RBCs through capillaries have shown that PO_2 across the RBC membrane can be greater than the PO_2 in plasma between the RBCs by as much as 30 mmHg, and the PO_2 in plasma drops by 9 mmHg over a distance of 50 μm [38]. Hence, the effective PO_2 gradient that is responsible for driving oxygen from the Hb molecules within the RBCs to the interstitial space and the cells into the mitochondria where it is eventually consumed can be markedly different from what is grossly measured at high level.

Oxygen delivery pathway ends primarily at the mitochondria, where over 90 % of the oxygen consumption by the body takes place, with oxygen being used as the ultimate electron acceptor to complete the aerobic respiration pathways and generate ATP [39]. Body oxygen consumption (VO_2) is the difference in oxygen content of the inspiratory air and the expiratory air. From a clinical point of view, VO_2 can be measured by multiplying cardiac output (CO) by the difference in oxygen content of systemic arterial and venous blood (CvO_2):

$$VO_2 = CO \times \left(CaO_2 - CvO_2 \right) \tag{25.4}$$

VO2 is often compared with another important parameter, oxygen delivery (DO_2), which is the total amount of oxygen delivered to the body per unit of time, and is a function of cardiac function (represented by CO) and the oxygen content of arterial blood:

$$DO_2 = CO \times CaO_2 \tag{25.5}$$

The key in maintaining adequate oxygen supply to the body is to ensure that DO_2 exceeds VO_2 at the systemic circulation level and, more importantly, at the level of microcirculation at individual tissues throughout the body. The difference between VO_2 and DO_2 can be expressed by the oxygen extraction ratio (O_2ER):

$$O_2ER = VO_2 / DO_2 \tag{25.6}$$

Normally DO_2 far exceeds VO_2 by a factor of 3–5, resulting in O_2ER of around 20–30 %. It should be remembered that the 20–30 % is an average range for the whole body and the O_2ER of individual organs and tissues can be markedly different. Notably in heart muscle, the O_2ER is much higher, around 60 % at rest and more as demand rises during exercise [29].

The large headroom in O_2ER across various tissues means that oxygen demand of tissues can still be met despite significant variations in DO_2, as is the case of anemia, a concept that is termed "supply independency." In contrast, conditions such as critical illness and septic shock are typically associated with increased VO_2, which can get dangerously close to DO_2, leading to a situation known as "supply dependency" (usually considered when O_2ER >50 % at rest). In this case, minor variations in either VO_2 or DO_2 of tissues can result in local oxygen demand exceeding the supply, leading to tissue ischemia and injury [40].

Red Blood Cell Life Span and Regulation of Red Cell Mass

RBCs live for around 120 days in the circulation. This life span is astonishingly long, when the far distances the RBCs travel, narrow capillaries they navigate (some even narrower than their own diameter), and shear stress they endure continuously are taken into consideration [31, 41].

The aging of RBCs is a complex process involving several phenomena that gradually erode the functionality and viability

of RBCs and lead to their removal from the circulation and destruction by macrophages. Being carriers of oxygen – an evolutionary toxin [42] – it is not surprising that RBCs are faced with significant oxidative stress in the form of various reactive oxygen species. RBCs are equipped with highly effective cytosolic antioxidant systems including glutathione peroxidase, catalase, and peroxiredoxin-2 that can neutralize many of these reactive oxygen species [43]. However, these protective systems have relatively limited access to the cell membrane, where auto-oxidation of membrane-bound Hb molecules may lead to stiffness and reduced fluidity of cell membrane, impairing the deformability of the RBCs – a key characteristic required for their survival [44]. Accumulating cytoskeletal damage further contributes to the problem. Other hallmarks of RBC aging include loss of membrane surface area, increased vesiculation and loss of cell volume (including loss of Hb content), increased cell density, and biochemical changes (e.g., decreased 2,3-DPG and lowered hexokinase and glucose-6-phosphate dehydrogenase activity) leading to diminished cellular energy level (reduced ATP), increased Hb-oxygen affinity, and reduced ability to neutralize oxidative stress [43, 45, 46].

Eventually, these and other signs of aging reach a critical level that alerts the molecular biosensing systems in the spleen and reticuloendothelial system to remove the aged RBC [47]. The oxidative stress and the resulting RBC aging process may become more pronounced when Hb molecules are partially oxygenated, as seen in hypoxic conditions [44]. Some deleterious aspects of aging may occur sooner in the lifetime of RBCs during critical illness, accelerating their demise, a factor that may contribute to higher prevalence of anemia and more therapeutic challenges in these patients [31, 41].

In addition to the aging of the RBCs, some RBCs are removed untimely through two other processes: eryptosis and neocytolysis [41]. Eryptosis is the premature death of mature RBCs. Its rhyming with apoptosis is not accidental as the phenomenon shares similarities with the extensively studied phenomenon of programmed cell death [48]. Eryptosis is in part triggered by the same oxidative stressors that lead to RBC aging, and it is characterized by a suicidal cascade of biochemical changes that result in cell vesiculation and shrinkage, cell membrane blebbing, and cell membrane phospholipid scrambling, which involves abnormal redistribution of components of the cell membrane which exposes some normally internal components (e.g., phosphatidylserine) to the outside of the RBC [41, 48]. The now-exposed internal molecules such as phosphatidylserine act as ligands for receptors on macrophages that signal them to bind the RBCs harboring the ligands and engulf them [49]. This process can be an effective way of eliminating defective cells with less "collateral damage" (compared with hemolytic pathway), reducing the potential for inflammation and other consequences of hemolysis [48], but when excessive, it can also contribute to the emergence of anemia [41, 48].

Neocytolysis is the process of selective removal of new RBCs just released from the bone marrow following a sudden reduction in the level of erythropoietin, as is physiologically encountered during rapid descent from altitude [41, 50]. Neocytolysis and eryptosis can be considered as tools for the body to rapidly adjust the RBC mass in response to the environmental factors and pathophysiological conditions [41].

Given the limited life span of RBCs and the associated large-scale turnover, maintaining the 20–30 trillion RBCs that normally reside in the body at any given time requires production of around 200 billion new RBCs every day, corresponding to around 15–20 mL of packed RBCs or 30–40 mL of blood with hematocrit of 50 %. This baseline production can be boosted up to ten times if needed (e.g., following acute anemia and heavy blood loss) in otherwise healthy, iron-replete individuals [41].

These numbers are indicative of the great logistics required to support hematopoiesis. Production of new RBCs requires adequate supply of iron, zinc, folic acid, and vitamin B_{12}, among other factors, and shortage of any of these can lead into impaired erythropoiesis and various types of anemia. The process is under tight regulation by a number of factors including erythropoietin, androgens, catecholamines, cortisol, and thyroxine, which act collectively to ensure that the supply of new RBCs keeps up (or down) with the demand while adapting to a host environmental, metabolic, and pathophysiological changes [41]. This ongoing regulation can respond effectively to acute changes (a rapid stress responds) and chronic conditions [51]. As a result, the mass of RBCs in the circulation is controlled to maintain an adequate supply of oxygen to the tissues.

It should be remembered that the impact of these regulators goes beyond erythropoiesis. The level of erythropoietin – produced by liver in fetus and kidney in adults – is primarily controlled by the oxygen-carrying capacity of blood, and it is stimulated by hypoxia, which works on hematopoietic cells to promote proliferation of progenitor cells and their differentiation and inhibit their apoptosis. In addition to these hematopoietic cells, the receptors for erythropoietin have been found on many other cells in endothelia, smooth muscles, heart, and nervous system, where it can impact ion flux, neurotransmitter synthesis, angiogenesis, ventilation, protection against ischemia, and more [52].

Mechanisms of Compensation

Several compensatory mechanisms assist body to maintain oxygen supply to the tissues in face of anemia. While the deleterious effects of anemia (even mild or moderate) on worsening the clinical outcomes of patients are well

documented [2, 27], reduced hematocrit of blood might not have an immediate negative impact on tissue DO_2. The way blood behaves in microcirculation can be markedly different from macrocirculation, and as RBCs file one after another to pass through capillaries with decreasing diameter, a point is reached where effective hematocrit of blood is significantly lower than the systemic hematocrit of blood, and it stays relatively unchanged over a wide range of changes in the latter (the Fahraeus effect) [53].

The body is equipped with accurate "oxygen sensors" which continuously monitor the level of oxygen delivery to the tissues and alert body of any deviations. These oxygen sensors exist and act at various levels throughout the body, ranging from subcellular level (e.g., the hypoxia inducible factor (HIF) signaling pathway) [54] to the tissue level (e.g., the chemoreceptors of aortic and carotid bodies and oxygen sensors in the renal cortex) [55–57]. One of the early response to anemia is elicited in the kidneys, where reduced PO_2 results in increased production of erythropoietin, working to enhance erythropoiesis to restore RBC mass [58]. Compensation of anemia occurs at various other levels and involves a plethora of mechanisms affecting literally every stage of oxygen delivery pathway from respiratory system to inside the cells where oxygen is consumed.

In anemia, CaO_2 is reduced while SaO_2 usually remains unchanged. As a matter of fact, a severely anemic patient can still have a SaO_2 of near 100 %, which simply means all oxygen-binding sites on available Hb molecules are occupied by oxygen molecules, but here the limiting factor is the reduced number of available Hb molecules. Even though availability of oxygen in alveoli is usually not the limiting factor in anemia, the body still responds to anemia by increasing respiration and ventilation. Additionally, ventilation-perfusion matching is improved through nitric oxide (NO)-mediated mechanisms, further ensuring PaO_2 and SaO_2 are maintained at the maximum level [59].

Another level of compensatory mechanisms takes place in the cardiovascular system. As discussed previously, DO_2 is a product of CO and CaO_2 (Eq. 25.5). Therefore in theory, any decrease in CaO_2 (e.g., resulting from anemia) can be neutralized by the same level of increase in CO. CO itself is a product of pulse rate and stroke volume [60]. During anemia, hypoxia sensors of chemoreceptors activate the sympathetic nervous system which increases CO, mediated by reduced afterload, increased venous return and preload, and positive inotropic and chronotropic changes increasing contractility of heart muscle and pulse rate. Reduced afterload is due to systemic vasodilatation and decreased vascular resistance, which resulted from a host of other changes, namely, increased NO activity, hypoxia-induced vasodilatation, increased recruitment of microvasculature (and even new angiogenesis in chronic anemia), as well as the reduced viscosity of diluted blood. These changes may even lead to left ventricular hypertrophy over time [60]. Reduced viscosity of blood in anemia can further help local perfusion by increasing the regional blood flow at the tissue and organ level leading to increased O_2ER [26]. On the other hand, maintaining microvascular perfusion and functional capillary density is dependent on maintaining a minimum level of blood viscosity, and extreme hemodilution may undermine this, further reducing DO_2 [61].

At the cellular and subcellular levels, compensatory mechanisms occur at RBCs as well as the target cells that consume oxygen. During anemia, the oxygen dissociation curve of Hb within the RBCs is shifted to the right following increased accumulation of 2,3-DPG, reduced pH, and other NO-mediated signaling events in RBCs at tissues [62–64]. This results in reduced affinity of Hb for oxygen and easier unloading of oxygen at tissue sites at relatively higher PO_2. Hence, despite reduced DO_2, oxygen extraction ratio increases, maintaining the oxygen supply. This phenomenon can be seen in experimental models in the brain where oxygen extraction can increase from a baseline of about 30 % to almost 50 % during anemia [65]. Nonetheless, dependence on increased O_2ER means that this strategy can only be helpful in tissues where baseline O_2ER is not high and there is some headroom to increase it. Organs with high baseline O_2ER such as heart may have very limited room to further increase it, and therefore they need to rely on another strategy – increased local blood flow – to maintain oxygen supply consistent with the demand during anemia [66, 67].

HIF signaling pathway – known as the master regulator of hypoxic cell signaling – plays an important role in compensation of anemia and hypoxia [68, 69]. Even a small reduction in tissue PO_2 can result in stabilization of HIF, an otherwise short-lived transcription factor, which activates and promotes the transcription of a host of other hypoxia response genes [68]. These hypoxia response genes are involved in modulating cardiovascular adaptation to anemia [69], promoting erythropoiesis through increased production of erythropoietin [70], promoting angiogenesis through inducing vascular endothelial growth factor (VEGF) [71], and increasing glucose transport to the cells and shifting cellular metabolism from aerobic to anaerobic (glycolytic) [72]. Studies have indicated that during acute anemia, cardiac oxygen consumption may increase at the expense of reduced oxygen consumption to other organs [73]. This shift makes sense given the critical role of heart in cardiovascular compensation of anemia and can be viewed as an attempt by the body to shift a limited resource (oxygen) from organs with less demand to those with highest and most critical need for it. This redistribution is also dependent on HIF-mediated metabolic adaptations at cellular level [73].

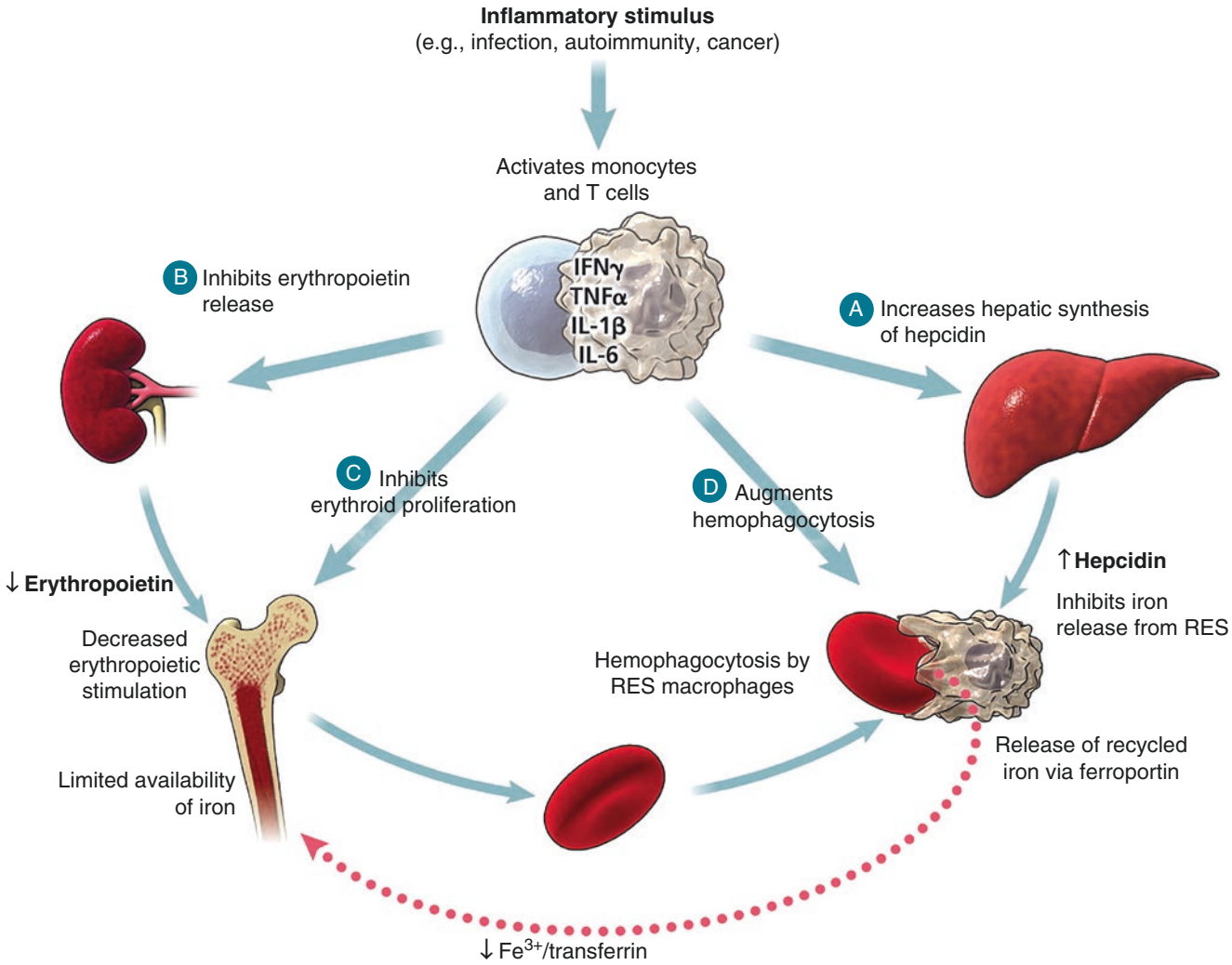

Fig. 25.2 Underlying mechanisms of anemia in critical care and trauma. In inflammatory diseases (including critical care, trauma, tissue injury, and hemorrhage), cytokines released by activated leukocytes and other cells exert multiple effects that contribute to the reduction in Hb levels and inability to recover from anemia: (**a**) induction of hepcidin synthesis in the liver (especially by interleukin-6 [IL-6] and endotoxin). Hepcidin in turn binds to ferroportin, the pore that allows egress of iron from reticuloendothelial macrophages and from intestinal epithelial cells. Binding of hepcidin leads to internalization and degradation of ferroportin; the corresponding sequestration of iron within the macrophages limits iron availability to erythroid precursors. (**b**) Inhibition of erythropoietin release from the kidney (especially by interleukin-1β [IL-1β] and tumor necrosis factor α [TNFα]). Erythropoietin-stimulated hematopoietic proliferation is in turn reduced. (**c**) Direct inhibition of the proliferation of erythroid progenitors (especially by TNFα, interferon-γ [IFNγ], and IL-1β). (**d**) Augmentation of erythrophagocytosis by reticuloendothelial macrophages (by TNFα). *RES* reticuloendothelial system (From Zarychanski and Houston [75]. This work is protected by copyright and the making of this copy was with the permission of Access Copyright. Any alteration of its content or further copying in any form whatsoever is strictly prohibited unless otherwise permitted by law)

Mechanisms of Anemia in Critical Care

While the role of inflammatory processes in the development of anemia in critically ill patients is often underscored (the so-called anemia of inflammation) [41, 74], anemia in these patients is almost always multifactorial. A number of underlying factors include pathologic iron homeostasis related to hepcidin, impaired erythropoiesis, shortened red blood cell life span, blunted erythropoietin response, RBC loss, and hemodilution (Fig. 25.2) [75, 76].

RBC Loss

Critically ill patients are at risk of losing significant amounts of blood. This is related to both (1) phlebotomy-related blood loss

for diagnostic laboratory testing and (2) acute blood loss and hemorrhage. Hb concentration decreases on average by 0.52 g/dL/day in non-bleeding ICU patients [10]. Mean daily blood loss related to diagnostic laboratory testing has been reported to be as much as 40 mL per day, contributing to 17–40 % of total blood loss in the ICU [13, 77]. Increased phlebotomy volume is associated with severity of illness, number of blood draws, and type of diagnostic testing tubes used. It has been documented that phlebotomy-related blood loss is associated with significant increased risk for RBC transfusion in critically ill patients with prolonged ICU length of stay [16].

A number of strategies can be used to reduce RBC loss in ICU patients. The use of closed blood conservation devices to reduce phlebotomy-associated blood loss is associated with reduced RBC transfusion requirements and decreased anemia in ICU patients [78–81]. Another effective strategy is to use pediatric or low-volume adult blood sampling tubes for blood draws [82]. A recent study compared the use of low-volume vs. conventional volume blood sampling tubes in 248 adult critically ill patients admitted to a surgical ICU. Low-volume sampling tubes were associated with significantly reduced phlebotomy volume (174 ± 182 mL vs. 299 ± 355 mL, $p = 0.001$). Daily blood draws also were less, 22.5 ± 17.3 mL vs. 31.7 ± 15.5 mL, $p < 0.001$. On the other hand, the difference in RBC transfusions was not statistically significant (4.4 ± 3.6 units vs. 6.0 ± 8.2 units, $p = 0.16$), but this may have been related to inadequate sample size of the study [83]. Patients should have daily assessment to eliminate any unnecessary diagnostic laboratory testing in the ICU, and standing orders and lab tests that are not likely to affect the course of management should be avoided.

Acute blood loss and hemorrhage are another etiology of anemia in the ICU. In a study of 211 ICU patients, 21 % had at least one episode of clinically significant hemorrhage. Of these patients, 65 % had one episode, 20 % had two episodes, and 15 % had three or more episodes of hemorrhage during their ICU stay [15].

Impaired Erythropoiesis: Reduced RBC Production and Shortened RBC Life Span

Another key reason for decrease of hemoglobin concentration in ICU patients is bone marrow suppression and inappropriate erythropoietic response [84–88]. Erythropoiesis is tightly regulated by erythropoietin circulating concentrations which are normally increased in states of anemia. A major feature of the anemia of critical illness is a failure of circulating erythropoietin concentrations to increase appropriately in response to the reduction in Hb concentration (Fig. 25.2) [84, 86, 87, 89]. This blunted endogenous erythropoietin response has also been documented in trauma patients [90].

During critical illness, there is reduced transcription of the erythropoietin gene by inflammatory mediators (IL-1, TNF-alpha, and TGF-beta). These inflammatory cytokines also directly inhibit RBC production through interactions with erythroid progenitor cells. Vasopressor agents also directly inhibit hematopoietic precursor maturation [91].

It has also been documented that a sudden and continued drop in erythropoietin production and concentrations with the onset of any acute inflammatory condition may promote neocytolysis (selective removal of young circulating RBCs just released from the bone marrow) and eryptosis (the premature death of mature RBCs) [50]. Eryptosis can be triggered by excessive oxidant RBC injury and is inhibited by erythropoietin which extends the life span of circulating RBCs. Excessive eryptosis can lead to anemia [48].

These observations suggest that treatment with pharmacological doses of an erythropoietin-stimulating agent (ESA) might raise the Hb concentration and as a result reduce allogeneic RBC transfusion requirements in critically ill patients. With the increasing adoption of restrictive transfusion strategies in critical care setting, the impact on reduction in RBC transfusion may become negligible [92]. Nonetheless, a meta-analysis of five randomized trials reported that there may be a dose-response ESA effect as the use of higher doses of ESAs resulted in a greater decrease in the number of units of blood transfusion [93].

ESAs are currently not indicated for treatment of anemia in general critically ill patients, but are indicated in those with chronic kidney disease and acute renal failure. Interestingly, analysis of the trauma cohort from two multicenter randomized controlled trials confirmed a survival advantage for critically ill trauma patients with ESA treatment [92, 94, 95].

Diminished RBC production can be due to nutritional deficiencies, but this is rare in ICU patients. Few studies have investigated this issue in critically ill patients. In one small study, only 2 % of patients were documented to have folate or B12 deficiency [86].

Iron Homeostasis and Hepcidin

Iron studies in critically ill patients consistently demonstrate low serum iron and transferrin saturation with high serum ferritin levels, likely to be related to the inflammatory state [96]. While absolute iron deficiency may not be very common in ICU patients and it can be difficult to diagnose in these patients [86], most critically ill patients have functional iron deficiency (FID) with low iron availability for endogenous RBC production. The percentage of hypochromic red cells and reticulocyte hemoglobin content are the best established tests for diagnosis of FID. Erythrocyte zinc protoporphyrin (eZPP) measurement is also a sensitive index of FID but is less sensitive to acute changes in iron availability, and it is essential that measurements be made on washed cells [97].

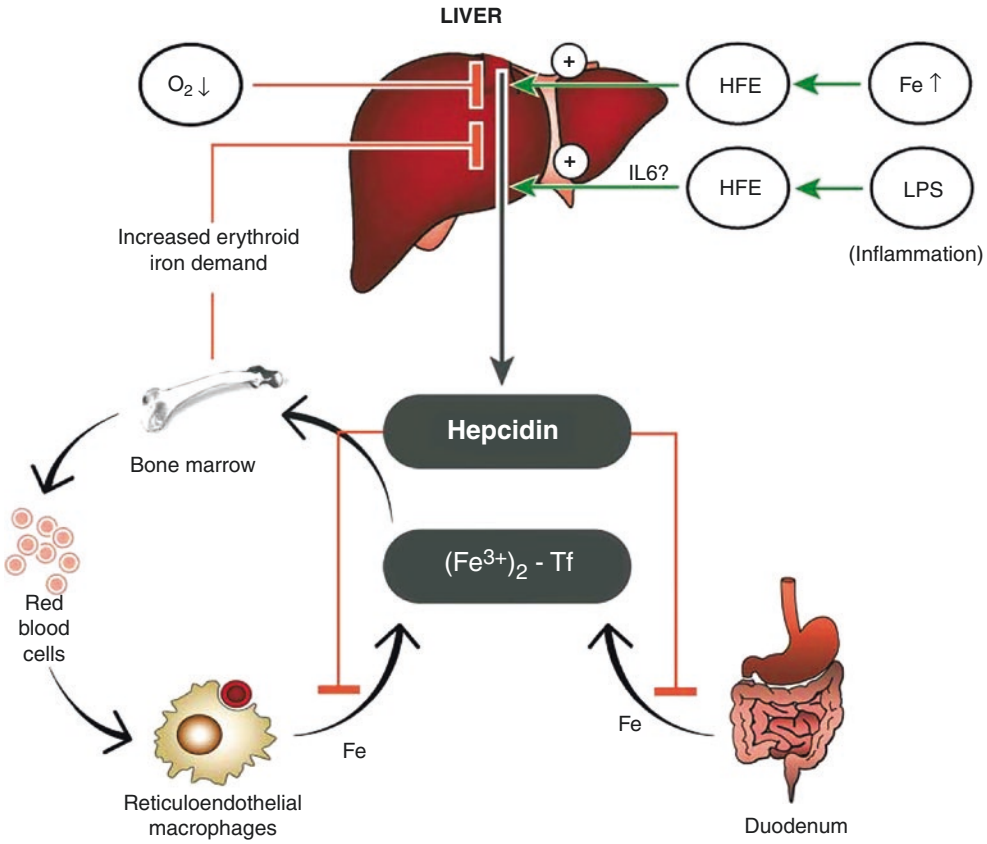

Fig. 25.3 Hepcidin induces functional iron deficiency in anemia of inflammation. Hepcidin reduces iron availability via two mechanisms: (1) decreased absorption of iron across the gastrointestinal tract and (2) decreased release of iron from the reticuloendothelial system

Numerous pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha, and others) impair iron homeostasis and normal reticuloendothelial system functioning and decrease intestinal absorption of iron via regulatory feedbacks [98, 99].

Recently, the role of hepcidin, a liver-derived 25-amino-acid peptide that is known as the master regulator of iron homeostasis, has gained more attention. Hepcidin is upregulated in inflammation, in infection, or when excess iron is detected, resulting in reduced iron bioavailability [100, 101]. Hepcidin mediates iron homeostasis by binding to the iron exporter ferroportin, inducing its internalization and degradation, with resultant decreased absorption of iron through the gastrointestinal tract and decreased release from the reticuloendothelial system (Fig. 25.3). Hepcidin is downregulated by iron deficiency, anemia, and tissue hypoxia [100, 101]. Additionally, hepcidin levels rise to extremely high levels after trauma and are positively correlated with injury severity and duration of anemia [102]. Erythropoietin stimulation via ESA treatment results in decreased hepcidin expression [103]. Further studies document that hepcidin is an important modulator of the acute inflammatory response [104, 105].

New studies are now targeting the hepcidin-ferroportin axis to develop new treatment strategies for anemia of inflammation [106, 107]. It has been documented that pharmacological ESA doses can overcome the erythropoietin resistance present in anemia of inflammation. Furthermore, a single ESA injection can cause rapid suppression of serum hepcidin concentrations in humans [108, 109].

Hepcidin neutralization has been proposed as a therapeutic treatment for anemia of inflammation, and several hepcidin antagonists are being developed and tested [110]. The hepcidin inhibitor NOX-H94 (a structured mirror-image RNA oligonucleotide) has undergone clinical trials to treat anemia associated with chronic disease [111]. LY2787106 is a humanized antibody designed to bind to hepcidin and neutralize its function and has been undergoing trial in patients with cancer-associated anemia (NCT01340976). PRS-080 is a type of anticalin (non-antibody proteins that can specifically bind to antigens similar to antibodies), and it specifically binds human hepcidin with subnanomolar affinity, and it is also considered for human study. The results of these clinical trials will help determine the efficacy of hepcidin antagonists as novel therapeutics for iron-restricted anemia and anemia of inflammation.

Most recently, a new hormone (erythroferrone, ERFE) has been identified that mediates hepcidin suppression (Fig. 25.4) [112]. ERFE mediates hepcidin suppression to allow increased iron absorption and mobilization from stores. Interestingly, ERFE is produced by erythroblasts in response to erythropoietin treatment [112]. These experimental findings suggest that ESA treatment, via modulation of both hepcidin and ERFE, may have significant impact on the acute inflammatory response in critical illness.

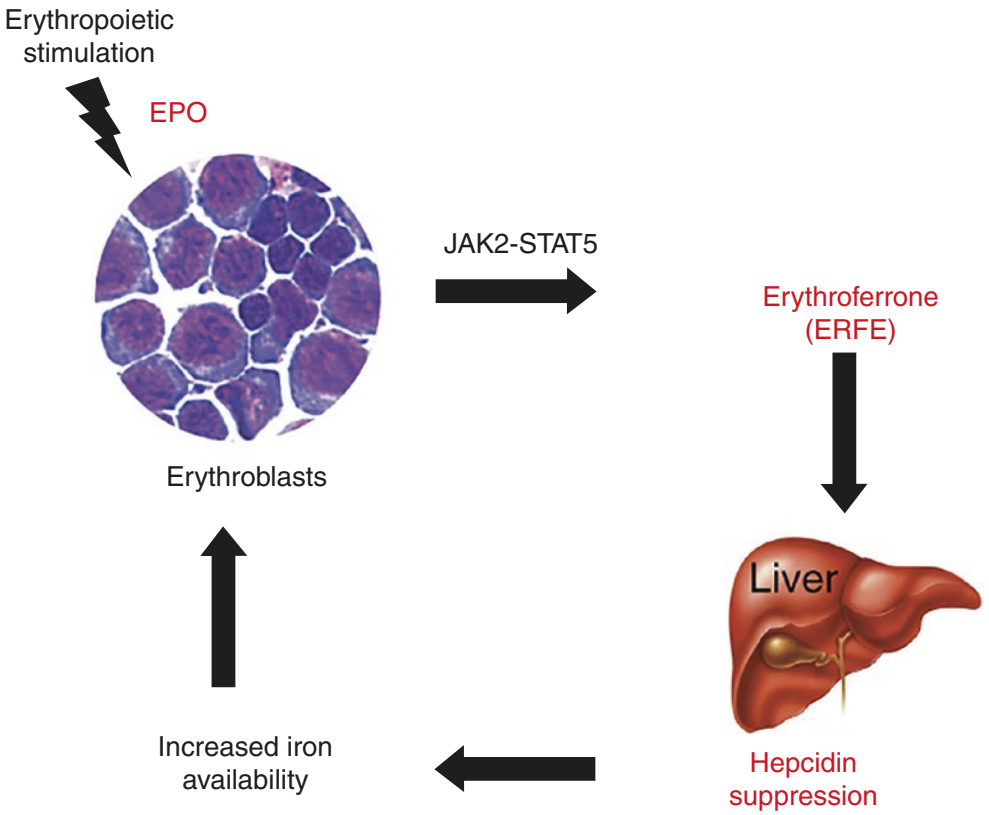

Fig. 25.4 Proposed role of the erythroid factor erythroferrone (ERFE). Prior studies suggested that high levels of EPO cause hepcidin suppression indirectly by inducing the secretion of erythroid regulators from the bone marrow, which in turn act on the liver to suppress hepcidin expression and increase iron delivery from dietary absorption and stores. A new hormone and erythroid regulator, erythroferrone (ERFE) has been identified that suppresses the hepatic synthesis of the principal iron-regulatory protein hepcidin, resulting in increased iron uptake. Erythroferrone production by erythroblasts is greatly increased when RBC synthesis is stimulated, such as after bleeding or in response to anemia. In normal volunteers, erythropoietin administration was sufficient to profoundly lower serum hepcidin levels in less than a day without any significant changes in serum iron concentrations, and its action was presumed to be mediated via ERFE (Reprinted by permission from Macmillan Publishers Ltd: Kautz et al. [112], copyright 2014)

Hemodilution

Anemia in ICU patients can also be in part related to hemodilution due to crystalloid fluid resuscitation for other disease processes (e.g., hypovolemic and septic shock, gastrointestinal, and other body fluid losses). It is important to consider the impact of crystalloid fluid resuscitation with resultant hemodilution on the development of anemia in the ICU and to decrease fluid resuscitation.

Management/Treatment of Anemia

The initial management of anemia begins with avoidance of any red blood cell loss. Patients in the ICU are at high risk for iatrogenic causes of blood loss, most likely from phlebotomy. Blood collection can lead up to 70 mL of blood taken from the patient on a daily basis. The body normally produces only 0.25 mL/kg of blood on daily basis [113]. In an average 70 kg patient, this is only 17.5 mL of RBC production daily. Clinical institutions have multiple methods to help reduce blood volumes withdrawn for laboratory testing. A goal of using small-volume or pediatric phlebotomy tubes can be instituted. The use of ordering routine multiple daily phlebotomies for blood sampling should cease, and lab testing should be initiated only when clinical signs or symptoms indicate the need. Nursing practices can implement closed-loop systems that return blood that is ordinarily wasted back to the patient. Point-of-care and inline bedside microanalysis of blood or noninvasive hemoglobin monitoring with pulse co-oximetry are other ways to monitor hemoglobin for anemia while minimizing blood loss [114].

In surgical patients where ongoing blood loss is expected, various methods for blood cell recovery are available. Continuous autotransfusion systems collect the shed blood from surgical fields via drains placed during surgical wound closure. The devices then filter, wash, and spin the collected blood in order to isolate RBCs to autotransfuse back to the patient. These devices are more commonly used for orthopedic and cardiac procedures. While in the general population

of patients with normal initial hemoglobin and hematocrit, these devices have not shown to consistently decrease costs or need for transfusion [115], in the setting of a critically ill patient who has higher risks of anemia for multiple other risk factors, the use of these devices could be considered appropriate.

Further assessment should include the evaluation of other therapies being administered to the patient that might be leading to blood loss or anemia. Many medications that are prescribed in the ICU can cause anemia via two pathways: hemolytic anemia or suppression of endogenous production and release of renal erythropoietin. Immune-mediated hemolytic anemia can be seen after administration of cephalosporins, beta-lactams, NSAIDS, antineoplastics, quinine, and methyldopa. The most common medications causing immune-mediated hemolytic anemia are piperacillin, cefotetan, and ceftriaxone [116]. Medications causing nonimmune-mediated hemolytic anemia that are more commonly used in the ICU are nitrofurantoin, phenazopyridine, primaquine, and sulfa drugs [117]. Treatment for drug-dependent, antibody-induced, macrophage-mediated hemolytic anemia is the discontinuation of the offending medication. For drug-independent hemolytic anemia, corticosteroids are the recommended first-line therapy [118]. Medications administered in the ICU can also suppress the release of erythropoietin. Such medications include angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers, theophylline, and beta-adrenergic blockers [41].

The critical care clinician should remain vigilant and continue to monitor for possible new bleeding sources in the surgical ICU patient. Critically ill patients are at risk for bleeding complications and ongoing blood loss. In a study of 100 ICU patients, a bleeding evaluation tool was used to examine the frequency, severity, and causes of bleeding complications in the medical surgical ICUs. Researchers reported that of the 100 patients, 90 % experienced bleeding, resulting in 480 separate bleeding events. One in five patients suffered from a major bleeding event, with a median length of time of 4 days. Interestingly, only 15 % of bleeding events were at the surgical site. More often, the site of bleeding was at the insertion site of a vascular catheter (38 %) and endotracheal tube site (16 %). Six percent of bleeds were gastrointestinal in nature [119]. Some correctable causes of ongoing blood loss include thrombocytopenia, acquired coagulopathies, and GI bleeding. Thrombocytopenia in the ICU can be multifactorial. Conditions leading to decreased overall number or decreased platelet activity include hemodilution from red blood cell transfusion due to massive blood loss, platelet consumption (from bleeding, trauma, or disseminated intravascular coagulation [DIC]), platelet destruction secondary to immune response in the septic patient, decreased platelet production caused by liver disease, suppressed bone marrow or viral infection, and increased splenic sequestration. Medications are also likely culprits in diagnosing the cause of thrombocytopenia in a critically ill patient. In the cardiac surgery patient, especially those requiring mechanical assist devices, there is continued consumption of platelets. Post-cardiac bypass patients routinely have thrombocytopenia secondary to sequestration and platelet activation and adhesion to synthetic surfaces of cardiac bypass machines [120, 121].

DIC is a much less common cause of anemia in the ICU, but the clinician should remain watchful for signs, especially in patients with severe sepsis or trauma. DIC is defined as a clinical state with abnormally low platelet count caused by consumption of platelets and other coagulation factors. Laboratory testing will reveal prolonged coagulation times. Mechanisms include aberrations in endothelial function and loss of balance between procoagulant, anticoagulant, and fibrinolytic factors in the body. The presence of DIC is considered an independent predictor of mortality in the hospitalized patient. While bleeding and anemia will be the most obvious clinical signs, there is often an underlying end organ damage occurring secondary to microvascular thrombosis [114]. Successful treatment of DIC is a challenge, since the underlying cause is usually difficult to absolutely eliminate acutely. Improvements have been made in the prevention of DIC by correcting acidosis, hypothermia, and avoiding hemodilution.

While limiting blood loss will help prevent worsening of anemia, there are other multiple factors that hamper the process of erythropoiesis in the critically ill patient. The ICU patient can be seen as a patient suffering from multiple inflammatory processes that impair RBC proliferation, iron metabolism, and erythropoietin production. One theory is that this is a broad-based evolutionary response to sequester and deny iron from invading microorganisms [41]. Iron homeostasis is impacted by numerous pro-inflammatory cytokines, including IL-1, IL-6, and tumor necrosis factor (TNF)-α, leading to impaired regulatory feedback between iron body needs and intestinal iron absorption [98]. Hepcidin, which is upregulated by pro-inflammatory cytokines, will lead to decrease duodenal iron absorption and block iron release from macrophages. This will then limit iron availability for progenitor cells. Pro-inflammatory mediators also lead to reduced transcription of the erythropoietin gene and transforming growth factors, creating another hurdle for RBC production [74]. Patients in shock suffer from further inhibition of hematopoietic precursor maturation secondary to high levels of vasoactive agents such as norepinephrine and phenylephrine [91].

Since there is consistent evidence that a major feature of the anemia of critical illness is the failure of circulating erythropoietin to increase appropriately in response to reduced hemoglobin levels, research into the effects of using

exogenous erythropoiesis stimulating agents (ESAs) to treat anemia of critical care is ongoing [87]. Three main trials by Corwin and colleagues are among the largest studies to date on this topic. EPO-1, the pilot study, included 160 adults from a multidisciplinary ICU. It demonstrated a reduction in red blood cell transfusion and a rise in hemoglobin with ESA treatment using a dose of 300 units/kg/day for 5 days and then every other day. Exclusion criteria were extensive and included vasopressor requirements and high levels of ventilatory support [122]. The second study EPO-2 enrolled 1,302 patients. A lower dose of 40,000 units weekly of ESA was administered. This study as well showed a reduction in red blood cell transfusion and maintenance of higher hemoglobin concentration, but no further clinical benefit or harm was identified [94]. The third trial (EPO-3) enrolled 1,460 patients who were given a dose of 40,000 units weekly. In this larger study, no difference was seen between rates of RBC transfusion between the two groups [92]. This may be related to a more restrictive transfusion practice across the board. Some benefits were seen in the subgroup analysis of trauma patients. Of note, the intervention group had a higher rate of thrombotic events, but in a post hoc analysis, this risk was not increased among patients receiving standard prophylactic or therapeutic doses of heparin [41]. Iron repletion was not standardized in these studies, and it is not known if the patients would have had improved outcomes if appropriate levels of iron were achieved to ensure appropriate erythropoiesis. The optimal dosing regimen and route of administration (intravenous versus subcutaneous) of ESAs in critically ill patients for the treatment of anemia have yet to be determined. Additional prospective clinical trials with larger sample size are needed to investigate population pharmacokinetic and pharmacodynamic parameters of ESAs, which should also incorporate alterations in iron metabolism associated with critical illness and inflammation and other patient characteristics, such as age, weight, and use of vasopressors [123]. Considered together, the clinical evidence for ESA therapy in critically ill patients suggests a decrease in mortality in trauma patients (but this effect does not appear to be related to a reduction in RBC transfusions) and an increase in the frequency of adverse events, particularly in patients with cancer or chronic renal failure. Therefore, exogenous administration of ESAs is used with caution in critically ill patients unless chronic conditions (such as chronic kidney disease) are present, and a thorough workup suggests that ESAs may be beneficial [114].

As mentioned above, it is not just stimulating the production of RBC which is necessary to have successful erythropoiesis. The body must have the building blocks available to produce progenitor cells. Diminished RBC production can also be due to nutritional deficiencies seen during this state of inflammation. In one study, 9 % of ICU patients were iron deficient, with an additional 2 % each to B12 and folate deficiency [86]. While iron has been shown to promote the growth and virulence of a number of microbes responsible for nosocomial infections in animal studies, evidence linking iron with increased risk of infection from human studies is lacking [41]. There have been some smaller studies examining iron supplementation in the critical care population. In a retrospective study of 27 surgical patients receiving intravenous iron therapy matched to control subjects, there did not appear to be any higher rates of bacteremia [124]. In another study of 863 post cardiopulmonary bypass patients, treated with both intravenous iron and ESA as needed or with blood transfusions, there was no difference in subsequent infection rate [125]. Intravenous iron supplementation may have better efficacy than enteral administration because of the block of intestinal absorption by hepcidin and compliance issues [41].

Transfusion Indications in the ICU

The fastest way to increase hemoglobin levels is by transfusing RBC. More than one-third of all ICU patients will receive a blood transfusion, and when ICU stay is longer than 1 week, greater than 70 % of patients will receive a blood transfusion (Table 25.2) [8, 13, 15–23]. The primary reason to prescribe a blood transfusion in the non-bleeding patient is to improve oxygen delivery and carbon dioxide removal. Oxygen delivery is determined by cardiac output, hemoglobin concentration, and oxygen saturation. Increasing hemoglobin concentration should improve oxygen delivery to the tissues, but in studies where blood transfusions were given to patients with acute respiratory distress syndrome (ARDS), sepsis, and trauma, any improvement was not shown in oxygen uptake [126–129]. This lack of improvement in oxygen delivery may be due to partially reversible biochemical and structural changes that occur in stored blood [41].

In 1999, Herbert et al. published a study comparing a restrictive transfusion policy (goal Hg 7–9 g/dL) to a liberal transfusion policy (goal Hg 10–12 g/dL) on mortality rates. The Transfusion Requirements in Critical Care (TRICC) trial randomized 838 patients admitted to the ICU without evidence of active bleeding to a restrictive transfusion strategy (transfusion to maintain hemoglobin >7 g/dL) versus a liberal strategy (transfusion to maintain hemoglobin ≥10 g/dL). Patients met criteria if they were euvolemic after initial fluid resuscitation. The restrictive transfusion treatment was associated with decreased rates of inhospital mortality compared to those seen with the liberal transfusion strategy. This benefit was most obvious among the less critically ill patients (APACHE II score ≤20) and <55 years old. Before the TRICC trial, critically ill patients were routinely transfused to a hemoglobin of 10 g/dL. This was one of the initial studies that led to updated transfusion guidelines [18]. While blood transfusions are clearly indicated in the setting of

hemorrhagic shock, we must further investigate when it is appropriate to transfuse each patient. In a review of 45 observational studies reporting the impact of transfusions on patient outcome (mortality, infections, acute respiratory distress syndrome [ARDS]) in populations of trauma, general surgery, orthopedic surgery, acute coronary syndrome, and ICU patients, Marik and Corwin identified RBC transfusion as an independent predictor of death, infectious complications, and ARDS [25]. More specifically for critical care patients, many of these studies have continued to document the harm of transfusions.

In the ABC study, 3,500 ICU patients, 37 % of which received a transfusion, were included. Older patients and patients with longer ICU stays were more likely to receive a transfusion. Both ICU and overall mortality rates were significantly higher in patients who had received transfusions versus those that had not received a transfusion (ICU rates: 18.5 % vs. 10.1 %; overall rates: 29.0 % vs 14.9 %). When comparing similar degrees of organ dysfunction, patients who had a transfusion had a higher mortality rate. For matched patients in the propensity analysis, the 28-day mortality was 22.7 % among patients with transfusions and 17.1 % among those without [13].

In 2004, the CRIT study showed among 4,982 ICU patients that the total number of RBC transfusions a patient received during the study was independently associated with longer ICU and hospital lengths of stay and increased mortality. Patients who received transfusions also had more total complications and were more likely to experience a complication during their hospitalization [8].

As ICUs across the world began to adopt more restrictive transfusion guidelines, the SOAP observational study of 3,148 European ICU patients showed direct relation between the number of blood transfusions and the mortality rate, but in multivariate analysis, blood transfusion was not significantly associated with a worse mortality rate. Furthermore, in 821 pairs matched according to a propensity score, there was a higher 30-day survival rate in the transfused patients compared with other patients [21]. One confounder is the higher use of leukoreduced red blood cells in the SOAP study compared with the ABC study [13, 21]. Is it possible that the SOAP study is showing that when a restrictive transfusion treatment plan is followed, the benefits of a needed transfusion will outweigh the risks?

Clinical practice guidelines for RBC transfusion in the critically ill and trauma patient published in 2009 have created a framework for intensivists to guide transfusion decisions [130]. As mentioned above, RBC transfusion is indicated for patients with hemorrhagic shock. Of special note, the guidelines advise against the use of a "transfusion trigger" of any number. Decision for RBC transfusion should be based on an individual patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters. When RBC transfusion is indicated in the absence of acute hemorrhage, only one unit at a time should be transfused and the patient should be reevaluated for further need of blood transfusions [130].

The guidelines also address the more specific subpopulations of critically ill patients. In a mechanically ventilated patient, no benefit to a "liberal" transfusion strategy has been recognized, but transfusion should be considered if Hg is less than 7 g/dL. For the critically ill trauma patients who are adequately resuscitated, transfusion can be indicated at an Hg of 7 g/dL. Again, there is no benefit in a "liberal" transfusion strategy for the critically ill trauma patients. Patients with stable cardiac disease in the ICU as well can tolerate a Hg of 7 g/dL, but RBC transfusion may be beneficial in patients with acute coronary syndromes (ACS) who are anemic (Hg 8 g/dL) on hospital admission [130].

Risks of Transfusions

Understanding the possible side effects of the transfusion is an important aspect of making transfusion decisions. Current data demonstrate that approximately 50 % of all blood product transfusions take place in the perioperative setting, underscoring the potential risks to the surgical critical care patient. Pulmonary edema, fever, acute transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion-related immunomodulation (TRIM), hypothermia, coagulopathy (dilutional), thrombocytopenia, and transfusion errors (incorrect blood components) are some of the adverse events associated with transfusion of blood components. If a patient requires repeated transfusion of RBCs for treatment of chronic conditions, it can lead to iron overload and resulting end organ damage [131].

TRALI

One the most common (and clinically identifiable) causes of transfusion-related morbidity and mortality is TRALI – transfusion-related acute lung injury. The term was coined in 1983. TRALI is described as a clinical state characterized by pulmonary edema (noncardiac in nature), hypoxemia, respiratory distress, and new bilateral pulmonary infiltrates on chest X-ray which occur within minutes to 6 h after transfusion. Other signs and symptoms include fever, tachycardia, cyanosis, hypotension, and frothy sputum [132]. Researchers report an occurrence of approximately 8.1 cases per 100,000 units of blood components transfused [133], although evidence suggests that the incidence can be significantly higher as the condition is believed to be underdiagnosed and underreported [134]. The risk of acquiring TRALI increases with

age, illness severity, and in cardiac patients, higher with increased length of time for cardiopulmonary bypass [135]. According to US Food and Drug Administration and other sources, TRALI is the second or third most frequent cause of death from transfusion [136]. Not surprisingly, the risk of developing TRALI increases with the number of units transfused. Blood components with the highest plasma content (i.e., FFP) or those containing antibodies against human leukocyte antigens (HLA) I and II and human neutrophils represent the highest risk of triggering TRALI, but any blood component can lead to this adverse event. The HLA antibodies are mostly present in blood which has been donated by women who have been previously pregnant [137]. There have been efforts to restrict female plasma donors to the blood supply which might decrease the incidence of TRALI.

The current management of TRALI is mainly supportive. Since hypoxemia is a main part of the clinical picture, supplemental oxygen support will likely be needed even if the patient does not require intubation. A high proportion of patient will require ventilatory support with "lung protective" small tidal volume settings [132]. If hypotension occurs, fluid resuscitation is often appropriate. This is one reason why it is important to distinguish the cause of the pulmonary edema. The additional intravenous fluid would worsen a patient with cardiac-related pulmonary edema or TACO (see below), but can be beneficial to a patient with TRALI and hypotension. Only anecdotal evidence has been provided for the use of corticosteroids [132]. Overall prognosis for a patient with TRALI is good. Mortality is relatively low (6–10 %) when compared with acute lung injury. For patients who do survive the initial episode, there is a return to baseline pulmonary function within days, and long-term function does not seem to be affected.

TACO

Transfusion-associated circulatory overload (TACO) is considered an under-recognized and serious transfusion complication. TACO occurs when a patient is unable to compensate for rapid or high-volume infusions of blood products. Risk factors include patients who are predisposed to volume overload, such as those with congestive heart failure, renal failure, and respiratory failure who require large or multiple transfusions [114]. TACO is often seen more commonly in patients who are 3 years or younger or 61 years or older. Respiratory distress and/or cyanosis associated with pulmonary edema presents within 2 h of transfusion. Elevated blood pressure, tachycardia, and increased pulmonary wedge pressure are the typical stigmata. TACO can be precipitated by even a single unit of RBC or other blood product. Clinical consequences include prolonged hospitalization, greater intensity of care, and death [138]. The incidence of TACO appears to be rising over the past years, but this is most likely related to increase reporting. In a study the prevalence of TACO is estimated to be 1 in 68 (95 % CI, 1 in 250 to 1 in 27) patients receiving plasma. These patients on average received multiple units of plasma (mean 4.0 units; SD 2.3 units) before TACO developed [139]. In another 2-year prospective cohort study of 901 ICU patients, researchers reported that TACO developed in 6 % of patients who received a transfusion [140].

TRIM

Since the 1980s, the risk of disease transmission through blood transfusions has massively declined due to the adoption of pathogen reduction technologies and increased hemovigilance systems. While the most common noninfectious side effects include TRALI, TACO, and hemolytic transfusion reactions, there is also the risk of transfusion-related immunomodulation (TRIM) which can increase the risk of acquiring nosocomial infections. The cause of suppression of immune system by blood transfusions is not clear, but likely is multifactorial and leads to a downregulation of the recipient's immune function. This can explain the long-recognized observation that transfusing patients undergoing allogenic renal transplantation can reduce the risk of rejection [141]. Likewise, it can be theorized that TRIM can lead to an increased rate of cancer recurrence and of postoperative bacterial infection, but exact causality has not been established yet by clinical trials. "Old" blood transfusions (red blood cell units with longer storage times) are associated with increased risk of acquiring nosocomial infections in critically ill trauma patients [142]. It is possible that the soluble mediators that concentrate in stored RBCs can be implicated in the initiation of the immune suppression cascade [114]. Further investigation into how the biochemical, structural, inflammatory, and physiological properties of RBCs change with storage and the possible effects of these changes on clinical outcomes in patients who receive transfusions is needed [143]. Based on more recent studies, there is data to suggest that TRIM is a biologic effect strongly associated with the infusion of allogeneic leukocytes. Leukoreduction is a proven method and plasma depletion is a proposed method to significantly reduce TRIM and its clinical effects [144].

Anemia After ICU Care

Many patients are discharged from the ICU and subsequently from the hospital with persistent anemia. A study looked at 1,023 sequential ICU admissions from admission to discharge or death in the ICU over 100 days, representing 44 % of all ICU admissions in Scotland during the study period.

The median transfusion trigger used in the absence of bleeding was 7.8 g/dL and 766 patients admitted to the ICU survived to discharge. The prevalence of anemia at ICU discharge was 87 % [14]. In 2006, a 3-year observational cohort study followed ICU survivors from the hospital. The median time from ICU discharge to hospital discharge was 13 days (IQR 6–22, range 1–119). At the time of discharge from the ICU (using the last recorded Hb concentration), 77 % of the patients met criteria for the diagnosis of anemia. Of the patients who were anemic, 32.5 % had a hemoglobin level less than 10 g/dL and 11.3 % had a hemoglobin level less than 90 g/dL. A longer stay in the ICU and the hospital was a risk factor for anemia. Multivariate regression analysis showed that patient age, gender, APACHE II score, and ICU length of stay were not independent predictors after including the ICU discharge hemoglobin level [145]. Critically ill patients who survive to discharge may likely be suffering from other serious illnesses such as cancer, renal failure, chronic cardiac disease, and other chronic inflammatory diseases, during which anemia is associated with poor quality of life and higher morbidity [145].

Many patients who survive the ICU continue to suffer reduced quality of life after hospital discharge, often associated with symptoms typical of anemia such as fatigue and breathlessness. In a 6-month prospective observational cohort study of intensive care survivors with moderate to severe anemia at the time of ICU discharge, erythropoietic and inflammatory markers were measured at regular intervals over 6 months to assess red cell production and factors limiting recovery from anemia. Thirty patients were recruited of which 19 completed the study, 6 died during the study period, and 5 only completed part of the follow-up; 47 % of the patients who completed the study at 6 months from discharge from the ICU had recovered from their anemia. The median time to recovery was 11 weeks. On the other hand, 53 % of patients continued to suffer from anemia at 6 months. An inappropriately low erythropoietic response to anemia was observed in almost all patients in the study. Patients with delayed recovery or persisting anemia during the 13 weeks following ICU discharge had higher levels of circulating inflammatory markers (IL-6 and C-reactive protein) and did not exhibit reticulocytosis during the weeks following discharge [146].

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