Chapter 3
Anemia in the Critically Ill Patient

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Clinical Vignette

Mr. T. was a 72-year-old man admitted to the ED with chest pain and initial pulmonary edema. Two years before he suffered a postero-inferior acute myocardial infarction treated with the positioning of two bare metal stents. From then on, the patient was treated with aspirin and clopidogrel and did not report any symptom attributable to the underlying coronary artery disease. Only in the last few days preceding the current admission, he complained of worsening fatigue associated with shortness of breath. The history revealed a cerebellar stroke occurred at the age of 48 years, a type 2 diabetes mellitus treated with metformin, a mild chronic renal failure (serum creatinine: 1.6 mg/dl), and a Hashimoto's thyroiditis treated with thyroxin. The symptoms resolved quickly with nitrates and diuretics and the patient was transferred to the coronary care unit. The blood chemistries were normal apart from transient mild elevation

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of troponin and BNP and a macrocytic anemia (Hb = 8.5 g/dl, MCV = 110 fL), which likely accounted for the cardiac symptoms; the reticulocytes were also abnormally elevated. In the following days, the anemia worsened despite multiple transfusions of packed red blood cells given in the following days aiming at achieving an Hb value of at least 10 g/dl. Initially, the cause of anemia was attributed to different factors, including (a) a gastroenteric chronic blood loss favored by the dual anti-aggregating agents; (b) a possible gastrointestinal neoplasm; and (c) the failed adsorption of the adsorption of Vitamin B12 and folate due to the presence of autoantibodies directed against the gastric ells, as often reported in patients with Hashimoto's thyroiditis. However, serum values of Vitamin B12, folate, and Fe were normal and the endoscopies of the digestive tract did not demonstrate any source of bleeding; also a biopsy of the gastric mucosa resulted normal. As either serum LDH was raised and haptoglobin was decreased, a hemolytic anemia was suspected, which was confirmed by the detection of cold hemoagglutinins belonging to the IgM class; a bone marrow biopsy was then obtained, which demonstrated a non-Hodgkin's lymphoma. The patient was subsequently transferred to the Dept of Hematology where an appropriate chemotherapy was carried on. Two years after the described episode, the patient is free of symptoms, his Hb values are normal, and is conducting a regular life.

3.1 Introduction

The patient just described represents a typical case of symptomatic and potentially dangerous anemia which had been initially attributed to a number of causes before arriving at a correct

diagnosis, with the subsequent potential risks for patients, which fortunately did not occur in his case. Actually, anemia, which is defined by the World Health Organization as a hemoglobin (Hb) concentration <10 g/dl and/or a hematocrit value (Ht) <30 % [1, 2], occurs frequently among critically ill patients admitted to the Intensive Care Unit (ICU). Indeed, roughly 70 % of them are anemic since the beginning and almost 100 % develop anemia during the first week after the ICU admission [3, 4]. In many circumstances, the source of anemia can be obvious (trauma, rupture of major vessels, etc.), but in other cases the underlying disorder(s) can be more elusive, thus requesting a diagnostic workup which could result unfamiliar even to an experienced intensivist. To further complicate the issue, both Hb and Ht can be influenced by factors other than the mere production and loss of red blood cells (RBC), including wide volume shifts between intravascular and extravascular compartments due to the alteration of the endothelial wall permeability, the administration of large amounts of fluids and the transfusion of blood and derivates [1].

The aims of this chapter are (a) to review the main causes leading to the occurrence of anemia in critically ill patients; (b) to provide some clues for the diagnosis, starting from some basic but fundamental variables related to the RBC (Table 3.1); and, perhaps more importantly, (c) to distinguish between forms amenable by the intensivists alone and others which require a more in-depth hematological competence.

3.2 The Kinetics of Red Blood Cells

RBC are generated in the bone marrow under the influence of erythropoietin (EPO) and their production requires a number of factors, including zinc, iron (Fe), vitamin B_{12}, folate, tyrosine, androgen hormones, and cortisol [4]; the basal release of RBC is

Table 3.1 Some biological variables used in the diagnosis of anemias. All values refer to adult patients

Variable (adults)	Normal values
Red blood cells count (/ml)	Male $4.5–5.9 \times 10^6$ Female $3.5–5.0 \times 10^6$
Hematocrit (%)	Male: 39–49 Female: 33–43
Blood hemoglobin level (Hb)	Male: 13–17 g/dl Female: 13–15 g/dl
Reticulocyte count (%)	0.8–2.5
Mean corpuscolar volume (MCV)	85–100 fL
Mean corpuscolar Hb concentration (MCHC)	31–35 g/dl
Mean corpuscolar Hb (MCH)	28–33 pg/cell
Serum transferrin	200–300 mg/dl
Serum Fe	75–160 mcg/ml (m) 60–150 mcg/ml (f)
Serum Ferritin	20–300 ng/ml (m) 20–120 ng/ml (f)
Serum haptoglobin	50–220 mg/dl
Vitamin B12	200–1,000 pg/ml
Folate	2–10 ng/ml

15–20 ml/day but this rate can decuplicate during acute anemia provided that the iron stores are repleted and in the presence of a normal renal function [5]. As the mature RBC are devoid of mitochondria as well as of intrinsic reparatory mechanisms, their ageing-related decrease of energy levels is associated with changes of the membrane properties, including the reduction of their fluidity and deformability and the increase of density and viscosity; all these changes ultimately lead to their removal from circulation and destruction in the spleen and in the reticuloendothelial system (RES) [6–8]. In normal conditions, the overall life span of RBC is 120 days. Other processes responsible for their anticipated elimination from the bloodstream include the premature death of mature RBC (eryptosis) and the removal of RBC

just released from the bone marrow (neocytolisis). Both mechanisms are responsible for the maintenance of an appropriate circulating mass of RBC and are inhibited by EPO [5].

3.3 The Physiological Consequence of Acute Anemia

Basically, Hb plays a dual role. First, as RBC carry O_2 from the lungs to the cells, according to the formula:

$$\text{Oxygen delivery}\left(DO_2\right)=\text{Arterial}\,O_2\,\text{content}\left(CaO_2\right)\times\text{Cardiac output}\left(CO\right)$$

it appears that a reduction of the CaO_2, which is mainly determined by the total Hb and its O_2 saturation (SaO_2), being negligible, the amount of O_2 dissolved in the plasma in normobaric conditions sets the stage for a reduced O_2 availability to the tissues with the subsequent onset of anaerobic metabolism [9, 10]. Second, since Hb scavenges CO_2 from the cells to the lungs, its drop is associated with the increase of the tissue CO_2 content. In a resting healthy organism, a number of mechanisms can counterbalance an acute isovolemic reduction of Hb to as low as 5 g/dl [11]; these include (a) the leftward shift of the Hb dissociation curve determining a facilitated download of O_2 toward the cells, leading to an increased extraction of O_2 (O_{2ER}); (b) a compensatory tachycardia and tachipnea; and (c) the concomitant increase of the heart rate (HR), stroke volume (SV), and CO driven by the hypoxia-induced increased production of catecholamines. However, if the anemia aggravates and/or in the presence of concomitant limited cardiac and respiratory reserves, all these adaptative mechanisms become exhausted and tissue respiratory and metabolic acidosis ensue due to

the contemporaneal increase of CO_2 and of the lactate produced under anaerobic conditions [4, 9, 12]. Moreover, it has become clear that the tissues are not equally vulnerable to a reduced O_2 availability and marked differences exist in terms of O_{2ER} capabilities among different organs and sometimes also within the same organ [12].

3.4 Causes of Anemia in the Critically Ill Patient

Similarly to other fields of medicine, either a reduced production of RBC and/or a decrease of their life span account for the occurrence of anemia in critically ill patients [4]; actually, both mechanisms can act simultaneously in many conditions commonly encountered in the ICU independently from the cause of admission, including advanced age, poor nutritional condition, recent surgical procedures, unresolved inflammatory conditions, etc. In these circumstances, a severe anemia can develop in 1 week from the onset of the disease, requiring the ICU admission [3].

3.4.1 Anemia Due to a Reduced Production of RBC

Albeit a reduced production of Hb can be caused by several factors, those more frequently encountered among patients admitted to the ICU include:

(a) Persisting inflammatory conditions, not only determined by chronic conditions such as neoplasms, vasculitides, and rheumatologic conditions but also by unresolving sepsis, post-operative states, etc. [13]. These conditions appear particularly relevant as more and more elderly subjects

survive the initial insult determining their admission to the ICU, only to become chronic critically ill patients who cannot be weaned from the mechanical ventilation [1]. In these circumstances, several inflammatory and counter-inflammatory mediators produced during either the initial or the more advanced phase of their disease, including Tumor Necrosis Factors-α (TNF- α) and Interleukin-1 (Il-1) and Il-6, negatively reduce Fe metabolism and impair the feedback existing between its enteric adsorption and the body stores [4]; this latter phenomenon is aggravated by an increased production of hepcidin, a protein synthetized in the liver, which also inhibits the release of the Fe stored into the RES. At the same time, since the production of EPO is inappropriately reduced even in the presence of abnormally low values of Hb and the number of its receptors on the target cells is decreased, the response of the bone marrow is blunted.

In the aforementioned circumstances and in the absence of other confounding factors, the anemia is mild to moderate, with Hb > than 8 g/dl, and with a normal mean cell volume (MCV) and mean cell hemoglobin (MCH) [4].

(b) Fe deficiency, caused by blood loss or inadequate dietary intake. Actually, Fe-deficiency anemia is rather common, having been reported in as many as 9 % of ICU patients [14]. The classic signs of iron deficiency anemia can be difficult to evaluate in ICU patients, and the diagnosis is based on the biochemical markers of the iron metabolism (Table 3.2). As in these patients factors other than iron deficiency can determine hyposideremia, other markers must be suited to confirm the diagnosis, including:

(i) Serum ferritin: Even if its value increases in the presence of sepsis and severe infections as it is an acute-phase reactant, low values are suggestive of iron deficiency.

Table 3.2 Differential features of anemia of chronic disease and iron deficiency anemia

Variable	Anemia of chronic disorders	Iron deficiency anemia
Hb	May be ≥8 g/dl	May be ≤8 g/dl
MCV	Normal/↓	↓
MCH	Normal/↓	↓
Serum Fe	↓	↓/↓↓
Serum Ferritin	Normal/↑	↓
Serum hepcidin	↑	↓
Reticulocytes	↓	↓

(ii) Serum transferrin and total serum binding capacity, which are increased during iron deficiency; in the same condition, the transferring saturation is reduced. However, it should be noted that other factors, including alcohol, neoplasm, and inflammatory conditions can decrease the sensibility and sensitivity of these markers.

(iii) RBC zinc protoporphyrin, whose values increase during iron deficiency and is not affected by a concomitant inflammatory state.

Hematological features of anemia associated with Fe-deficiency anemia include Hb values <8 g/dl and reduced MCV and MCH [14].

(c) Vitamin B12 and folate deficiencies have been reported in 2 % of ICU patients and are associated with a reversible failure of the bone marrow causing the disturbed synthesis of DNA and megaloblastic hematopoiesis, leading to the release of RBC larger than normal [15]. In case of isolated Vitamin B12 deficiency, a demyelinating disease of the nervous system can coexist or anticipate the onset of anemia [16]. Since the enteral adsorption of Vitamin B12 requires the action of the Intrinsic Factor (IF), which is synthetized by the gastric parietal cells and of another receptor located in the distal ileum, conditions associated with gastric or enteric mucosal disuse or atrophy, extensive gastric and/or

ileal resections can determine the occurrence of Vitamin B12 maladsorption and subsequent deficiency [16]. Moreover, H_2 receptor antagonists, proton pump inhibitors can impair the absorption of both Fe and Vitamin B12 [17–19]. The diagnosis of Vitamin B12 deficiency can be elusive, because (a) as many as 15–25 % of patients have normal Hb and MCV [20]; and (b) the affected patients admitted to the ICU cannot report the symptoms associated with the neuropathy. However, the diagnosis should be suspected in the presence of a progressive reduction of Hb and contemporaneal increase in MCV. The diagnostic workup of Vitamin B12 and folate deficiency-related anemia should include the following [16, 20]:

(i) The measurement of blood Vitamin B12 levels should be interpreted with caution, because, with the exclusion of extremely low values (<100 pg/ml) which are diagnostic, both false negative and false positive results have been reported, which have been ascribed to protein carrier other than cobalamin.
(ii) The measurement of serum methylmalonic acid and total homocysteine levels are useful in patients with suspected Vitamin B12 deficiency who have not been treated yet; the values of these markers are markedly elevated even before the appearance of anemia and sharply decrease after the initiation of Vitamin B12 supplementation.
(iii) The measurements of serum and RBC folate levels, which reflects the folate intake in the last 3 months and the measurement of serum methylmalonic acid and total homocysteine levels.

(d) Acquired Aplastic Anemia (AA) is characterized by pancytopenia and bone marrow aplasia determined by an autoimmunitary process mediated either by cytotoxic T lymphocytes directed against hematopoietic stem cells and/or by

antibodies directed against kinectin, which is a polypeptide expressed on the surface of human hemopoietic cells as well as of other organs, including the liver, the ovary, testis, and brain cells. The onset of AA can be abrupt and the presentation symptoms can resemble those commonly encountered in septic shock patients. In these circumstances, a thorough medical history is mandatory and a particular attention should directed on the possible assumption of drugs known to cause myelotoxicity [21–23]

3.4.2 Anemia Due to a Loss of RBC

This disorder occurs frequently in ICU patients. In some cases the source of hemorrhage can be rapidly identified and treated, but in other circumstances, and especially when the blood loss occurs subacutely, it can go unnoticed for a long time and the cause(s) can be difficult to recognize.

(a) Repeated blood samples represent a source of blood loss which is largely underrecognized. Actually, as many as 40–70 ml can be withdrawn each day from critically ill patients for various purposes, including blood chemistries, blood gas analysis and culture, etc. [3]. This amount exceeds the normal replacement rate in healthy individuals. Not surprisingly, it is likely that the amount of blood sent to the lab could be somewhat related to the severity of the underlying conditions, being larger in patients with more unstable conditions. Paradoxically, the volume of blood really processed for the required investigations is roughly 2 % of that sampled.

(b) Hemophagocytic Lymphohiatiocytosis (HLH) is characterized by fever, peripheral lymph nodes enlargement, pancytopenia, and splenomegaly possibly associated with the rapidly deteriorating function of multiple organs

ultimately leading to a multiple organ dysfunction syndrome (MODS). The cause of HLH is an inappropriate activation of macrophages which become engulfed with RBC, leukocytes and platelets occurring isolated, or in association with a number of pathologic conditions, including bacterial, viral, and fungal infections, hematological and solid malignancies, and systemic and rheumatologic diseases. The clinical picture of rapid deteriorating MODS is generally ascribed to a severe sepsis or septic shock and treated consequently. The diagnosis requires a wide array of clinical and laboratory investigations and must be confirmed by the microscopical examination of the bone marrow [6, 24].

(c) Autoimmune hemolytic anemia (AHA) is a relatively uncommon disorder due to the action of different categories of autoantibodies against mature circulating RBC. Albeit in many cases the clinical course is chronic, in some cases the onset of AHA can be abrupt and is associated with a dramatic drop of Hb levels, hyperbilirubinemia, and hemoglobinuria. Both, the site of hemolysis and the related symptoms can vary according to the class of autoantibodies involved: IgG-coated RBC are destroyed by the RES primarily in the spleen, liver, and bone marrow (extravascular hemolysis), whereas IgM-coated RBC are lysed into the bloodstream (intravascular hemolysis) after the activation of the complement [25]. Basically, although mixed forms exist, AHA can be subdivided (a) according to the body temperature level at which hemolysis occurs; and (b) by the absence (primary forms) or presence (secondary forms) of underlying disorders leading to the production of autoantibodies of the different classes. The secondary forms of AHA are mainly associated with lymphomas and systemic disease such as lupus erythematosus. According to their characteristics, the autoantibodies causing AHA can be subdivided as follows:

(i) Warm autoantibodies (WA), usually belonging to the IgG class, determine the RBC destruction after their binding on some receptors on the cell surface; the autoantibody-coated RBC are then eliminated mainly into the spleen and for a lesser extent by the Kupffer cells. Trapped RBC can partially escape the destruction and are released back in the bloodstream: however, this process is associated with the partial loss of the cell membrane and the subsequent change of the RBC shape which become spherical, more rigid, and less deformable than normal RBC. This cycle continues with the ongoing fragmentation and destruction at every passage through the liver and the spleen until their complete destruction occurs. Actually, although several types of WA can activate the complement, the occurrence of intravascular lysis is uncommon. The clinical suspicion arises in the presence of unexplained anemia, reticulocytosis of various degree and unconjugated hyperbilubinemia, and the final diagnosis requires the identification of antibodies and/or complement of the BRC surface, usually with the Coombs' direct test [25].

(ii) Cold autoantibodies (CA), belonging primarily to the IgM-class, although either IgG or IgA can be occasionally involved. The responsible autoantibody is detected in vitro as it causes hemolysis of circulating RBC with a double-step process, requiring an initial incubation in the cold, followed by another incubation at 37 °C. The symptoms are caused by the cooling of blood flowing through the acral parts of the circulation, allowing CA to bind the epitopes on the RBC surface, thus causing their agglutination and the activation of the complement via the classical pathway. Once returned in the warm core compartment, the CA detaches from the RBC, but the C3b fragment of the complement remains bound, allowing their uptake in the hepatic RES cells. Moreover, complement activation

can proceed until the production of the C5, which attacks the RBC membrane causing also an intravascular hemolysis. The laboratory diagnosis is based on the presence of anemia, by the autoagglutination of blood samples kept at room temperature for 30–60 min and on the positivity of the direct Coombs' test using an anti-C3 serum in association with its negativity when the patient's RBC are challenged with an anti-IgG serum. Albeit less frequent than the WA-AHA, the widespread use of therapeutic hypothermia after cardiac arrest and of norepinephrine in the treatment of septic shock could represent a trigger factor in predisposed patients [26].

3.5 Conclusions

The occurrence of anemia in the critically ill patient is so common to be considered almost normal, thus preventing a more in-depth analysis of its origin. In many cases, the cause(s) are evident and/or easy to detect, but in some circumstances an apparently mild and asymptomatic anemia can represent the tip of an iceberg constituted by severe systemic conditions, including AHA, leukemias, etc., that the intensivist could be not accustomed to deal with. A high index of suspicion is warranted especially in those patients who remain anemic despite multiple transfusions and in whom an appropriated diagnostic workup failed to demonstrate any accountable source of bleeding.

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