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Anaemia in the Critically Ill: What is the Major Culprit?

Anaemia is commonly encountered in the critically ill and is associated with poor outcomes. The cause is multifactorial and includes high hepcidin levels and a blunted response to erythropoietin.

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Anaemia is defined by haemoglobin (Hb) < 12 g/dL for women and Hb below 13 g/dL for men, according to the WHO (1968). Anaemia is a prevalent condition that affects nearly all critically ill patients. Approximately two-thirds of patients are anaemic at admission in Intensive Care Units (ICU) (Vincent et al. 2002); nearly 100% of the remainder become anaemic during their ICU stay (Napolitano et al. 2017), 77% of patients are still anaemic at hospital discharge (Walsh et al. 2006), and many persist to be anaemic for several months after leaving the hospital. Warner et al. (2020) showed that the prevalence of anaemia post hospitalisation was 56% at 3 months, 52% at 6 months, and 45% at 12 months among those alive and with available haemoglobin (Hb) measurements. In addition, there is scientific evidence that lower mean Hb levels are associated with higher SOFA scores, a longer length of stay, and higher mortality rates (Vincent et al. 2002). Anaemia becomes an issue when it is linked with insufficient oxygen supply to vital organs.

The cause of anaemia in critical illness is complex and multifactorial and has been a topic of debate in critical care medicine for many years. Primary mechanisms of anaemia may include haemodilution, blood loss, increased hepcidin levels, reduced erythropoietin levels, neocytolysis, drug reactions, and nutrient deficiency (Astin and Puthucheary 2014).

Haemodilution

Fluid administration may cause a relative reduction in Hb concentration, producing a secondary decrease in oxygen delivery (DO_2). This phenomenon was observed by Perel et al. (2017) in patients who received more colloids as part of perioperative goal-directed therapy (GDT); moreover Otto et al. (2017) reported that in approximately half of cases, anaemia could be explained as a result of increased plasma volume (PV) rather than by a reduction in red cell mass (RCM). Drevon et al. (2021) retrospectively analysed RCM and PV of normal, anaemic and polycythemic patients using direct measurements of red cell and plasma volumes and demonstrated that Hb is a good surrogate marker of decreased RCM for severely anaemic patients but not for moderately or mildly anaemic patients. Finally, Yan et al. (2011) analysed blood volume in patients admitted to the ICU and showed that anaemia is over diagnosed in hypervolaemic patients, potentially producing unnecessary interventions. An accurate measurement of intravascular status, coupled with fluid balance might be useful to differentiate hypovolaemic real anaemic patients from haemodiluted ones.

Blood Loss

Although blood loss is considered a significant cause of anaemia in critically ill patients, it is not the only explanation for the high prevalence of anaemia. A study reported that bleeding was the reason for transfusion in 46% of patients (Westbrook et al. 2010). Another study showed that 18% percent of critically ill patients received transfusion associated with haemorrhage, while 26% received transfusion not associated with haemorrhage (Walsh et al. 2004). Potential causes of blood loss are trauma, surgery, gastrointestinal, vascular, and obstetric bleeding. Moreover, coagulopathies, thrombocytopenia, and phlebotomy can cause blood loss. Phlebotomy is highly associated with changes in Hb and haematocrit levels, can contribute to anaemia and is an underrecognised cause of anaemia in critically ill patients. A prospective blood sampling study of 1136 patients being cared for in 145 intensive care units across Europe revealed that the mean number of blood samples taken per day was 4.6, and the mean total volume of blood sampled per day was 41.1 mL (Vincent et al. 2002). Strategies to reduce anaemia due to blood sampling procedures include switching to small-volume phlebotomy tubes and replacing routine multiple daily phlebotomies for blood sampling with phlebotomy only when essential (McEvoy and Shander 2013).

Hepcidin

Hepcidin is the main regulator of plasma iron concentrations. It is a small 25-amino acid peptide mainly synthesised by the liver. Hepcidin is produced from a pre-pro-peptide of 84 amino acids that is biologically inactive. After an inflammatory stimulus, cytokines released by activated leukocytes induce hepcidin synthesis, and hepcidin binds to ferroportin, the pore that allows egress of iron from intestinal epithelial cells and reticuloendothelial macrophages. Ferroportin is predominantly expressed in duodenal cells and macrophages, allowing iron absorption from the digestive lumen **(Figure 1)** and iron recycling after erythrophagocytosis. Inflammation and iron overload induce hepcidin synthesis, whereas iron deficiency, hypoxia, and erythroid expansion inhibit hepcidin synthesis (Lasocki et al. 2011). Therefore, high hepcidin levels block intestinal iron absorption and macrophage iron recycling, inhibiting iron entry into plasma and causing decreased iron delivery for erythropoiesis and functional iron deficiency anaemia (Heming et al. 2011; Pagani et al. 2019).

Reduced Levels of Erythropoietin

Human erythropoietin (EPO) is a 30.4 kDalton glycoprotein hormone composed of a single 165 amino acid residue chain to which four glycans are attached. It is produced mainly by peritubular cells in the kidneys of adults and by hepatocytes in the foetus. EPO is essential for the survival, proliferation, and differentiation of erythrocyte progenitors in the bone marrow, and its level is continuously adjusted to regulate erythrocytes production and to optimise tissue oxygenation. Systemic hypoxia activates hypoxia-inducible factor (HIF), which stimulates EPO production and iron uptake and utilisation in the bone marrow to facilitate erythroid progenitor maturation and proliferation. EPO needs a receptor (EPO-R) that is expressed on erythroid cell progenitors and in a variety of tissues and cell types, such as the brain, retina, heart, kidneys, vascular smooth muscle cells, myoblasts, and vascular endothelium (McCook et al. 2012). While absolute EPO levels are not necessarily decreased in critically ill patients, there is evidence for a blunted EPO response to anaemia secondary to increased levels of cytokines such as IL-1, Il-6 and TNF-alpha (Rogiers et al. 1997; von Ahsen et al. 1999), reinforcing that a blunted EPO response is a factor contributing to anaemia in critical illness. Mainly IL-1 and TNF-alpha seem to be responsible for the defect in EPO production in severe systemic inflammatory diseases (Jelkemann 1998).

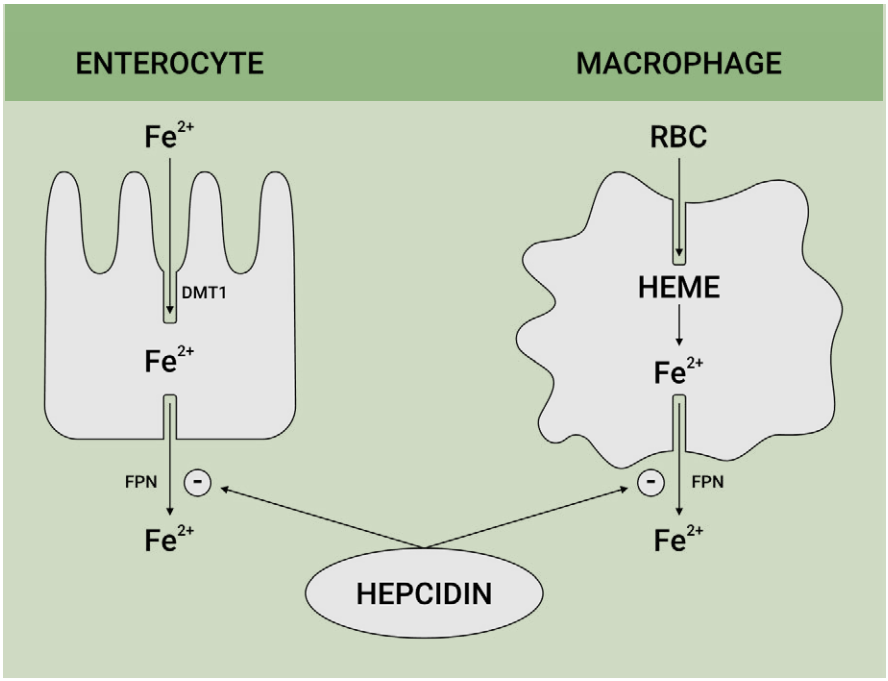

Figure 1. Iron obtained from the diet is passed through the intestinal enterocyte apical membrane via divalent metal transporter 1 (DMT1), either stored as ferritin or moved into the plasma by ferroportin (FPN) as an exporter. Macrophages play important roles in recycling iron derived from the clearance of red blood cells (RBCs). The senescent erythrocytes are recognised and phagocytosed by macrophages. After heme catabolism, iron can be stored in ferritin molecules or recycled towards the circulation via the ferroportin. High hepcidin levels reduce ferroportin expression, blocking intestinal iron absorption and decreasing iron release from macrophages.

Neocytolysis

Neocytolysis is the selective destruction of erythrocytes that have been formed during stress erythropoiesis in conditions of hypoxia, with the objective of decreasing the excess number of erythrocytes that are no longer required (Mairbäurl et al. 2018). This phenomenon was first described in astronauts after returning from space and people descending from high altitude. Upon entering microgravity, astronauts' blood volume in the extremities pools centrally. The body adapts by transudating approximately 20% of the plasma volume into the soft tissues and suppressing EPO production (Rice and Alfrey 2005). Similar processes seem to occur in descent from high altitude. Rice et al. (2001) studied polycythaemic residents of high altitude upon travel to sea level and found a rapid decrease in erythrocyte mass within 3–7 days after descent. They also demonstrated a rapid decrease in EPO levels, and increased bilirubin levels. In both situations, there is a rapid reduction in erythrocyte levels upon return to normoxia that cannot be accounted for by cessation of cell production despite a reduced EPO level. Therefore, EPO insufficiency, a known mechanism of decreased RBC production, cannot elucidate the reduction in Hb in critically ill patients

over the first few days. Neocytolysis can explain how red cell mass can be reduced over a short time frame of a few days, leading to rapid development of anaemia. Although the mechanism of neocytolysis has not been clearly defined, it is likely dependent on decreased EPO serum levels.

Nutrient Deficiency

Due to inadequate nutritional support and increased demands, vitamin B12 and folate deficiency may worsen in critically ill patients, potentially producing anaemia. Deficiency of iron, vitamin B12, folate, or copper can result in acquired microcytic or macrocytic anaemia. Rodriguez et al. (2001) studied 184 critically ill patients and demonstrated that 4 (2%) were B12 deficient and 4 (2%) were folate deficient. Thus, these deficiencies probably do not play an important role in the pathogenesis of anaemia. Serum vitamin B12 level should be measured in all patients with unevaluated macrocytosis. All individuals who are nutritionally compromised or who have had gastric surgery should also have serum folate measured (McEvoy and Shander 2013).

> **"the cause of anaemia in critical illness is complex and multifactorial and has been a topic of debate in critical care medicine for many years"**

Drug Reactions

Drugs administered in ICU can have adverse effects that can lead to anaemia by two distinct pathways, one by causing haemolysis and the other way by suppressing normal renal release of erythropoietin. Drug induced haemolytic anaemia, although rare, is a serious adverse effect. Few antimicrobials like piperacillin and ceftriaxone can cause it, whereas suppression of erythropoietin can be caused by commonly used drugs like angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, calcium channel blockers, theophylline and β-adrenergic blockers.

Conclusion

Anaemia is a common occurrence in critically ill patients, and it is associated with poor outcomes. The cause of anaemia is complex and often multifactorial, and in many cases, it can be due to inflammation. Humans, as rationalising beings, generally trust that they are accurately perceiving where the problem is, and they like to find a culprit to blame. In the case of anaemia in the critically ill, we can blame, in most cases, high hepcidin levels and a blunted response to EPO.

Conflict of Interest

None. ■

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