# Anaemia in the ICU

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## INTRODUCTION

Anemia is a common clinical problem in ICU. Almost universal by the end of first week after admission [1].How ever these result can be misleading because it is based on Hemoglobin concentration in blood as marker of Anemia. In ICU in critical illness it is a distinct entity although it is similar in many aspect to the anemia of chronic diseases, inflammation appears to be a measure factor. There are 3 major categories of anemia 1- Hypoproleferative anemia secondary to marrow production defects.2- In effective erythropoiesis caused by red cells maturation defects.3-Decreased servival of red blood cells. Secondary to blood loss, Hemolysis. Majority of anemia cases in ICU(75%) are hypoproliferative type. This article presents the current knowledge on defining various parameters of   anemia in ICU, etiopathogenesis its relation to tissue oxygenation and overall highlights the common practice of transfusing red blood cells to correct anaemia which is an arbitrary intervension in critical care medicine.

## DEFINITION

Anemia is defined as "decrease in oxygen carrying capacity of blood which is a function of total volume of circulating red blood cells."This parameter can be measured by chromium tagged erythrocytes, (normal values shown in table-1),but the methodology is not readily available in the clinical setting. Therefore an clinical alternative definition of anaemia that is based on hematocrit and hemoglobin concentration in blood. This practice id problematic in critically ill patient, the problem with the clinical definition of anaemia is the influence of plasma volume on  the hema tocrit and hemoglobin concentration, as plasma volumes changes frequently patients as a result of 1-They are hemodynamicaly unstable due to fluid shifts between extra vascular compartment and intravascular  compartment.2-Hypoalbuminemia, is common in critical ill patient, this shifts fluids out of compartment.3-I.V fluids, increases plasma volume and diuretics which are frequently used in ICU. Therefore hematocrit and hemoglobin are unreliable markers of anaemia in critically ill patient.[2,3]

**Table:-1**-Reference Ranges for Red Cell Parameters In Adults

| | |
|---|---|
| Red Blood Cell Count | Mean Cell Volume (MCV) |
| Males:4.6-6.2x$10^{12}$/lit | Females: same |
| Reticulocyte Count | Hematocrit |
| Males:25-75x$10^9$/l     it | Males:40-54% |
| Females: Same | Females:38-47% |
| Red Blood Cell Volume | Hemoglobin |
| Males:26 mL/kg | Males:14-18g/dl |
| Females:24mL/kg | Females: 12-16 g/dl |

Normal value are 10% lower in the elderly(≥65 years of age.)

Normal values are 0.5 g/dL lower in blacks.

## Common etiology and pathogenesis of anemia In ICU

There are two established common causes of anemia in ICU are 1-Systemic inflammation 2-Repeated phlebotomy and blood loss .Failure of erythropoisis can also occure without this two predisposing condition if the energy needs of erythropoesis is not satisfied.

An Adult has six trillion (6x$10^{12}$)RBC per leter of blood  (Table 1) using a blood volume of 5 leters the average turnover of circulating RBC is 1% per day, which means that (0.01x 30 trillion)300 billion RBCs must be produce daily to maintain a constant poll of circulating erythrocyts. Failure to meet the energy requirements of this effort could lead to failure of erythropoiesis and subsequent anemia.

This daily production of RBCs (which takes place in the cavities of the axial skeleton in adults) is regulated by erythropoietin, a hormone produced in the peritubular capillary endothelium in the kidney that stimulates erythropoiesis in marrow cavities. The cells that manufacture erythropoietin can respond to decreases in the arterial O2 content (either hemoglobin or arterial pO2) by increasing the secretion of erythropoietin. The subsequent actions of erythropoietin on marrow erythropoiesis would then help to correct the deficit in the O2 content of blood. Interruption of the erythropoietin regulatory system is considered one of the major mechanisms for ICU-acquired anemia[4]

## INFLAMMATION AND ANEMIA

Inflammatory cytokines (e.g.,tumer necrosis factor) have several effects that can promote anemia, including inhibition of erythropoietin release from the kidneys, reduced marrow responsiveness to erythropoietin, iron sequestration in macrophages, and increased destruction of RBCs [4,5]. The anemia associated with inflammation has the same characteristics as the *anemia of chronic disease:* i.e., a decrease in iron, total iron binding capacity, and transferring levels in plasma, combined with increased ferritin levels in plasma and iron sequestration in retculoendothelial cells. This is the most common pattern observed in the anemia that develops in ICU patients, so inflammatory cytokines are believed to play a major role in ICU-acquired anemia.

## Phlebotomy and Anemia

The volume of blood withdrawn from ICU patients to perform laboratory tests averages 40ml to 70ml daily [6,7].Cumulative increases in this phlebotomy volume can reach 500 ml (1 unit of whole blood) after one weeks, and this volume can augment the severity of anemia from other causes (by removing iron that is needed for erythrocyte production),or can itself become a source of anemia if allowed to continue.

The daily phlebotomy volume is at least 4 times higher in ICU patient than in other hospitalized patients [6], and the difference is not entirely due to increased diagnostic testing in ICU patients.

Blood samples for laboratory analysis are usually withdrawn through indwelling vascular catheters, and the initial aliquot of blood (usually 5 ml) withdrawn through the catheter is discarded because it contains fluid from the catheter lumen instead of the bloodstream.Summary of cascade of events contributing to anaemea in the critical ill is shown in figure -1.

**Figure-1**,-Summary of cascade of events contributing to anaemia in the critical ill.

Critical illness
↓
Blood turn over
Blood Loss
   DecreaseProduction
↓
Immune activation
↓
Decrease Iron in circulation
↓
Decrease erythropoesis

## Anemia and Oxygen Transport

The uptake of oxygen into peripheral tissues ($VO_2$) is using the equation shown below (where Q is cardiac output, Hb is hemoglobin concentration in blood, and $SaO_2 - SvO_2$ is the arteriovenous oxyhemoglobin saturation difference).

$VO_2 = Q \times 13.4 \times Hb \times (SaO_2 - SvO_2)$   (Eq.1)

The oxygen transport system operates to maintain a constant VO2 in the face of changes in any of the variables in (Eq. 1). In the case of anemia, VO2 remains constant because the decrease in hemoglobin (Hb) is accompanied by increases in both cardiac output (Q) and peripheral O2 extraction ($SaO_2 - SvO_2$). These compensatory responses to anemia are described next.

### Cardiac Output

The influence of anemia on circulatory blood flow is The hematocrit is the principal determinant of blood viscosity , and thus a decrease in hematocrit will decrease the viscosity of blood. According to the Hagen-Poiseuille equation shown below, a decrease in viscosity (u) will result in an increase in circulatory blood flow (Q) as long as the pressure gradient along the circulation (Δ P) and the dimensions of the blood vessels (r for radius and L for length) remain constant.

$$Q = \square P \times \Delta \square r^{4} / 8 \square L \qquad (Eq.2)$$

A decrease in blood viscosity augments cardiac stroke output by reducing ventricular afterload.

Anemia can also be accompanied by activation of the sympathetic nervous system [4] which will augment cardiac output by increases in both myocardial contractility and heart rate.

However, this response is not promonent, and thus tachycardia is not a prominent finding in anemia at least at rest.

When considering the isolated effects of anemia on cardiac output the blood volume should be normal or unchanged ( this condition is reffered to as **isovolemic anemia**) The changes in cardiac output associated with progressive, isovolemic anemia are shown in Figure -2, Note that the increase in cardiac output is proportionally much greater than the decrease in hematocrit. This response is attributed to the flow dependency of blood viscosity; i.e., an increase in blood flow (cardiac output) will decrease blood viscosity. Thus, anemia decreases blood viscosity, which then increases cardiac output, which then decreases blood viscosity, and so on. Ketchup is another fluid with a flow-dependent viscosity, so if you can picture what happens when you pour ketchup (the flow is sluggish at first, then increases as you continue to pour), you will get the idea.

Figure-2.
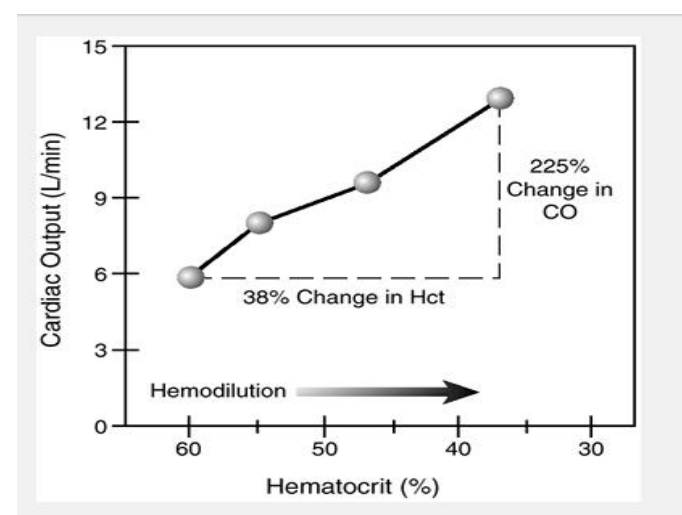
In addition to the global changes in cardiac output, anemia can preferentially increase flow in the cardiac and cerebral circulations, and decrease flow in the splanchnic circulation . This will have a protective effect on myocardial and cerebral metabolism in the presence of of anemia.

### Peripheral Oxygen Extraction :

The effects of progressive isovolemic anemia on systemic oxygen transport is (8) the initial decrease in hematocrit is accompanied by a decrease in systemic oxygen delivery ($DO_2$), and this is counterbalanced by an increase in O2 extraction ($SaO_2 – SvO_2$). The reciprocal changes in DO2 and O2 extraction keep the $VO_2$ constant ($VO_2 = DO_2$ x $O_2$ extraction). However, when the hematocrit falls below 10%, the increase in $O_2$ extraction is no longer able to match the decreasing $DO_2$, and the $VO_2$ begins to fall. The decrease in VO2 is a sign of dysoxia (defined in as oxygen-limited aerobic metabolism), and is accompanied by an increase in lactate production. The point at which the VO2 begins to fall is thus the threshold for tissue dysoxia, and it usually occurs when the $O_2$ extraction reaches a maximum level of 50 to 60%. This means that an $O_2$ extraction ($SaO_2 – SvO_2$) that is 50% or higher is a sign of inadequate tissue oxygenation.

Thus, because of the compensatory changes in cardiac output and peripheral O2 extraction, progressive anemia will not impair tissue oxygenation until the hemoglobin and hematocrit reach dangerously low levels. The hematocrit had to fall below 10% (corresponding to a hemoglobin concentration of 3g/dL) before tissue oxygenation is compromised. The experimental animals in this study were anesthetized and breathing pure oxygen (which could favour tolerance to severe anemia), but similar results have been reported in awake animals breathing room air [9]. The lowest hemoglobin or hematocrit that is capable of supporting tissue oxygenation in humans in not known, but one study by Weiskopf RB, Viel and Feiner et al,of isovolemic anemia in healthy adults showed that hemoglobin levels of 5g/dL had no deleterious effects on tissue oxygenation [10].

### Paradoxical Effect:

Isovolemic anaemia can have a paradoxical effect that increases tissue oxygenation. Which is from an animal study that evaluated the effects of isovolemic anemia on skin flaps using a specialized oxygen electrode to measure the PO2 in subcutaneous tissues below the skin [11]. As indicated in the graph, reductions in hematocrit were associated with increases in the subcutaneous PO2 in both normal and ischemic skin regions. Furthermore, the increase in tissue PO2 persisted until the hematocrit fell to 10 to 15% (which is about the same hematocrit where tissue oxygenation became compromised in the study). The improvement in tissue oxygenation can be explained if the cardiac output response to anemia is a so exaggerated that the oxygen delivery increases despite the decrease in serum hemoglobin. Anemia can preferentially increase flow in certain regional circulations, as mentioned earlier, and the skin may be one of these regions. In fact, the beneficial effects of isovolemic anemia on blood flow to the skin has led to the use of isovolemic anemia as a clinical tool for promoting the viability of skin flaps.

### CONCLUSIONS

Anemia is almost universal in patients who spend more than a few days in the ICU and about half of ICU patients with anemia are given one or more transfusions of concentrated erythrocytes (packed red blood cells) to correct the problem . This practice of transfusing red blood cells to correct anemia is one of the most fickle and arbitrary interventions in critical care medicine. Few ICUs employ practice guidelines to standardize transfusion therapy, and in most cases blood transfusions are given without documented evidence of need or benefit. A single most important point is to remember that anaemia is well tolerated as long as intravascular volume is maintained , hemoglobin level has to drop to

3gm/dl to demonstrate evidence of impaired tissue oxygenation because (as indicated in the introductory quote) anemia does not compromise tissue oxygenation as long as the intravascular volume (and hence cardiac output) is maintained. The important role of blood volume in supporting tissue oxygenation is often overlooked, even by the American Red Cross, whose popular slogan , blood saves lives, deserves a more accurate update ,blood volume saves the life.

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