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RESEARCH **REVIEW ARTICLE**

Anemia and Blood Transfusions in the Intensive Care Unit: A Review Article

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ABSTRACT

Anemia is common among critically ill patients and can be iatrogenic. Various factors, such as age, comorbidities, and transfusion practices influence its prevalence. Blood transfusion remains a pervasive practice, with most critically ill patients receiving blood. The decision to transfuse blood in the intensive care unit (ICU) should be individualized, considering the patient's clinical status and comorbidities. Recent studies have highlighted the safety and effectiveness of a restrictive transfusion strategy that can reduce the risk of transfusion-related complications. However, it is crucial to consider the specific needs of certain patient populations, such as those with cardiovascular diseases. The workup starts with a directed history and examination, followed by tailored investigations to answer specific questions. Massive transfusions, when indicated, require a multidisciplinary team to be orchestrated by the physician and require knowledge of the criteria for implementing a Massive Transfusion Protocol (MTP), as well as the logistical aspects of obtaining and transfusing blood products. Thromboelastography (TEG) can be useful for guiding blood transfusions in such cases. Transfusion reactions (TR) are potential complications of blood transfusion with varying presentations and degrees of severity. This article delves into the different types of TR, their clinical manifestations, and the necessary workup and management steps, emphasizing the importance of timely intervention.

KEYWORDS - Anemia, Critical illness, Intensive care units,Transfusion reactions

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INTRODUCTION

Anemia prevalence among critically ill patients has been reported with variation depending on patient case mix, severity of illness, and pre-existing comorbidity. The prevalence of anemia in critically ill patients is high, with a mean hemoglobin level of approximately 11 g/dL on admission. Approximately two-thirds of these patients have a hemoglobin level < 12 g/dL, and a third had a hemoglobin below 10 g/dL, indicating a mixed population (1). Alarmingly, anemia seems to be partly iatrogenic in the ICU. This is partly due to the frequent blood draws that mount up to a significant volume in critically ill patients (2). As a result, it is not surprising that up to 90% of patients are anemic by the third day in the ICU (3). Therefore, it is crucial to highlight that extended stay in the ICU is a key factor leading to anemia in this group of patients. This results in a significant incidence of anemia in the ICU, with a drop in hemoglobin that starts early in the course and continues throughout the patients' stay and will mostly be there on ICU discharge (4). Thus, despite different patient comorbidities, underlying pathologies, and transfusion practices, the prevalence of moderate to severe anemia (with hemoglobin concentration <9 g/dL) at any time during the ICU stay is close to 50% (1)

Blood transfusion is a common practice in the critically ill, as large cohorts demonstrated that 39–53% of patients admitted to the ICU receive blood transfusions, with an average of 2-4 units. The trigger for this practice remains variable (1). Thus, a knowledge of anemia work-up, management, and potential transfusion complications in the critically ill is vital.

With blood transfusion being a common practice in the ICU, TR should be monitored and reported. Although rare, some can be fatal. Early recognition and timely intervention are pivotal in changing the outcome in patients with TR.

ETIOLOGY

There are multiple mechanisms of anemia in critically ill patients. Keeping in mind that the underlying pathophysiology can be multi-factorial, etiologies are due to blood loss or reduced blood production.

A. Blood Loss
In critically ill patients, blood loss can occur due to bleeding from a surgical site or trauma, phlebotomy, and gastrointestinal bleeding.

Phlebotomy is a significant contributing factor to anemia in ICU patients. An estimated 40-70 ml of blood is withdrawn daily to conduct laboratory tests. This is equal to a unit of blood weekly, an amount the body is unable to replenish, leading to anemia (5) .

In addition, ICU patients are prone to blood loss from gastrointestinal bleeding due to stress ulcers. The risk of ulcers is increased in mechanical ventilation, anticoagulation, previous gastric ulcers, renal failure, liver disease, and brain injury. Although uncommon due to the prophylactic use of proton pump inhibitors (PPIs), gastrointestinal bleeding should be monitored, especially in at-risk patients (3, 6).

B. Decreased Blood Production
Critically ill patients have decreased erythropoiesis due to low erythropoietin (EPO), iron sequestration, and decreased bone marrow response (7). A low EPO response to anemia in these patients is attributed to elevated inflammatory markers and cytokines, namely IL1 and TNF alpha. In addition, these patients may have an element of kidney injury, which may further contribute to low EPO production (7). Finally, in critically ill patients, the inflammatory response produces cytokines, which in turn stimulate the secretion of Hepcidin from the liver. Hepcidin functions to sequester iron inside macrophages, which leads to low availability of iron for erythropoiesis (3).

ANEMIA WORKUP IN ICU

Although the etiology of anemia in ICU patients is mostly multifactorial, workups for anemia should follow a clear algorithm to help physicians make the right diagnosis while being efficient with the available resources. The essential steps of history, physical examination, and investigations should be followed.

TAKING A PROPER HISTORY - This is mostly helpful in dividing the causes into either acute (like bleeding) or chronic, such as anemia of chronic disease. It should also be directed toward risk factors of bleeding (like recent medications, including over-the-counter) and symptoms of blood loss (8). This will, in turn, narrow the differential diagnoses and help guide the investigation.

PERFORMING A THOROUGH PHYSICAL EXAMINATION - A thorough physical examination should be the next step; this includes general

findings like pallor, change in mental status, and changes in vital signs like tachycardia, tachypnea, and hypotension. Changes in vital signs happen more in acute anemia rather than in chronic cases. Tachycardia usually starts early, even with mild loss. However, hypotension doesn't usually happen till more than 30% of blood has been lost. A systematic exam, including aspects such as a rectal exam, may be warranted to help rule out gastrointestinal hemorrhage (9).

INVESTIGATIONS - Complete Blood Count (CBC) could easily divide the causes into either microcytic, normocytic, or macrocytic based on the mean corpuscular volume (MCV).

A. Microcytic anemia differential diagnosis tools: This is identified by MCV less than 80 fL. To differentiate between the different causes of microcytic anemia, start with CBC, inflammatory markers, and iron studies. Traditionally, Ferritin level, Transferrin saturation (TSAT), and Total Iron Binding Capacity (TIBC) may help differentiate iron deficiency anemia, anemia of chronic disease, or Thalassemia (10,11). In a recent study, researchers showcased a more accurate approach using Fluorescence Flow Cytometric Hemoglobin Biomarkers. The study hypothesized that ferritin and iron studies, commonly employed for assessing inflammation, exhibit high false-positive rates, particularly as they can be elevated in response to inflammatory conditions (12).

B. Macrocytic anemia differential diagnosis tools: This is identified by MCV more than 100 fL. The major causes of macrocytic anemia can be divided into either megaloblastic or non-megaloblastic anemia. Megaloblastic anemia has two major causes: B12 deficiency anemia and folate deficiency. This might be differentiated by investigating methylmalonic acid and homocysteine levels (both elevated in B12 deficiency, while folate deficiency is just associated with elevated homocysteine) (13). In addition to these common causes, megaloblastic anemia can also result from various less common etiologies. These include inborn errors of metabolism, drugs affecting DNA synthesis, and erythroleukemia (13). The non-megaloblastic causes are mostly due to liver disease, alcohol use, myelodysplastic disease, or even hypothyroidism (14).

C. Normocytic anemia differential diagnosis tools: This is identified by MCV more than 80 and less than 100 fL. This category may have caused confusion with the other two categories because of additional causes that need to be investigated to rule out hemolytic anemia, which can also cause macrocytic anemia in the initial stages. Investigating reticulocyte count, haptoglobin level, Coomb's test (indirect and direct), and indirect bilirubin level, as well as performing a blood smear, if indicated, may help discern the etiology. It is crucial to suspect and rule out serious etiologies, like DIC, which can lead to acute bleeding and, ultimately, acute anemia (14,15).

INDICATIONS FOR BLOOD TRANSFUSION

The decision to transfuse a patient with anemia in the ICU should be individualized based on a comprehensive evaluation of clinical status, comorbidities, and patient preferences (16,17) . While clinical trials provide guidance on hemoglobin thresholds (Table 1), blood transfusion remains a temporalizing intervention as it does not address the underlying cause of anemia (18). Over the past few decades, multiple studies in a plethora of critically ill patient populations compared a restrictive strategy, mostly aiming for a threshold of 7 g/dL, with a more liberal strategy, a transfusion threshold of 10 g/dL, imitating the historic practice of blood transfusion (31-36).

There was a clear lack of benefit from the liberal strategy, which resulted in a change in the approach to transfusions. Roubinian et al. conducted a series of retrospective cohort studies to evaluate the effects of multiple interventions, including educating providers on evidence-based transfusion guidelines, targeting high-use departments, and implementing a clinical decision support system within the electronic medical record (19). The interventions were associated with an observed reduction in transfusion threshold from 8.1 g/dL to 7.5 g/dL, resulting in a reduction of around 25% in RBC use over three years without adversely affecting mortality rates – despite adjusting for age, sex, comorbid disease burden, emergency or elective presentation, medical or surgical admission, admission diagnosis, severity of illness, first inpatient ward, and hospital facility (19,20). The same group examined the incidence and prevalence of moderate anemia at discharge in 685,753 adults with 801,261 hospitalizations and its impact on outcomes within six months of discharge. This revealed an increasing trend in the incidence and prevalence of moderate anemia at discharge over time; however, it did not significantly affect RBC transfusion rates, rehospitalization, or mortality (21). These studies suggest that blood conservation strate-

gies effectively reduce RBC utilization without adversely affecting mortality rates in diverse inpatient populations.

In 2021, Carson and colleagues conducted a comprehensive meta-analysis comparing liberal and restrictive red blood cell (RBC) transfusion thresholds in anemic hospitalized non-critical care patients to determine their effects on clinical outcomes, including 30-day mortality. This study included 48 trials that met the eligibility criteria and involved 21,433 participants across various clinical contexts. The researchers found that a restrictive transfusion strategy reduced the risk of receiving at least one RBC transfusion by 41% without affecting 30-day mortality or other clinical outcomes, such as cardiac events, myocardial infarction, stroke, or thromboembolism. The liberal transfusion threshold did not affect the risk of infection, including pneumonia, wound infection, or bacteremia. The researchers noted that the included studies were at a low risk of bias, and the evidence was of high or moderate quality. However, the strength of evidence supporting the safety of restrictive transfusion thresholds for clinical subgroups such as myocardial infarction, vascular surgery, hematological malignancies, and chronic bone marrow disorders is less certain. In conclusion, this study suggests that adopting a more restrictive approach to RBC transfusions could be recognized as the standard of care for patients with anemia (17) . Salpeter et al. conducted a meta-analysis of three randomized trials with 2,364 participants to compare the effects of a restrictive hemoglobin transfusion trigger of less than 7 g/dL to a more liberal trigger. The study found that a restrictive strategy resulted in significant reductions in mortality, acute coronary syndrome, pulmonary edema, re-bleeding, and infections (22).

Simon and colleagues performed a systematic review and meta-analysis that investigated transfusion outcomes in older adults aged 65 years and above. The primary outcome measures were 30-day and 90-day mortality events in the restrictive and liberal transfusion groups. The meta-analysis included nine RCTs with a total of 5,780 patients from various clinical specialties such as orthopedic, cardiac, and oncology surgery. The authors concluded that liberal transfusion approaches may offer superior outcomes in geriatric patients compared to the current restrictive transfusion methods. This unusual result, contradicting the restrictive protocols, may reflect different physiologic norms and warrants further research in this population (23). Hovaguimian et al. conducted a systematic review of 31 trials that were categorized into five strata based on patient characteristics and clinical settings. The restrictive transfusion approaches increased the risk of mortality and composite morbidity in patients undergoing cardiac/vascular procedures and in elderly orthopedic patients. Specifically, the risk of complications was higher in patients with cardiovascular disease undergoing cardiac or vascular procedures owing to inadequate oxygen supply, which also increased the mortality rate (24) . These findings underscore the importance of considering patient clinical contexts when developing transfusion strategies to improve outcomes.

Meybohm et al. are conducting an RCT with 2470 elderly patients (≥ 70 years) undergoing intermediate- or high-risk non-cardiac surgery. This study compares a liberal transfusion strategy (Hb ≤ 9 g/dL) with a restrictive strategy (Hb ≤ 7.5 g/dL) for these patients. The primary outcome includes mortality, myocardial infarction, stroke, kidney injury, mesenteric ischemia, and peripheral vascular ischemia within 90 days of surgery. The study also examines IV antibiotic-requiring infections with rehospitalization as a secondary endpoint. The aim is to determine the benefits of a liberal strategy. The study is still recruiting participants and further investigation is ongoing (25).

Few trials were conducted on children, as mentioned in Table 1. (26-28). In summary, these studies suggest that a restrictive transfusion strategy may be non-inferior to a liberal strategy in critically ill children with anemia and may lead to fewer complications. In pediatric postoperative cardiac surgery patients, a lower transfusion threshold may not result in significant differences in organ dysfunction; however, further research is required to confirm this. Additionally, immediate transfusion may not necessarily improve clinical outcomes or reduce readmission rates in children > 6 months of age. Based on the current literature, a restrictive threshold is non-inferior and occasionally safer than a liberal threshold. Patients with cardiovascular disease were always a point of debate, with many guidelines recommending targeting a hemoglobin of 8-10 g/dL (29). Most recently, the long-awaited Myocardial Ischemia and Transfusion (MINT) trial randomized patients with an acute myocardial infarction and a hemoglobin lower than 10 g/dL to a transfusion threshold of lower than 7 to 8 g/dL or 10 g/dL. (30). There was no difference in the composite primary outcome of myocardial infarction or death at 30 days, although there was a trend toward a worse outcome in the restrictive arm (16.9% vs. 14.5%; RR 1.15, 95% CI 0.99-1.34, p = 0.07).

Finally, it is imperative to remember that a hemoglobin threshold is only one aspect of the

approach. Given the diversity of patients and the variations in their diseases and comorbidities, clinical judgment remains the most important factor. Future studies should continue teasing out the high-risk ICU patients who may benefit from blood transfusions.

MASSIVE TRANSFUSION

Massive transfusion is defined as the replacement of 10 or more units of blood in 24 hours. However, in the actively bleeding patient, clinical assessment always precedes, and activating the massive transfusion begins accordingly. Alternatively, some authors advocate for using an hourly transfusion score, like the Critical Administration Threshold for 1 hour (CAT-1) score, in which the hourly number of units transfused can identify further transfusion needs (37,38).

There is no consensus in the literature about the best approach for giving blood products in massive transfusion. Early data argued for a transfusion strategy where 1 unit of plasma, 1 unit of Platelets, and 1 unit of packed RBC are given, also known as the 1:1:1 approach. The PROPPR trial is a randomized control trial that compared a 1:1:1 and a 1:1:2 (2 units of packed RBC for a unit of plasma and a unit of platelet) approaches. There was no difference in the all-cause mortality at 24 hours or at 30 days between both groups. On the other hand, exsanguination, the most common etiology of death in the first 24 hours, was lower in the 1:1:1 approach (39). The order of giving the blood products and giving plasma sooner to preserve blood transfusion are areas where further research is required.

MASSIVE TRANSFUSION PROTOCOL (MTP)

The criteria for activating the Massive Transfusion Protocol are based on the variable institutional regulations and the physician's decision. According to the American College of Surgeons guidelines (40), MTP should be activated when one or more of the following criteria are met:

1. Assessment of Blood Consumption (ABC) score of two or more (41): The ABC score consists of four variables: pulse >120 beats per minute, systolic blood pressure (SBP) <90 mmHg, positive Focused Assessment with Sonography for Trauma (FAST) (42), and penetrating torso injury; each one point.

2. Persistent hemodynamic instability.

3. Active bleeding requires operation or angioembolization.

4. Blood transfusion in the emergency department.

The implementation of MTP significantly relies on logistics. It encompasses the multidisciplinary communication between the ICU team and the blood bank to secure the required blood products. The following elements are the main constituents of MTP (43,44):

1. Obtaining intravenous (IV) access: Two peripheral large bore (14 to 16 gauge) cannulas or central venous access (7).

2. Contacting the blood bank to prepare the required products.

3. Running frequent laboratory tests: Patients who undergo massive transfusions should be monitored closely by frequent lab tests. An individual who is dedicated to withdrawing blood, transferring it to the lab, and getting the results back promptly should be taken into consideration.

4. Nurses have a pivotal role in coordinating the transfusion process and monitoring patient's reactions to transfusion.

A thromboelastogram (TEG) is a diagnostic test that measures various parameters related to blood clot formation, propagation, stability, and dissolution (45). It can play an important role in guiding transfusion in the context of MTP. It helps determine the need for platelets, plasma, and other products like cryoprecipitate. In addition, TEG reduces the amounts of blood products needed and allows for their efficient use (46). If TEG is not available, conventional coagulation assays (CCA), PT, INR, PTT, D-dimer, and fibrinogen, can be used to guide the transfusion process and monitor for coagulopathies. However, TEG-guided transfusion is associated with higher survival rates and more ICU-free days compared to CCA-guided transfusion (47).

COMPLICATIONS OF BLOOD TRANSFUSION

Serious Transfusion Reactions (TR) are seen in up to 1.1% of transfused patients (48). Chronologically, they are divided into acute and delayed.

A. Acute TR: up to 24 hours from the start of the transfusion.

B. Delayed TR: from 24 hours and up to 28 days post-transfusion.

The severity and morbidity of transfusion reactions are usually proportional to the volume of transfused blood. Although mortality is not clearly reported, it ranges from 0.06-0.95% for the reported TRs (49) .

With the clinical presentation being usually non-specific, the physician should have a good clinical suspicion of patients receiving a blood transfusion and experiencing any clinical changes. These include fever, chills, back pain or discomfort, hypotension, reduction in urine output, and hematuria. In unconscious or anesthetized patients, the clues are hypotension, tachycardia, hemoglobinuria, and uncontrolled bleeding (oozing).

A physician practicing in the ICU should also be aware of the pathogenesis of these reactions as management varies significantly. The following transfusion reactions are acute and can happen either during or within 24 hours of the transfusion:

A. Hemolytic reactions: This is the result of ABO or other RBC antigen incompatibility. The rate of acute hemolytic reactions doubles when given unmatched blood, like in emergency conditions (50). It can happen within minutes of starting the transfusion and may result in serious end-organ damage, most notably an acute kidney injury. There are two groups of patients worth mentioning as they may have more severe presentations; one is patients with long-term transfusions, like patients with sickle cell disease, as they form antibodies due to multiple transfusions. The other group is patients who are solid-organ and stem cell transplant recipients who may have new antibodies (51,52).

B.Non-hemolytic febrile reactions: Fever with blood transfusion can happen in 1.1-2.15% of transfusions and is lower in leuko-reduced blood (53). It usually happens within the first 4 hours and is characterized by an increase in temperature of 1 C to > 38 C along with fever and chills; it remains a diagnosis of exclusion, especially since the fever may recur with subsequent transfusions (54).

C. Allergy: This varies from pruritus to anaphylaxis. It usually happens in the first 4 hours, even within minutes in the case of anaphylaxis. The diagnosis remains clinical.

D.Transfusion-associated circulatory overload (TACO): TACO is the leading cause of transfusion-related morbidity (55). Although volume overload is the driving pathophysiology, inflammatory pathways may play a role (49) . Blumberg's Diagnostic criteria for TACO include acute respiratory distress within 12 hours along with three of the following: elevated Brain natriuretic peptide (BNP), elevated central venous pressure, radiologic changes, positive fluid balance, and history of heart failure (56). Prevention, especially for patients at risk, is of paramount importance; slowing the transfusion rate, reducing the transfused volume, or splitting the volume into aliquots can be considered (57).

E.Transfusion-related acute lung injury (TRALI): TRALI remains an under-reported entity with high mortality (58). It is a clinical diagnosis based on the timing of transfusion and onset of lung injury clinically and on chest imaging. With hypoxemia and lung infiltrates being the mainstay of the presentation, fever, frothy secretions, and hypotension can occur as well.

F.Infectious: This includes bacteria, viral infections (AIDS, hepatitis), and others. Although the risk of transmitting infections has been reduced with extensive testing of donated blood, it should still be considered in the right clinical setting.

The initial workup should focus on ruling out immune-mediated hemolysis, including clerical verification, pre- and post-direct antiglobulin test (DAT), and pre-and post-hemolysis assessments. Returning the unit to the blood bank for further evaluation and confirmation of the ABO group is crucial. Additional tests should be selected based on the patient's clinical presentation, such as BNP level for TACO. A comprehensive hemolysis workup, including tests for total and direct bilirubin, haptoglobin, LDH, D-dimer, Coomb's tests, and fibrinogen, should be selectively ordered to avoid unnecessary overutilization (48). If you suspect infection, send blood cultures and monitor the patient for early signs of sepsis.

Management: Timely intervention is paramount in TRs. If an acute hemolytic reaction is suspected, consider, and follow these steps:

1. Immediately stopping the transfusion. Send the blood being transfused for analysis.

2. Cardiac monitoring and hemodynamic support: If a hemolytic reaction is suspected, start normal saline at a high rate,

aiming for a urine output of 0.5-1 mL/Kg/hour. In severe cases, you may need to start vasopressors. There is limited evidence to support the benefits of alkalization of urine, although some authors suggest a sodium bicarbonate drip at a rate of 200 mL an hour, aiming for a pH of > 6.5 (50).

3.Supportive care for coagulopathy.

4.Other supportive care: Antipyretics for fever and Meperidine is effective for rigors but should be used cautiously in patients prone to seizures.

5.If there is a suspicion of infection, early broad-spectrum empiric antibiotics should be started.

6.In allergic reactions, start with an H1-blocker, like Diphenhydramine or Hydroxyzine. Consider adding an H2-blocker (like famotidine) or steroids (Methylprednisolone).

7.If TACO is suspected, the focus on management is supportive care with Oxygen, diuresis with Furosemide, and repositioning the patient with head of bed elevation to 45 degrees.

8.If TRALI is suspected, provide supportive care and avoid diuresis.

If this is a recurrent problem, a review of clerical workflow is warranted, as it is the most common culprit and is considered largely prevented (57,59) .

CONCLUSION

Anemia is a common entity in the critically ill and has implications on the patients' morbidity and mortality. Navigating the diagnosis and workup is an art led by proper history and physical examination.

Massive transfusion is always protocolized. Transfusion reactions are a rare yet serious entity. Basic knowledge of its pathophysiology and management is valuable for physicians caring for the critically ill.

DISCLAIMER

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Table 1. European Society of Cardiology 2019 pulmonary embolism stratification.

Reference	Study design	Sample size	Patient characteristics	Intervention	Outcomes	Conclusion
Herbet et al (31)	RCT	n=838 ICU	- Euvolemic patients - Respiratory and cardiac diseases as most common causes of admission	Comparing restrictive (7.0 g/dL) vs. liberal (10 g/dL) transfusion strategy	Primary outcome: 30-day mortality Secondary outcome: organ dysfunction severity	Restricted red-cell transfusion is as effective as liberal transfusion for critically ill patients except for those with acute myocardial infarction and unstable angina.
Holst et al (32)	RCT	n=998 ICU	- Septic shock - Hemoglobin level of 9 g/dL or less	Comparing restrictive (7.0 g/dL) vs. liberal (10 g/dL) transfusion strategy	Primary outcome: death from any cause at 90 days Secondary outcomes: ischemic events, life support utilization, and number of blood transfusions.	Results showed similar 90-day mortality and rates of ischemic events and life support use for both higher and lower hemoglobin threshold groups, with the latter receiving fewer transfusions.
Villanueva et al (33)	RCT	n=921 ICU	-Adults aged > 18 years with gastrointestinal bleeding, including hematemesis, melena, or both.	Comparing restrictive (7.0 g/dL) vs. liberal (9.0 g/dL) transfusion strategy	Primary outcome: death rate within 45 days. Secondary outcomes: bleeding rate and in-hospital complications.	Restrictive transfusion strategy superior to liberal strategy in patients with acute upper GI bleeding
Ducrocq et al (34)	RCT	n=668 ICU	-Myocardial infarction -Hemoglobin level between 7 and 10 g/dL	Comparing restrictive (8.0 g/dL) vs. liberal (10 g/dL) transfusion strategy	Primary outcome:major adverse cardiovascular events (death, stroke, recurrent myocardial infarction, or emergency revascularization prompted by ischemia) at 30 days. Secondary outcomes: individual components of the primary outcome.	Restrictive transfusion strategy in anemic patients with acute myocardial infarction showed similar MACE rates at 30 days compared to liberal strategy.
Murphy et al (35)	RCT	n=2003	Adults undergoing nonemergent cardiac surgery with cardiopulmonary bypass	Comparing restrictive (7.5g/dL) vs. liberal (9 g/dL) transfusion strategy	Primary outcome: Serious infection(sepsis or wound infection) or ischemic event (permanent stroke, myocardial infarction, infarction of the gut, or acute kidney injury) within 3 months after randomization; Secondary outcome: health care costs (composite).	Restrictive transfusion threshold didn't show superiority in terms of morbidity or healthcare costs compared to liberal threshold.

Palmieri et al (36)	RCT	n=345	Patients with burn injury >20% TBSA	Comparing restrictive (< 7 g/dL) vs. liberal (< 10 g/dL) transfusion strategy	Primary outcome: number of Blood stream infection (BSI) Secondary outcomes: Mortality, pneumonia, UTI, wound infection, hospital/ICU stay duration, organ dysfunction, wound healing.	Restrictive transfusion strategy reduced volume but had no significant impact on primary or secondary outcomes.
Lacroix et al (26)	RCT	n=1377 ICU	Children aged 3 months to 18 years who were stable critically ill and had a hemoglobin level below 9.5 g/dL within a week of admission.	Comparing restrictive (< 70 g/L) vs. liberal (< 100 g/L) transfusion strategy	rimary outcome: Death, had two or more organ dysfunctions in MODS$ or progressive MODS within 28 days. Secondary outcomes: Individual components of primary outcome, number of ventilator-free days, and number of intensive care unit-free days.	Restrictive transfusion strategy = noninferior to liberal strategy for anemic, critically ill children. Less transfusions and complications with restrictive strategy.
Willems et al (27)	RCT	n=101 ICU	A subgroup analysis of the TRIPICU trial (11). Children who had cardiac surgery and were admitted to the pediatric ICU.	Comparing restrictive (< 7 g/dL) vs. liberal (< 10 g/dL) transfusion strategy	primary outcome: New/progressive MODS. Secondary outcomes: mortality, PICU length of stay, and other clinical outcomes.	A restrictive strategy showed no significant difference in MODS development compared to a liberal strategy in pediatric postoperative cardiac surgery patients.
Maitland et al (28)	RCT	n=1565	-Ugandan and Malawian children with uncomplicated severe anemia were studied -62.9% of the children had malaria. -The median age of the children was 26 months	Children were randomly assigned to receive immediate transfusion with 20 ml or 30 ml of whole-blood equivalent per kg body weight, or no immediate transfusion. In the control group, transfusion with 20 ml/kg was triggered by new signs of clinical severity or hemoglobin drop below 4 g/dL.	measuring 28-day mortality as the primary outcome and assessed secondary outcomes such as mortality at 180 days, readmissions, serious adverse events, hemoglobin recovery at 180 days, and hospital stay length.	No evidence of differences in clinical outcomes over 6 months between the children who received immediate transfusion and those who did not.

$ multiple organ dysfunction syndrome

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