International Journal of Medical Toxicology & Legal Medicine **Volume 27, No. 4S, 2024**
e-ISSN: 0974-4614
p-ISSN: 0972-0448
https://doi.org/10.47059/ijmtlm/V27I4S/146

Effect of Anaemia and Transfusion on Outcomes in Mechanically Ventilated Infants and Children

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Received: 18.09.2024 Revised: 13.10.2024 Accepted: 20.11.2024

ABSTRACT
Background: Anemia is a common problem in mechanically ventilated children, with consequences including prolonged duration of ventilation, high rates of morbidity, and increased deaths. Red cell distribution width (RDW) has become an important marker for prognosis, but blood transfusion, with its benefits, carries significant risks.
Objective: To assess anemia, RDW, and transfusion practice impact on outcomes in mechanically ventilated pediatric patients and explore best practice for managing anemia and transfusion in such cases.
Methods: An analysis was conducted for anemia classification, use of RDW for prognosis, and concomitant risks for transfusion. Several approaches, including restrictive transfusion triggers, use of erythropoiesis-stimulating drugs, and blood conservation techniques, have been evaluated.
Results: Anaemia worsens pulmonary function, impedes successful weaning, and increases complications. Higher RDW reflects poor prognosis, but transfusion can improve oxygenation but with added complications in terms of pulmonary trauma and modulates the immune system. Targeted anemia management and restrictive transfusion protocols can contribute to positive patient outcomes.
Conclusion: Successful anemia management in mechanically ventilated children will require a multi-disciplinary intervention. Future studies must explore refinement in transfusion triggers and improvement in non-transfusion therapy for enhancing survival and successful discharge.

Keywords: Anemia, Mechanical Ventilation, RDW, Blood Transfusion, Pediatric Intensive Care, Critical Illness.

INTRODUCTION

Anemia is the most common hematologic abnormality identified in infants and children. Approximately a quarter of the world's population suffers from anemia, almost 2 billion people, with almost half of children <5 years of age affected in 2016[1].
Anemia is associated with increased morbidity and mortality in children, particularly children of preschool age. There are many causes of anemia, both inherited and acquired, and these causes vary widely in populations worldwide. Anemia is not a specific disease but represents a heterogeneous group of pathologic conditions. Anemia is defined quantitatively as a decreased number of circulating erythrocytes or functionally as a condition where number of erythrocytes, carriers of oxygen, are insufficient to meet metabolic demands [2].
Anemia is defined as a reduced blood hemoglobin level or red blood cell (RBC) mass that is unable to meet the oxygen demands of peripheral tissues and organs. The laboratory threshold for defining anemia is a hemoglobin level at or below the 2.5th percentile based upon reference data from healthy children. This threshold varies across age, race, and gender and may also be influenced by environmental factors(Patrick G Gallagher, 2022).[2].
Anemia can be classified in many ways, such as congenital or acquired, acute or chronic, hemolytic or nonhemolytic, based on peripheral blood (PB) smear findings, or based on erythrocyte size[2].
fig. (1) initially classifies anemias as microcytic, normocytic, and macrocytic based on MCV, then further refines the differential diagnoses based on the reticulocyte count.
This classification scheme will be used to review etiologies of anemia in infants and children [3].

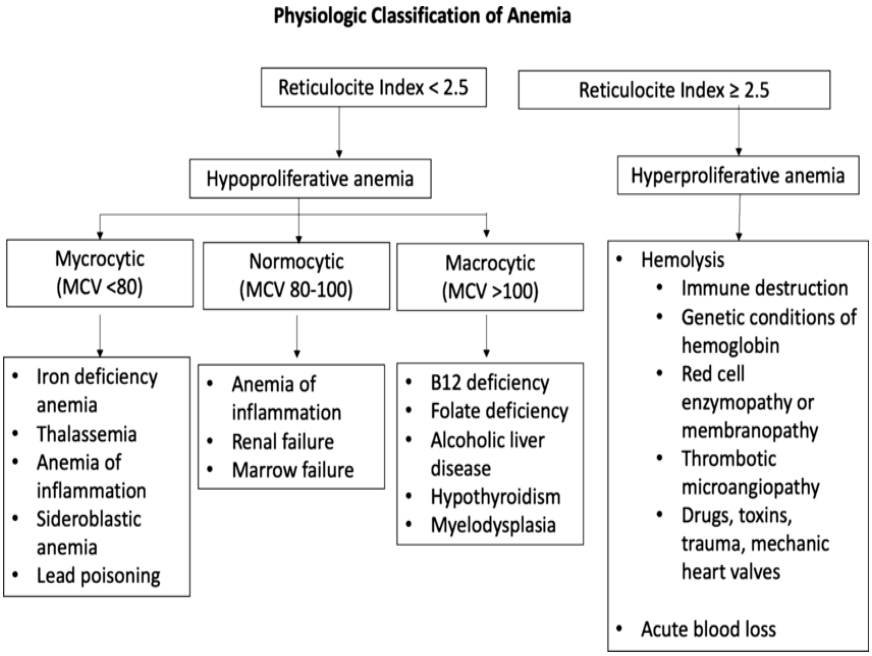

Fig. 1: A clinical classification of anemia based on MCV and reticulocyte count (adapted after [3]).

Patient and family history often reveal important clues to the etiology of anemia. Review of birth history should include labor, delivery, and neonatal course, including the history of anemia, jaundice, phototherapy, or blood transfusion. History of other medical issues and medication use should be elicited. History of trauma, infections, surgery, travel, and exposure to drugs, chemicals, toxins, or oxidants should be sought, as should sources of blood loss such as epistaxis, gastrointestinal (GI) bleeding, or in young women, dysmenorrhea. Dietary history should include a review of growth and food intake focusing on key nutrients such as iron, folate, vitamin B12, and in infants, milk intake. The age of the patient should be considered as different disorders are common in different age groups[4].

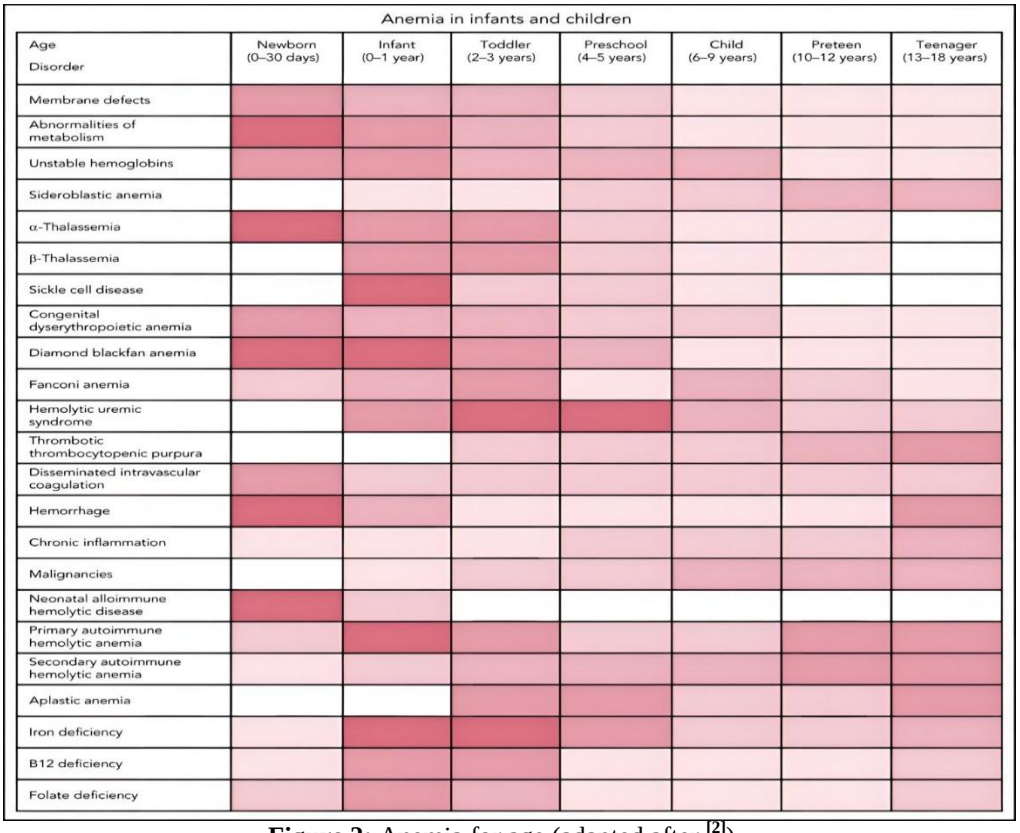

Figure 2: Anemia for age (adapted after [2]).

Clinical manifestations

Symptoms and signs vary based on the duration and severity of anemia. Patients with acute, severe anemia are overtly symptomatic with hypoxia, hypovolemic shock, congestive heart failure, and seizures which may lead to death. Common findings in chronic anemia include pallor, dyspnea, fatigue, exercise intolerance, dizziness, anorexia, and syncope. If there is hemolysis, jaundice and dark urine may be present. In young children, chronic anemia may lead to poor growth and failure to thrive, and if there is iron deficiency or iron deficiency anemia, affects on neurocognitive and behavioral development. Patients with mild to moderate chronic anemia are sometimes asymptomatic relative to the degree of anemia as compensatory mechanisms have had time to be activated [1].

Laboratory investigation

Initial basic laboratory evaluation includes a complete blood count (CBC), examination of a PB smear, reticulocyte count, direct antiglobulin test (DAT), and serum bilirubin determination. CBC allows assessment of the anemia and identifies whether there are concomitant alterations in leukocyte and platelet counts to suggest a disorder not confined to the erythrocyte lineage or indicating systemic illness. The PB smear may provide insights into the diagnosis such as spherocytes in hereditary spherocytosis or autoimmune hemolytic anemia, elliptocytes in hereditary elliptocytosis, fragmented cells, schistocytes, and helmet cells in microangiopathic hemolytic anemia, target cells in hemoglobinopathies, liver disease, and post-splenectomy, and inclusions of various types seen in malaria or babesiosis. Red cell distribution width is a measure of the size and volume of populations of circulating erythrocytes. Reticulocyte Hb concentration is included on many cell counters, providing information on iron status [5].

An elevated reticulocyte count indicates increased erythropoietic response to blood loss or hemolysis, whereas a low reticulocyte count, especially relative to the degree of anemia, indicates inadequate erythropoietic response. A positive DAT test suggests immune-mediated hemolysis. The presence of anemia with findings of hemolysis on PB smear and hyperbilirubinemia in a child with a negative DAT suggests an intrinsic erythrocyte defect. The child with acute onset normocytic, normochromic nonhemolytic anemia and a negative DAT test should be suspected of having had acute blood loss. Additional diagnostic evaluation is indicated. The use of a diagnostic algorithm may facilitate evaluation [6].

Mechanical Ventilation

The movement of gas into and out of the lung using automatic machine defined as ventilator connected directly to the patient [7].

It is a measure to assist or replace spontaneous breathing when respiratory failure develops and other measures like oxygen therapy and airway suctioning are not effective to improve oxygenation and ventilation [8].

Mechanical ventilation is an essential, life-saving therapy and one of the most used interventions in pediatric intensive care units (PICUs) [9].

the respiratory system is characterized by physiological peculiarities in childhood. First, since birth and up to school age, children have a higher metabolic rate, with a rate of oxygen consumption at rest that is more than double that of adults (7–9 vs. 3 mL·kg−1·min−1) [10].

Moreover, in the case of hypoxemia, oxygen release decreases even more due to bradycardia caused by activation of the parasympathetic nervous system, whose activity is dominant in newborns and infants. Because children have a mostly stable TV, the only way to guarantee the required oxygen supply at rest is through a higher RR, normal paediatric RR values during rest were described in evidence-based percentile charts by [11].

Types of Mechanical Ventilation:

1) Negative pressure ventilation (NPV):

Negative-pressure ventilators provide ventilatory support using a device that encases the thoracic cage starting from the neck, and devices range from a whole-body tank to a cuirass shell [12].

2) Positive pressure ventilation (PPV):

It refers to the process of forcing air into the lung of the patient utilizing positive pressure, so the flow of air into the lung depends on the pressure difference between the upper airways and the alveoli [13].

a) Non-invasive positive pressure ventilation (NIPPV)
b) Invasive positive pressure ventilation (IPPV)

Ventilator control parameters:

These are found on the ventilator control panel and can be manipulated by the operator including the following [14].

(1) Fraction of inspired oxygen (FiO2)
(2) Positive end-expiratory pressure (PEEP)
(3) Peak inspiratory pressure (PIP)
(4) Tidal volume (VT)

(5) Inspiratory time (Ti)
(6) Respiratory Rate (RR)
(7) Flow rate
(8) Rise time (RT)
(9) Trigger sensitivity
(10) Expiratory trigger sensitivity (ETS)

Impact of Anemia on Mechanically Ventilated Children

Anaemia in mechanically ventilated children contributes to prolonged ventilator dependency, as reduced oxygen-carrying capacity increases respiratory muscle workload. This prolongation not only delays weaning from mechanical ventilation but also heightens the risk of ventilator-associated complications such as pneumonia and barotrauma. Additionally, systemic oxygen delivery is compromised, leading to end-organ dysfunction, including myocardial ischemia, impaired renal function, and cognitive decline(Hansmann, Morrow et al. 2017)[15].

Impact on Outcomes

1) Increased Mortality Risk: Anemia is independently associated with higher mortality rates in PICUs. Studies indicate that children with persistent anemia exhibit worse Pediatric Risk of Mortality (PRISM) scores and increased susceptibility to complications such as sepsis and multiple organ dysfunction syndrome (MODS)[16].
2) Prolonged Hospitalization: Children with anemia often experience longer PICU stays, attributable to delayed recovery, increased need for interventions, and the compounded impact of transfusion-associated risks[17].
3) Psychosocial and Developmental Effects: Chronic anemia during critical illness can impair growth and neurodevelopment, especially in younger children. This underscores the long-term implications of anemia management in critically ill pediatric populations[18].

Emerging Perspectives

Recent advancements in anemia management emphasize early identification and targeted interventions to mitigate its impact. Strategies include:

1) Restrictive Transfusion Practices: Evidence suggests that restrictive transfusion thresholds (e.g., maintaining hemoglobin levels at 7–8 g/dL) are non-inferior to liberal strategies in stable patients, reducing exposure to transfusion-associated risks[19].
2) Erythropoiesis-Stimulating Agents (ESAs): These agents show promise in promoting red blood cell production, particularly in cases of chronic anemia with low erythropoietin levels. However, their use requires careful evaluation of risks such as thrombosis[20].
3) Optimized Nutrition: Addressing iron, folate, and vitamin B12 deficiencies through targeted supplementation can enhance erythropoiesis and reduce transfusion dependency[21].
4) Minimizing Phlebotomy Loss: Innovations such as micro-sampling techniques and closed-loop blood collection systems help reduce iatrogenic blood loss, especially in neonates and infants[22].

In conclusion, anemia in mechanically ventilated children is a multifaceted condition that significantly impacts clinical outcomes. Addressing the underlying causes through multidisciplinary approaches and adopting evidence-based management strategies are paramount in improving the care and prognosis of this vulnerable population[23].

Red Blood Cell Transfusions: Benefits and Risks

Red blood cell (RBC) transfusion remains a cornerstone in the management of anemia in critically ill children. The primary goal of transfusion is to improve oxygen delivery (DO2) to hypoxic tissues by increasing arterial oxygen content (CaO2)[24].

This is particularly critical in mechanically ventilated patients, where compromised oxygen transport exacerbates respiratory muscle fatigue and systemic hypoxia. The benefits of RBC transfusions include:

1. Enhanced Oxygen Delivery: Transfusions increase hemoglobin concentration, directly improving the oxygen-carrying capacity of blood and tissue oxygenation[25].
2. Stabilization of Hemodynamics: In cases of acute blood loss or hypovolemic shock, RBC transfusions can restore intravascular volume and stabilize hemodynamic parameters[26].
3. Improved Clinical Outcomes: For children with severe anemia, transfusions can alleviate fatigue, improve mental status, and reduce respiratory muscle workload, facilitating the weaning process from mechanical ventilation[27].

Despite these benefits, RBC transfusions carry significant risks that necessitate cautious clinical judgment. Key risks include:

1. Transfusion-Related Acute Lung Injury (TRALI): This life-threatening complication involves an inflammatory response in the lungs, leading to non-cardiogenic pulmonary edema. It is particularly concerning in mechanically ventilated patients[28].
2. Fluid Overload: Excessive transfusion can precipitate pulmonary edema, especially in children with compromised cardiac or renal function[29].
3. Infectious Risks: Although modern screening practices have significantly reduced the transmission of infectious agents, the potential for pathogen transmission persists[30].
4. Immunomodulatory Effects: Transfusions can alter the recipient's immune response, increasing susceptibility to infections and impairing long-term immune function[31].
5. Iron Overload: Repeated transfusions can lead to iron accumulation, which may cause organ damage over time[32].

Transfusion Thresholds and Practices

The determination of when to transfuse is a critical aspect of care. Current guidelines advocate for restrictive transfusion practices, emphasizing individualized thresholds based on clinical context(Stubbs, Klompas et al. 2021). For stable, non-bleeding pediatric patients, a hemoglobin threshold of 7–8 g/dL is generally recommended. Higher thresholds may be warranted in specific scenarios, such as:[33].

- Cyanotic Congenital Heart Disease: To support oxygen delivery in children with impaired baseline oxygenation.
- Severe Pulmonary Dysfunction: Where enhanced oxygen-carrying capacity is needed to counteract hypoxemia.
- Critical Illness with Multi-Organ Dysfunction: To prevent exacerbation of ischemia in vital organs.

Strategies to Mitigate Risks

To enhance the safety and efficacy of RBC transfusions, several strategies have been implemented:

1) Leukoreduction: The removal of white blood cells from transfused blood reduces the risk of febrile non-hemolytic reactions and immunomodulatory effects[34].
2) Pathogen Reduction: Techniques to inactivate potential pathogens in blood products further decrease the risk of transfusion-transmitted infections[35].
3) Monitoring and Support: Close monitoring of hemodynamic and respiratory parameters during and after transfusion ensures early identification and management of adverse reactions[36].
4) Adjunct Therapies: The use of erythropoiesis-stimulating agents and iron supplementation as part of a comprehensive anemia management plan can reduce reliance on transfusions[37].

Red Cell Distribution Width (RDW) in Critical Illness

Red cell distribution width (RDW) measures the variability in the size and volume of circulating erythrocytes and is typically reported as part of a complete blood count (CBC). Traditionally used to differentiate types of anemia, RDW has emerged as a valuable prognostic biomarker in critically ill populations, including children. Elevated RDW reflects anisocytosis, which is often a consequence of impaired erythropoiesis, inflammation, or oxidative stress all common features of critical illness[38].

Mechanically ventilated children often exhibit elevated RDW levels, particularly in conditions such as pneumonia, sepsis, and acute respiratory failure. Hypoxia, a frequent complication in these conditions, triggers the release of erythropoietin (EPO) from the renal cortex, stimulating erythropoiesis. However, systemic inflammation and oxidative stress can impair this process, leading to the release of immature and heterogeneous erythrocytes into circulation. Studies have linked elevated RDW to prolonged mechanical ventilation, increased ICU stays, and higher mortality rates, making it a critical parameter in assessing disease severity and predicting outcomes in pediatric critical care[39].

Elevated RDW in critical illness is also influenced by systemic inflammation. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β impair erythropoiesis, reduce red blood cell (RBC) lifespan, and increase the production of immature reticulocytes. This inflammatory milieu directly contributes to RDW elevation and is linked to adverse clinical outcomes, and respiratory failure. Additionally, oxidative stress, which is prevalent in critically ill children, compromises the integrity of RBC membranes and shortens their survival, further contributing to anisocytosis and elevated RDW values[40].

Emerging evidence suggests RDW correlates with other markers of disease severity, such as lactate levels and oxygenation indices, and may provide a broader picture of the physiologic derangements in critical illness. RDW has also been proposed as a potential marker for predicting the length of ICU stays and ventilator-free days. Furthermore, elevated RDW has been associated with immune dysregulation, which exacerbates the inflammatory response and hinders recovery in critically ill children[41].

Interplay Between Inflammation, Oxidative Stress, and RDW

The elevated RDW observed in critically ill children results from a complex and multifaceted interaction between systemic inflammation and oxidative stress. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β, and interleukin-6 (IL-6), act on multiple pathways that impair erythropoiesis, inhibit iron metabolism, and promote the premature destruction of red blood cells. These cytokines disrupt the maturation of erythroid progenitor cells in the bone marrow, leading to the release of immature erythrocytes into circulation. This contributes to the observed anisocytosis, a hallmark of elevated RDW[42].

Inflammation also induces hypoferremia, a reduction in serum iron levels mediated by increased hepcidin activity. Hepcidin, a liver-derived hormone, reduces iron availability by inhibiting intestinal iron absorption and sequestering iron within macrophages. This restriction of iron availability limits effective erythropoiesis, compounding the effects of inflammation on red blood cell production and variability[43].

Oxidative stress, another critical factor, arises from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses. ROS directly damage red blood cell membranes, reducing their deformability and lifespan. This oxidative injury accelerates erythrocyte turnover and promotes the release of younger, larger, and less uniform red blood cells into circulation, further elevating RDW levels. Additionally, oxidative stress affects the structural integrity of the bone marrow microenvironment, impairing its ability to support effective hematopoiesis[44].

In critically ill children, oxidative stress is exacerbated by hypoxia, ischemia-reperfusion injury, and systemic inflammatory states, all of which are common in PICU settings. Hypoxia stimulates the production of erythropoietin (EPO), which drives erythropoiesis. However, in the context of inflammation and oxidative stress, this compensatory mechanism is inefficient, resulting in the production of dysmorphic red blood cells that contribute to elevated RDW[45].

The clinical implications of this interplay extend beyond the hematologic system. Elevated RDW has been linked to poor outcomes in various critical conditions, including sepsis, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS). It reflects not only hematologic derangements but also systemic inflammatory and oxidative stress burdens. Consequently, RDW serves as an integrative biomarker that encapsulates the severity of the underlying pathophysiology in critically ill children[46].

Pediatric-Specific Considerations

While extensive research has explored RDW in adult critical care settings, its implications in pediatric populations remain less well-defined. Emerging evidence indicates that RDW may serve as a reliable marker for predicting ventilator-free days, the incidence of multiple organ dysfunction, and overall mortality in critically ill children. Additionally, RDW has been proposed as a complementary tool alongside established scoring systems, such as the Pediatric Index of Mortality (PIM2) and the Acute Physiology and Chronic Health Evaluation (APACHE II), for stratifying risk and guiding clinical decisions[47].

Unique pediatric challenges include variations in baseline RDW values due to developmental hematologic differences and the influence of growth and nutritional status on erythropoiesis. The dynamic nature of critical illness in children further underscores the need for age-specific research to optimize the utility of RDW as a prognostic tool. Furthermore, integrating RDW trends with other biomarkers of inflammation and organ dysfunction could enhance its predictive accuracy in pediatric critical care[48].

CONCLUSION

Anemia constitutes a prevalent disorder seen in mechanically ventilated infants and children and profoundly impacts their disease courses. Identification of anemia, its relation to red cell distribution width (RDW), and transfusion therapy is critical for prognosis evaluation in critical care settings. Anemia worsens impairments in oxygen delivery, prolongs mechanical ventilation duration, and raises complications such as infection and organ failure risk. An increased RDW reflects systemic oxidative and inflammatory processes, and it is correlated with poor prognosis.

Red blood cell transfusion is an important therapeutic intervention for anemia in mechanically ventilated children but must be performed with careful regard for transfusion-related complications, such as transfusion-related acute lung injury, iron overload, and immune suppression. Emerging studies increasingly promote a restrictive transfusion practice, administration of erythropoiesis-stimulating agents, and nutritional supplements for enhancing independence from transfusion and efficient delivery of oxygen. Considering the complex pathophysiologic factors in anemia in critical care children, an overall intervention that incorporates hematologic, nutritional, and pulmonary care is important. Transfusion triggers must be optimized, new therapeutic options must be developed, and individualized therapy must be adopted for survival and long-term improvement in such a high-risk population in future studies.

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