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ACUTE ANEMIA IN CRITICAL PATIENTS: ETIOLOGICAL APPROACH AND CLINICAL IMPACTS

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Abstract: INTRODUCTION Acute anemia in critically ill patients is a common and multifaceted condition, driven by factors such as systemic inflammation, gastrointestinal bleeding, nutritional deficiencies, and iatrogenic blood loss. Its pathophysiology is complex, involving disrupted erythropoiesis, iron metabolism dysfunction, and increased red blood cell destruction. Despite its high prevalence in intensive care units, the diagnostic limitations of conventional tools often delay targeted interventions, further complicating clinical management. **OBJETIVE** To analyze the etiologies, diagnostic challenges, and clinical implications of acute anemia in critically ill patients while evaluating the effectiveness of current management strategies. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: **"**Acute anemia" AND "Critical care" OR "Blood transfusion" OR "Inflammation and anemia" OR "ICU management" in the last 5 years. **RESULTS AND DISCUSSION** Results highlight the significant impact of acute anemia on oxygen delivery, organ function, and patient outcomes. Restrictive transfusion strategies have gained prominence, reducing complications associated with liberal transfusions, but their applicability remains patient-specific. Alternative therapies, such as parenteral iron supplementation and erythropoiesis-stimulating agents, show promise but are not without risks. Emerging therapies targeting inflammatory pathways and iron recycling offer potential for more effective management. However, the long-term clinical and economic consequences of untreated anemia remain a critical concern. **CONCLUSION** Addressing acute anemia in critical care requires a multidisciplinary approach that integrates advanced diagnostics, personalized therapies, and proactive monitoring. While current strategies provide valuable frameworks, further research is essential to close the gaps in our understanding of its pathophysiology and treatment. Optimizing the management of acute anemia in ICUs can improve patient outcomes and reduce the burden of complications in this high-risk population.

Keywords: Acute anemia; Critical care; Blood transfusion; Inflammation and anemia; ICU management

INTRODUCTION

Acute anemia in critically ill patients represents a multifaceted challenge in intensive care units (ICUs), combining intricate pathophysiological mechanisms, diverse etiological factors, and profound clinical implications[1]. Defined as a rapid decrease in hemoglobin concentration or hematocrit below thresholds required to maintain adequate tissue oxygenation, acute anemia often develops in the setting of preexisting comorbidities and systemic dysfunctions that exacerbate its impact on critically ill patients[1]. The classification of anemia in this context typically distinguishes between blood loss anemia, hemolytic anemia, and anemia of critical illness, each with distinct etiologies but often overlapping clinical presentations[1]. Despite advances in ICU care, the management of acute anemia remains a significant determinant of patient outcomes, mandating a nuanced understanding of its pathophysiology and clinical course[2].

Epidemiological studies have underscored the high prevalence of anemia in ICUs, with more than 60% of patients exhibiting some degree of anemia within the first 24 hours of admission[2]. This prevalence increases with prolonged ICU stays, largely driven by repeated phlebotomies, hemodilution, and ongoing inflammatory responses[2]. However, the epidemiological burden is not uniformly distributed across patient populations, with indivi-

duals presenting with trauma, gastrointestinal bleeding, or septic shock at disproportionately higher risk[3]. Moreover, the cumulative effects of anemia over time have been shown to correlate with increased morbidity, longer ICU stays, and higher mortality rates, emphasizing the necessity of prompt diagnosis and tailored interventions[3].

The pathophysiology of acute anemia in critical care is a complex interplay of factors that impair oxygen delivery and utilization at the tissue level[3]. Blood loss during surgical or traumatic events, hemodilution secondary to fluid resuscitation, and the systemic inflammatory response commonly seen in critical illnesses collectively contribute to anemia's development[3]. Inflammatory mediators such as interleukin-6 and tumor necrosis factor-alpha play pivotal roles in reducing erythropoiesis by suppressing bone marrow activity and altering iron metabolism[4]. This inflammatory blockade further compounds the effects of preexisting comorbidities such as chronic kidney disease, where erythropoietin production is already compromised[4]. Consequently, patients with acute anemia face a dual burden of reduced oxygen-carrying capacity and impaired compensatory mechanisms to restore erythropoiesis[4].

Among the primary causes of acute anemia in critically ill patients, gastrointestinal bleeding stands out as a significant contributor[4]. Stress-related mucosal disease, often exacerbated by coagulopathy or the use of anticoagulants, is a frequent cause of upper gastrointestinal hemorrhage in ICUs[5]. Additionally, lower gastrointestinal bleeding, while less common, is increasingly recognized in patients with ischemic colitis or diverticular disease[5]. Blood loss is not limited to the gastrointestinal tract; trauma-induced hemorrhage and perioperative blood loss also account for substantial reductions in hemoglobin levels[5]. Despite improvements in surgical techniques and blood conservation strategies, these remain major drivers of anemia in the ICU setting[6].

Hemodilution, while often an iatrogenic consequence of fluid resuscitation, is another critical factor in the development of acute anemia[6]. The administration of large volumes of crystalloids or colloids during shock or resuscitation efforts reduces hemoglobin concentration, even in the absence of overt blood loss[6]. This phenomenon is particularly pronounced in patients requiring aggressive fluid management for septic shock or acute respiratory distress syndrome (ARDS)[7]. Furthermore, the inflammatory response in critical illness can exacerbate this process by increasing vascular permeability and promoting intravascular volume shifts, thereby compounding the hemodilutional effect[7].

Sepsis and systemic infections are notable contributors to the development of acute anemia, with mechanisms that extend beyond inflammation and include hemolysis and bone marrow suppression[7]. Sepsis-associated anemia results from a combination of increased destruction of red blood cells, reduced lifespan of erythrocytes, and impaired erythropoietic response[8]. Hemolysis in these patients can be precipitated by disseminated intravascular coagulation (DIC) or direct bacterial toxin-mediated damage[8]. Additionally, septic patients often present with significant reductions in iron availability, mediated by hepcidin, further hampering erythropoiesis[8].

Drug-induced anemia, though less frequently discussed, is an important etiological consideration in critically ill patients[8]. Medications such as chemotherapeutic agents, certain antibiotics, and heparin can induce anemia through mechanisms ranging from marrow suppression to immune-mediated hemolysis[9]. Identifying and discontinuing the offending agent is essential but often complicated by the multifaceted pharmacological regimens employed in ICU patients[9]. Moreover,

the role of transfusion-related complications, including hemolytic reactions and iron overload, cannot be ignored in the broader context of managing anemia in this patient population[9].

The diagnostic approach to acute anemia in ICUs is fraught with challenges, particularly in distinguishing between anemia caused by ongoing blood loss, hemolysis, or bone marrow suppression[9]. Laboratory markers such as reticulocyte counts, serum ferritin, and transferrin saturation are often used to elucidate the underlying etiology[10]. Imaging modalities, while less commonly employed, can play a role in identifying sources of bleeding or marrow abnormalities in selected cases[10]. However, the dynamic nature of critical illness often necessitates serial evaluations to accurately assess the progression and response to therapy[10].

The clinical impact of acute anemia in critically ill patients extends beyond oxygen delivery and includes profound effects on organ function and overall prognosis[10]. Anemic patients are at higher risk of developing cardiac complications, particularly in the setting of preexisting coronary artery disease or heart failure[11]. Additionally, the reduced oxygen-carrying capacity can exacerbate tissue hypoxia, contributing to secondary organ dysfunction[11]. These effects underscore the importance of timely and effective management strategies to mitigate the adverse outcomes associated with acute anemia in this vulnerable population[11].

Ethical considerations in managing acute anemia further complicate clinical decision-making, particularly with respect to transfusion thresholds and resource allocation in ICUs[11]. While blood transfusion remains a cornerstone of therapy for severe anemia, concerns regarding transfusion-related complications, immunosuppression, and limited blood supply necessitate a judicious approach[12]. Alternative strategies, including erythropoiesis-stimulating agents and iron supplementation, have emerged as adjuncts but are not without their limitations[12]. As such, the management of acute anemia in critically ill patients represents a delicate balance between addressing immediate clinical needs and minimizing long-term complications[12].

OBJETIVES

To analyze the etiologies, diagnostic challenges, and clinical implications of acute anemia in critically ill patients while evaluating the effectiveness of current management strategies.

SECUNDARY OBJETIVES

1. To examine the most common causes of acute anemia, including blood loss, inflammation, and nutritional deficiencies.
2. To assess the diagnostic limitations of traditional tools and explore novel biomarkers and imaging techniques.
3. To evaluate the risks and benefits of current therapeutic approaches, including transfusion thresholds and alternative treatments.
4. To investigate the long-term outcomes and recovery challenges faced by patients with acute anemia in ICU settings.
5. To identify emerging therapies and future research directions for optimizing anemia management in critical care.

METHODS

This is a narrative review, in which the main aspects of the etiologies, diagnostic challenges, and clinical implications of acute anemia in critically ill patients while evaluating the effectiveness of current management strategies in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using

as descriptors: "Acute anemia" AND "Critical care" OR "Blood transfusion" OR "Inflammation and anemia" OR "ICU management" in the last 5 years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case--control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

The results of this review highlight the multifaceted etiologies and clinical implications of acute anemia in critically ill patients, revealing the complexity of its management in intensive care settings[13]. Gastrointestinal bleeding emerged as one of the leading causes of acute anemia in ICUs, with studies showing that stress-related mucosal disease and anticoagulant use contribute significantly to upper gastrointestinal hemorrhage[13]. Patients with preexisting risk factors such as coagulopathies and mechanical ventilation exhibit a disproportionately higher incidence of such bleeding, complicating their clinical management[13]. Lower gastrointestinal bleeding, while less frequent, remains clinically significant, particularly in elderly patients or those with ischemic colitis[14].

Trauma-related acute anemia is another critical area, accounting for a substantial proportion of ICU admissions[14]. Hemorrhage from blunt or penetrating trauma often requires immediate surgical intervention, with outcomes heavily dependent on the speed of hemostasis[14]. Advanced trauma management protocols, including damage control resuscitation, have been instrumental in reducing mortality associated with hemorrhagic shock[15]. However, secondary factors such as coagulopathy and systemic inflammation can perpetuate anemia in the days following trauma, underscoring the need for vigilant monitoring[15]. Surgical procedures contribute significantly to the development of acute anemia, particularly in cases involving major vascular or abdominal surgeries[15]. Intraoperative blood loss remains a primary driver, with studies highlighting the limitations of current blood conservation techniques in completely mitigating anemia[16]. Postoperative anemia is further exacerbated by inflammatory responses, fluid shifts, and nutritional deficiencies, which delay recovery and extend ICU stays[16]. Strategies such as the use of cell salvage and antifibrinolytic agents have shown promise in reducing perioperative anemia, though their adoption remains inconsistent[17].

Systemic inflammation plays a pivotal role in the pathophysiology of acute anemia, with cytokine-mediated suppression of erythropoiesis emerging as a central mechanism[17]. The interplay between interleukin-6 and hepcidin disrupts iron metabolism, leading to functional iron deficiency and impaired red blood cell production[17]. This inflammatory blockade is particularly evident in septic patients, where high levels of proinflammatory mediators correlate with more profound anemia[18]. Additionally, the bone marrow's inability to adequately respond to erythropoietin further complicates the clinical picture in critically ill individuals[18]. Nutritional deficiencies are frequently underappreciated contributors to acute anemia in ICUs[18]. Iron, vitamin B12, and folate deficiencies are prevalent among critically ill patients, driven by inadequate intake, malabsorption, and increased metabolic demands[19]. The use of parenteral nutrition, while beneficial in addressing caloric deficits,

often fails to correct micronutrient deficiencies unless specifically supplemented[19]. Emerging evidence suggests that early and targeted nutritional interventions may mitigate anemia's progression, particularly in patients with prolonged ICU stays[20].

Iatrogenic factors, including excessive phlebotomy, are significant contributors to anemia in ICU patients[20]. Frequent blood sampling for diagnostic purposes can lead to substantial cumulative blood loss, particularly in patients requiring daily monitoring[20]. Point-of-care testing and the use of pediatric-sized blood collection tubes have been proposed as strategies to minimize iatrogenic anemia, though their implementation varies widely across institutions[21]. These interventions, when combined with judicious ordering of laboratory tests, have shown promise in reducing anemia's incidence without compromising diagnostic accuracy[21].

Acute kidney injury (AKI) and its associated complications are also strongly linked to anemia in critically ill patients[21]. Reduced erythropoietin production in the setting of AKI leads to impaired red blood cell production, which is further compounded by fluid overload and hemodilution[22]. Renal replacement therapies such as hemodialysis can exacerbate anemia by causing blood losses and promoting inflammatory responses[22]. The integration of erythropoiesis-stimulating agents into AKI management protocols has shown mixed results, warranting further investigation into their efficacy in this population[22]. Bone marrow suppression, whether due to underlying comorbidities or medication use, is a critical determinant of anemia severity in ICUs[23]. Chemotherapeutic agents, immunosuppressants, and antibiotics have all been implicated in disrupting marrow function, with reversible and irreversible consequences[23]. Identifying and discontinuing the offending agent, where possible, is a cornerstone of managing drug-induced anemia[23]. However, this is often challenging in critically ill patients, where polypharmacy and the necessity of life-saving medications complicate therapeutic decisions[24].

Sepsis and systemic infections are prominent etiological factors, contributing to anemia through direct and indirect mechanisms[24]. Disseminated intravascular coagulation and hemolysis are common sequelae of severe infections, leading to accelerated red blood cell destruction[24]. Additionally, bacterial toxins and immune-mediated responses can exacerbate hemolysis, further depleting red blood cell reserves[25]. The overlap of these mechanisms with inflammatory anemia underscores the complexity of treating septic patients with anemia[25]. Hemolytic anemia, while less prevalent, represents a critical diagnostic challenge in the ICU[25]. Causes range from autoimmune hemolysis to microangiopathic processes, each requiring distinct therapeutic approaches[26]. Laboratory markers such as haptoglobin, lactate dehydrogenase, and bilirubin levels are essential for differentiating hemolysis from other forms of anemia, though their interpretation is often confounded by the underlying critical illness[26]. Emerging biomarkers and imaging techniques offer promise in improving diagnostic accuracy in this challenging patient population[26].

Diagnostic limitations in acute anemia remain a significant hurdle, particularly in the use of hemoglobin thresholds to guide management[27]. Hemoglobin levels often fail to capture the dynamic nature of anemia in critically ill patients, necessitating a more comprehensive approach that includes reticulocyte counts, iron studies, and inflammatory markers[27]. Advanced diagnostic algorithms incorporating these parameters have shown potential in better characterizing anemia and tailoring treatment strategies[28]. The utility of reticulocyte counts in differentiating anemia

etiologies is particularly noteworthy[28]. Elevated reticulocyte counts typically indicate a compensatory marrow response, aiding in the identification of hemolytic or blood loss anemia[28]. Conversely, low reticulocyte counts suggest marrow suppression or nutrient deficiencies, directing clinicians toward targeted interventions[29]. Despite their clinical utility, reticulocyte counts remain underutilized in many ICU settings, highlighting a gap in anemia diagnostics[29].

Iron studies are invaluable in diagnosing anemia, particularly in distinguishing between absolute and functional iron deficiencies[29]. Serum ferritin, transferrin saturation, and soluble transferrin receptor levels provide critical insights into iron metabolism, guiding supplementation strategies[30]. However, the inflammatory milieu of critical illness often confounds these markers, necessitating cautious interpretation and correlation with clinical findings[30]. Blood transfusion remains a cornerstone of acute anemia management, though its indications and thresholds are widely debated[30]. Restrictive transfusion strategies, favoring lower hemoglobin thresholds, have gained traction due to their association with reduced complications such as infection and iron overload[31]. However, the applicability of these strategies varies across patient populations, with evidence suggesting that more liberal thresholds may be beneficial in patients with cardiac comorbidities[31]. Parenteral iron supplementation has emerged as a valuable adjunct in managing anemia, particularly in patients with functional iron deficiency[32]. Intravenous formulations bypass the limitations of oral absorption, providing a rapid and effective means of replenishing iron stores[32]. However, concerns regarding adverse reactions and the potential for oxidative stress remain barriers to widespread adoption in critical care[33].

Erythropoiesis-stimulating agents (ESAs) have shown promise in select patient populations, though their use remains controversial[33]. While ESAs effectively stimulate red blood cell production, their association with thromboembolic events and tumor progression in oncology patients has limited their utility[34]. Ongoing research aims to identify subgroups that may benefit from these agents without undue risk[34]. Emerging therapeutic approaches, including hepcidin antagonists and iron-recycling modulators, offer exciting prospects for anemia management in ICUs[35]. Preliminary studies suggest these agents may address the inflammatory blockade of erythropoiesis, potentially transforming the therapeutic landscape[35]. However, their efficacy and safety in critically ill populations require further validation through rigorous clinical trials[36].

The clinical outcomes of untreated anemia in ICUs are profound, with associations between anemia severity and increased organ dysfunction, mortality, and length of stay[36]. Early recognition and targeted interventions are critical in mitigating these adverse outcomes, emphasizing the need for a multidisciplinary approach[37]. By integrating advances in diagnostics, therapeutics, and supportive care, the management of acute anemia in critically ill patients can be optimized, ultimately improving patient outcomes[37].

CONCLUSION

The management of acute anemia in critically ill patients remains a complex and multifaceted challenge, deeply rooted in the diverse etiologies, pathophysiological mechanisms, and clinical implications associated with this condition. The interplay between systemic inflammation, nutritional deficiencies, blood loss, and organ dysfunction requires a tailored and multidisciplinary approach to ensure optimal outcomes. Despite advances in cri-

tical care medicine, significant gaps persist in both diagnostic accuracy and therapeutic strategies, underscoring the need for ongoing research and innovation in this field.

One of the most pressing challenges is the accurate diagnosis of anemia in the dynamic and often unpredictable context of critical illness. While traditional markers such as hemoglobin and hematocrit levels remain central to clinical decision-making, their limitations highlight the need for more comprehensive diagnostic tools. The integration of biomarkers, advanced imaging, and point-of-care technologies holds promise in providing a clearer understanding of anemia's underlying causes and facilitating timely interventions.

Therapeutic approaches to acute anemia have evolved significantly, with a growing emphasis on restrictive transfusion strategies and alternative treatments such as parenteral iron supplementation and erythropoiesis-stimulating agents. However, these interventions are not without risks, including potential complications and variable efficacy across different patient populations. The emerging role of novel therapies targeting the inflammatory and metabolic pathways of anemia offers hope for more targeted and effective management, though their applicability in ICU settings requires further validation.

The clinical consequences of untreated or inadequately managed acute anemia are far-reaching, impacting oxygen delivery, organ function, and overall prognosis. Patients with severe anemia are at heightened risk for complications such as cardiac ischemia, impaired wound healing, and prolonged ICU stays, emphasizing the critical importance of early recognition and intervention. A proactive approach that combines personalized treatment strategies with robust monitoring protocols is essential to improve short- and long-term outcomes in this vulnerable population.

In conclusion, addressing acute anemia in critically ill patients demands a concerted effort to refine diagnostic methodologies, optimize existing treatments, and explore innovative therapies. By prioritizing multidisciplinary collaboration and evidence-based practice, clinicians can navigate the complexities of this condition more effectively. Future research should focus on bridging the gaps in our understanding of anemia's pathophysiology and management, ultimately aiming to enhance the quality of care and patient survival in intensive care settings.

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