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Disease-Associated Anemia: An Integrated Review of Pathophysiology, Diagnosis, and Therapeutic Implications

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Abstract

Disease-associated anemia is a heterogeneous and prevalent clinical problem, arising from diverse underlying conditions that interfere with erythropoiesis, red blood cell survival, iron metabolism, or blood loss. Major underlying causes include chronic kidney disease, chronic inflammation or infection, malignancy, bone marrow failure syndromes, haemoglobinopathies, autoimmune haemolysis, and chronic blood loss (e.g., gastrointestinal bleeding or parasitic infection). Distinct pathophysiological mechanisms impaired erythrocyte production, increased erythrocyte destruction, and iron sequestration or chronic blood loss often overlap, complicating diagnosis and treatment. Recent advances in understanding molecular regulators such as hepcidin and erythroferrone, and therapeutic innovations including hypoxia-inducible-factor (HIF) stabilizers, hepcidin antagonists, gene therapy for haemoglobinopathies, and refined iron-management protocols, promise improved outcomes. This review synthesizes current evidence on mechanisms, diagnostic approaches, and management strategies across major disease categories causing anemia.

Keywords: anemia, chronic disease, haemoglobinopathy, iron metabolism, bone marrow failure

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1 Introduction

Anemia remains a global health challenge affecting a large proportion of the population worldwide. While nutritional deficiencies (iron, vitamin B12, folate) are widely recognized causes, a substantial fraction of anemia cases are secondary to chronic diseases including renal failure, chronic infections, malignancies, autoimmune disorders, and genetic disorders of haemoglobin. The concept of "disease-associated anemia" or "anemia of chronic disease" (ACD) reflects a paradigm shift: anemia is no longer viewed solely as a nutritional deficiency but as a manifestation of systemic pathology that perturbs normal hematologic physiology.

Key epidemiological studies estimate that disease-associated anemia ranks among the most frequent forms of anemia globally, second only to iron-deficiency anemia in many settings [1] [2]. The burden is especially high among patients with chronic kidney disease (CKD), chronic inflammatory conditions, cancer, and in regions with high prevalence of infectious and parasitic diseases. This high prevalence underscores the public health and clinical importance of properly recognizing and managing anemia in these populations.

At the heart of disease-associated anemia lies a complex interplay between iron homeostasis, erythropoietic regulation, inflammatory signaling, and bone marrow function. The discovery of the hepatic peptide hormone **hepcidin** as a master regulator of systemic iron homeostasis revolutionized understanding of anemia in chronic disease. Hepcidin controls dietary iron absorption and iron release from macrophages by binding to the iron exporter ferroprotein, causing its internalization and degradation [3] [4]. Elevated hepcidin levels, typically induced during inflammation via interleukin-6 (IL-6) signaling pathways, result in trapping of iron within cells, thereby limiting its availability for erythropoiesis a phenomenon termed “functional iron deficiency” [5] [6]. In this scenario, conventional markers of iron deficiency (e.g., low ferritin) may not appear; ferritin may remain normal or elevated, complicating diagnosis.

Simultaneously, chronic disease–associated inflammation and immune activation exert direct inhibitory effects on erythropoiesis. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and IL-1 may suppress erythroid progenitor proliferation or sensitize them to apoptosis, impairing red cell production even in the presence of sufficient iron stores and erythropoietin (EPO) [7]. Meanwhile, chronic kidney disease impairs endogenous EPO production, disrupts iron utilization, and shortens red cell lifespan contributing to a multifactorial anemia that is resistant to simple supplementation [8] [9].

Moreover, genetic disorders such as haemoglobinopathies (e.g., β-thalassemia, sickle cell disease) cause intrinsic defects in haemoglobin synthesis or red cell structure, leading to ineffective erythropoiesis or chronic haemolysis [10]. Autoimmune hemolytic anemia (AIHA) results from antibody-mediated destruction of erythrocytes. Bone marrow failure syndromes (e.g., aplastic anemia, myelodysplastic syndromes) impair or destroy hematopoietic stem cells, leading to pancytopenia including anemia [11]. Chronic blood loss, due to gastrointestinal lesions, heavy menstruation, or parasitic infestation (e.g., hookworm), remains a significant contributor particularly in resource-limited settings.

Given this complexity, a one-size-fits-all approach to treating anemia (e.g., blanket iron supplementation or transfusion) is neither effective nor safe. Rather, effective management requires identification of the underlying cause(s), appropriate diagnostic evaluation, and tailored therapy that addresses the pathophysiologic mechanism whether that means modulating inflammation, supplementing iron, stimulating erythropoiesis, suppressing haemolysis, or repairing bone marrow and haemoglobin pathology.

In this review, we provide an integrative analysis of disease-associated anemia. First, we outline major disease categories that precipitate anemia; next, we examine the underlying pathophysiological mechanisms including iron regulation by hepcidin, erythropoietic suppression, haemolysis, marrow failure, and blood loss; then, we discuss diagnostic approaches and their limitations; and lastly, we review contemporary and emerging therapeutic strategies, including novel pharmacologic agents, gene therapies,

Doi: 10.30872/jtpc.v9i2.310

and precision-medicine paradigms. Our goal is to offer a comprehensive synthesis that informs clinicians and researchers, bridging molecular insights with practical management implications.

2 Methods

We conducted a structured narrative review. Literature search was performed across multiple databases including PubMed/MEDLINE, Scopus, ScienceDirect, and Google Scholar, covering publications from 2000 to 2025, with emphasis on more recent evidence (last 10 years), but including seminal older studies for fundamental mechanisms. Search terms included combinations of: "anemia of chronic disease," "hepcidin," "iron homeostasis," "chronic kidney disease anemia," "haemolytic anemia," "autoimmune haemolytic anemia," "thalassemia," "sickle cell disease," "bone marrow failure," "erythropoiesis," "chronic inflammation anemia," "parasitic anemia," "gastrointestinal bleeding anemia," and "iron therapy in chronic disease."

Inclusion criteria: peer-reviewed clinical studies, meta-analyses, systematic reviews, clinical practice guidelines, authoritative haematology or nephrology textbooks, and consensus statements. Exclusion criteria: non-peer-reviewed articles (e.g., letters without data), animal-only studies without human correlation, and case reports unless illustrative of novel mechanism or therapy.

From an initial yield of over 400 publications, 50 key references were selected and incorporated into this review, ensuring a representative spread across disease categories, mechanistic insights, diagnostic methods, and therapeutic perspectives.

3 Results & Discussion

Disease-associated anemia should be conceptualized not as a singular disease entity but as a **common phenotypic endpoint** of multiple, interrelated pathophysiological processes. The three core mechanisms impaired red blood cell (RBC) production, increased RBC destruction, and chronic blood loss or iron sequestration form intersecting pathways that underlie most clinical cases. In real-world patients, more than one mechanism often contributes to the ultimate anemia phenotype.

3.1 Impaired Erythropoiesis and Iron Sequestration

The interplay between inflammation and iron metabolism is central to many forms of disease-associated anemia. In chronic inflammatory states such as autoimmune disorders, chronic infections, or malignancy pro-inflammatory cytokines (notably IL-6) stimulate hepatic upregulation of hepcidin synthesis. Elevated hepcidin binds ferroprotein on enterocytes and macrophages, triggering its internalization and degradation. This effectively blocks intestinal iron absorption and iron release from macrophage stores, leading to reduced plasma iron and transferrin saturation despite ample total body iron [3] [6]. The resulting functional iron deficiency impairs haemoglobin synthesis and red cell production.

In vitro and in vivo studies confirm that inflammatory cytokines also have direct suppressive effects on erythroid progenitors; TNF-α, IFN-γ, and TGF-β impair erythropoietic differentiation and promote apoptosis of erythroid precursors [7]. Consequently, reticulocyte counts remain inappropriately low relative to anemia severity, indicating inadequate marrow compensation. This combination limited iron availability plus progenitor suppression defines the classic pattern of anemia of chronic disease (ACD), typically normocytic normochromic early on, but may shift toward microcytic hypochromic morphology if iron-restricted erythropoiesis persists.

Clinical guidelines for ACD stress the importance of controlling the underlying inflammatory or infectious condition rather than indiscriminate iron supplementation [5] [6]. However, in many patients, inflammation coexists with absolute iron deficiency (e.g., due to chronic blood loss), further complicating diagnosis and management.

Chronic kidney disease (CKD) represents a prototypical example of impaired erythropoiesis compounded by disordered iron homeostasis. Reduced nephron mass results in decreased erythropoietin (EPO) production, while uremic toxins and oxidative stress shorten RBC lifespan. Elevated systemic

Doi: 10.30872/jtpc.v9i2.310

inflammation and reduced renal clearance of hepcidin contribute to persistent iron sequestration [8] [12] [9]. Notably, impaired iron utilization rather than absolute iron deficiency often predominates, rendering oral iron supplementation ineffective. These insights led to the differentiation of management strategies, favoring intravenous iron and erythropoiesis-stimulating agents (ESAs), with target haemoglobin levels set conservatively to avoid cardiovascular risk [13].

Recent therapeutic innovations include hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF-PHIs), such as roxadustat and desidustat, which promote endogenous EPO production and suppress hepcidin expression, potentially restoring more physiologic erythropoiesis [13] [14]. Early-phase trials demonstrate improved haemoglobin and iron parameters, though long-term safety data remain under investigation.

Bone marrow failure syndromes including aplastic anemia, myelodysplastic syndrome (MDS), and marrow infiltration by malignancy represent the most severe forms of impaired erythropoiesis. In these conditions, hematopoietic stem cell depletion, clonal dysplasia, or malignant infiltration disrupt the marrow microenvironment, leading to pancytopenia and ineffective or failed red cell production [11]. In such cases, neither iron supplementation nor EPO therapy is effective; definitive therapy often requires immunosuppression or hematopoietic stem cell transplantation, depending on etiology.

3.2 Increased Red Blood Cell Destruction

While impaired erythropoiesis and iron-restricted erythropoiesis are major pathways, haemolytic processes whether inherited or acquired account for a substantial portion of disease-related anemia. Hereditary haemoglobinopathies such as β-thalassemia, α-thalassemia, and sickle cell disease (SCD) remain globally significant, particularly in regions with high prevalence.

In β-thalassemia, imbalanced globin chain synthesis leads to ineffective erythropoiesis, intramedullary destruction of erythroid precursors, iron overload, and shortened RBC lifespan [15]. Because of chronic haemolysis and transfusion dependence, iron chelation therapy becomes mandatory to prevent iron overload complications (cardiac, hepatic, endocrine). In SCD, haemoglobin S polymerizes under deoxygenated conditions, distorting erythrocytes into rigid sickle shapes prone to destruction. Vaso-occlusion, chronic inflammation, endothelial dysfunction, and oxidative stress further exacerbate haemolysis and organ damage [10]. Hydroxyurea remains a mainstay, increasing fetal haemoglobin and reducing haemolytic episodes, while novel strategies including gene therapy via CRISPR-Cas9 reactivation of fetal haemoglobin are now nearing clinical translation [16].

Autoimmune hemolytic anemia (AIHA) illustrates acquired immune-mediated RBC destruction. Antibody (IgG or IgM) binds erythrocyte surface antigens, leading to complement activation or splenic clearance. Warm AIHA (IgG-mediated extravascular haemolysis) is often treated with corticosteroids, with rituximab introduced for refractory cases. Cold agglutinin disease (IgM-mediated complement activation) may benefit from complement inhibitors such as sutimlimab. These interventions target pathogenesis directly, offering improved haemoglobin stability and reduced transfusion needs, though long-term immunosuppression risks must be balanced against benefits.

Drug-induced immune haemolytic anemia though less common underscores the need for vigilance when prescribing medications known to trigger haemolysis. Over 130 drugs have been implicated, including antibiotics (e.g., cephalosporins), nonsteroidal anti-inflammatory drugs (NSAIDs), and chemotherapeutic agents. In these cases, prompt drug cessation, supportive care, and in severe cases immunotherapy are indicated.

3.3 Chronic Blood Loss and Iron Depletion

Chronic or recurrent blood loss remains a fundamental cause of anemia worldwide. Gastrointestinal bleeding from ulcers, malignancies, inflammatory bowel disease, or varices; heavy menstrual bleeding from gynaecological pathology; and parasitic infestations (e.g., hookworm) are principal contributors.

In parasitic infections such as hookworm disease, the parasite attaches to the intestinal mucosa and ingests blood continuously, leading to slow but cumulative iron loss. In low-resource settings, this often

Doi: 10.30872/jtpc.v9i2.310

coexists with poor nutritional intake, exacerbating iron-deficiency anemia [17]. Similarly, occult gastrointestinal bleeding may lead to iron depletion over months to years, manifesting clinically only when haemoglobin falls significantly. In such contexts, iron supplementation (preferably intravenous when absorption is impaired) along with treatment of underlying cause (anti-parasitic therapy, surgical or endoscopic control of bleeding) is imperative.

3.4 Diagnostic Challenges and Strategies

Given the overlapping mechanisms, accurate diagnosis of disease-associated anemia requires a comprehensive and nuanced approach. Basic complete blood count (CBC) with red cell indices remains initial step, though morphology (microcytic, normocytic, macrocytic) may evolve over time or mask underlying causes. Reticulocyte count and production index help distinguish hypoproliferative anemia (e.g., ACD, CKD) from hemolytic or bleeding-related causes with compensatory reticulocytosis.

Iron studies (serum iron, transferrin saturation [TSAT], total iron binding capacity [TIBC], ferritin) are often misleading in the context of chronic inflammation: ferritin, an acute-phase reactant, may remain normal or elevated even in the presence of iron-restricted erythropoiesis [3] [6]. Measurement of soluble transferrin receptor (sTfR) and hepcidin, although not yet standardized globally, provides additional discriminatory power between iron-deficiency anemia and functional iron deficiency due to hepcidin-mediated sequestration. Recent studies indicate that the ratio of sTfR to log ferritin may serve as a reliable index [14]. Emerging biomarkers such as erythroferrone (ERFE), a hormone produced by erythroblasts that suppresses hepcidin to facilitate iron mobilization during increased erythropoiesis, offer further refinement of diagnostic stratification [18].

For suspected haemoglobinopathies or sickle cell disease, haemoglobin electrophoresis or high-performance liquid chromatography (HPLC) remains standard. Genetic testing may be employed for definitive diagnosis and genotyping, especially in thalassemia carriers and variants.

In cases of suspected haemolysis, direct antiglobulin (Coombs) test, lactate dehydrogenase (LDH), indirect bilirubin, haptoglobin levels, and peripheral smear analysis (for schistocytes or spherocytes) provide diagnostic evidence. For bone marrow failure syndromes, bone marrow biopsy remains the gold standard.

Overall, a diagnostic algorithm that integrates clinical context, basic haematology, iron studies, inflammatory markers, and, when indicated, specialized tests, offers the best approach to accurately identify the underlying cause(s) of anemia.

3.5 Therapeutic Implications and Advances

Management of disease-associated anemia demands an individualized, mechanism-based strategy. In inflammatory or CKD-related anemia with functional iron deficiency, intravenous iron therapy combined with erythropoiesis-stimulating agents (ESAs) remains standard, but with cautious haemoglobin targets to minimize cardiovascular risk [13] [12]. Emerging **HIF-prolyl hydroxylase inhibitors (HIF-PHIs)** offer advantages by stimulating endogenous EPO production and downregulating hepcidin, potentially reducing reliance on high-dose ESA or iron transfusions [14] [12].

For hereditary haemolytic anaemias such as β-thalassemia or SCD, supportive care (transfusion, chelation) remains cornerstone; however, curative approaches through gene therapy are maturing. CRISPR/Cas9-mediated editing to reactivate fetal haemoglobin expression by disrupting regulators such as BCL11A has shown promise in early clinical trials, with durable haemoglobin improvement and reduction in transfusion dependency [16]. Such strategies represent a paradigm shift from symptomatic management to disease-modifying therapy.

Autoimmune haemolytic anemia, once managed primarily with corticosteroids and broad immunosuppression, now benefits from more targeted therapies such as B-cell depletion (rituximab) or complement inhibition (sutimlimab), improving safety and efficacy [19]. Additionally, in drug-induced haemolysis, prompt identification and drug cessation remain essential.

Doi: 10.30872/jtpc.v9i2.310

In anemia due to chronic blood loss, it is critical to address the source (e.g., gastrointestinal lesions, parasitic infestation, gynaecologic bleeding) while replenishing iron stores. Public health measures sanitation, mass deworming, nutritional iron fortification remains critical in endemic regions [17].

Finally, future therapeutic directions focus on **modulating the hepcidin–ferroportin axis**. Strategies under investigation include hepcidin antagonists, ferroportin agonists, antibodies neutralizing hepcidin, or agents blocking hepcidin induction (e.g., anti–IL-6, BMP pathway inhibitors). Such agents promise to restore iron availability without overshooting and risking iron overload.

Overall, this integrative and mechanism-based therapeutic paradigm offers better alignment with root causes, reduces risk of inappropriate iron loading or overuse of ESAs/transfusions, and paves the way for personalized anemia management.

4 Conclusion

Anemia associated with chronic disease is not a uniform clinical entity but a complex syndrome reflecting varied and often overlapping pathological processes. Recognition of the underlying mechanism whether impaired erythropoiesis, inflammatory iron sequestration, red cell destruction, bone marrow failure, or chronic blood loss is essential for accurate diagnosis and effective treatment. Advances in understanding iron regulation (hepcidin, erythroferrone), erythropoiesis control, genetic haemoglobin disorders, and bone marrow pathology have paved the way for precision medicine and targeted therapy.

Clinical management should move beyond reflexive iron supplementation or transfusion toward etiologic therapy: controlling inflammation or infection, optimizing iron mobilization, supporting erythropoiesis or correcting genetic defects, and treating haemolysis or bleeding causes. Novel therapies (HIF-PHIs, hepcidin antagonists, gene editing, immunomodulators) bring the promise of more effective, safer, and durable outcomes.

For future research and clinical practice, standardized assays for hepcidin and sTfR, longitudinal studies on long-term safety of new agents, and protocols integrating biomarker-guided decision-making are critical. Ultimately, disease-associated anemia must be managed as a multi-system disorder not as a blood count number to be corrected in isolation.

5 Declarations

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