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– REVIEW –

Infectious Causes of Anemia: Mechanisms, Pathogens and Precision Management

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Abstract

Infectious causes of anemia represent a major global health burden, particularly in low- and middle-income countries, where malaria, HIV, and bacterial infections are prevalent. Infections contribute substantially to global anemia via coexistent mechanisms: accelerated red-cell destruction (direct parasitism, immune hemolysis), impaired erythropoiesis (transient aplasia, marrow niche injury, inflammatory dyserythropoiesis), and iron dysregulation or outright loss (hepcidin-mediated sequestration, gastrointestinal bleeding, malabsorption). Our aim is to synthesize the principal mechanisms of causing anemia across malaria, parvovirus B19, Helicobacter pylori, hookworm infections, Mycoplasma pneumoniae and tuberculosis, babesiosis, HIV, and visceral leishmaniasis, linking pathobiology to diagnostics and targeted therapy.

Keywords: anemia, infection, hepcidin, dyserythropoiesis, HIV, Helicobacter pylori

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Introduction

Anemia is characterized by a decline in hemoglobin concentration, hematocrit, or red blood cell count below reference values for age, sex, and physiological condition, leading to a reduced oxygen-carrying capacity of the blood [1]. It is among the most common clinical problems worldwide and remains deeply connected with infectious disease. This is a well-established relationship in the medical literature: anemia affects around one-third of the world's population. The most severe cases and the highest burden can be found in children, women of reproductive age, and populations in low- and middle-income countries [2,3]. Infectious diseases including malaria, tuberculosis, HIV, and helminthic infections are major contributors to

anemia in these regions, all of them having direct effects on erythropoiesis and via chronic inflammation [2-4].

Many infectious diseases are causes of anemia. It is possible through several pathophysiological mechanisms, including both acute and chronic infections. Infections can induce anemia by initiating the systemic inflammatory response. This leads to increased levels of cytokines (e.g., interleukin-6, TNF- α , interferon- γ) that inhibit erythropoiesis, reduce erythropoietin production, and promote iron retention in macrophages, but also limiting the availability of iron for hemoglobin synthesis. This type of anemia is known as “anemia of inflammation” or “anemia of chronic disease” [5,6]. Viral infections (e.g., parvovirus B19, HIV) can affect in a direct way the erythroid precursors in the bone marrow,

leading to their inhibition or destruction and decreased erythrocyte production [7]. Other infections, like malaria or helminth infections, cause anemia through hemolysis, blood loss, or interference with iron metabolism [8]. In chronic infections, such as tuberculosis or mycobacterial infections, anemia can be caused by a reduction in the lifespan of erythrocytes through phagocytosis mediated by activated macrophages and a blockage of iron release from stores. This can take place under the action of hepcidin [9]. These mechanisms can coexist with nutritional deficiencies, especially in resource-limited countries, where infections and malnutrition are frequently associated.

Young children (especially under 5 years old), pregnant women, adolescents and women of reproductive age, as well as people from resource-limited environments or with low socioeconomic status are population groups at increased risk for infectious anemia, in the context of infections such as malaria, helminth infections, schistosomiasis, HIV and tuberculosis [3,4].

From a public health perspective, these infectious causes of anemia can increase morbidity and mortality. Not only can reduce cognitive performance and economic productivity, but also can affect child development [3,10,11]. Effective interventions include integrated infection control programs (e.g., antimalarial treatment, routine deworming, prevention of HIV/TB transmission), food fortification with micronutrients, and improved access to clean water and health services [4,12,13]. Collecting local epidemiological data to tailor prevention and treatment strategies is important, as the etiology of anemia can differ based on the regional context and prevalence of infections [14]. Integrating nutritional and infection control interventions is recommended in order to reduce the number of people with anemia [12].

The aim of this review is to synthesize current understanding across infectious causes of anemia and to define the principal mechanisms: hemolysis, marrow suppression/ineffective erythropoiesis, and iron dysregulation. For this review, we performed a comprehensive search of PubMed, Web of Science, and MDPI. Sources were selected for clinical relevance, methodological rigor, and their contribution to understanding the mechanisms of anemia and how infections contribute to its development. The search strategy combined terms such as ‘anemia,’ ‘infections,’ ‘mechanisms,’ ‘pathogens,’ ‘hemolysis,’ ‘red-cell destruction,’ ‘dyserythropoiesis,’ ‘parasitism,’ ‘malaria,’ ‘helminths,’ ‘babesiosis,’ ‘HIV,’ and ‘tuberculosis,’ among

others. Letters and opinions were not taken into consideration.

Mechanisms

Hemolysis

Hemolysis is the process of premature destruction of erythrocytes, with the release of their contents, especially hemoglobin, into the blood plasma. This phenomenon can occur intravascularly (directly in the circulation) or extravascularly (in the reticuloendothelial system, predominantly in the spleen and liver) [15].

Hemolysis can be the result of intrinsic causes (erythrocyte membrane defects, hemoglobinopathies, enzyme deficiency) or extrinsic (antibodies, complement, toxins, infections, mechanical trauma, drug or transfusion reactions [16]. Clinically, hemolysis is manifested by anemia, jaundice, increased unconjugated bilirubin, reticulocytosis, decreased haptoglobin, and increased lactate dehydrogenase [16]. In the laboratory, hemolysis is defined as the destruction of the erythrocyte membrane with the release of intracellular components into the serum or plasma, a phenomenon that can affect the accuracy of biochemical analysis results [17].

Young children in malaria-endemic areas, immunocompromised patients (including those with HIV/AIDS, transplant, or immunosuppressive therapy), splenectomized individuals, the elderly, and patients with hemoglobinopathies or G6PD (glucose-6-phosphate dehydrogenase) deficiency are the groups most commonly affected by infectious hemolytic anemia, depending on the mechanism involved.

In children in tropical areas, malaria (*Plasmodium* spp.) is the main cause, with severe hemolytic anemia resulting from direct destruction of infected erythrocytes, macrophage activation and hemophagocytosis, and systemic inflammation [18]. Babesiosis mainly affects immunocompromised and splenectomized patients. It can also appear in immunocompetent children, with acute intravascular hemolysis [19]. Severe bacterial infections (e.g., sepsis, *Clostridium perfringens*) can lead to toxin-mediated hemolysis, microangiopathy, and disseminated intravascular coagulation, particularly influencing the elderly and people with comorbidities [20,21].

Dyserythropoiesis and bone marrow suppression

Anemia of infectious origin (anemia of inflammation) can disorganize erythropoiesis via a combination of immunological and metabolic mechanisms. Proinflammatory cytokines, as an example interleukin-6

(IL-6), interferon- γ (IFN- γ), and tumor necrosis factor alpha (TNF- α), can trigger a reprogramming of the bone marrow, having a bias towards myelopoiesis over erythropoiesis and inhibiting erythroid precursor and NF- α proliferation [22]. Over and above that, IL-6 directly inhibits the differentiation and proliferation of erythroid precursors, and IL-6 stimulates hepatic synthesis of hepcidin. This process blocks macrophage iron export and intestinal absorption, leading to hypoferremia and limiting iron availability for erythropoiesis [23].

In chronic infections for instance HIV and malaria, microorganisms can straightly begin to affect the hematopoietic niche or induce oxidative stress and dysfunction in erythroid precursors [22]. Hence, anemia of infectious cause is characterized by inadequate, hypoproliferative erythropoiesis, among others such as low iron availability and reduced erythrocyte survival [5]. The mechanism of bone marrow suppression in infectious anemia stimulates the synergistic action of proinflammatory cytokines, iron loss or malabsorption, and activation of bone marrow macrophages, all leading to inhibition of erythropoiesis and the onset of hypoproliferative anemia.

Iron dysregulation or outright loss

Anemia of infectious diseases results from a combination of hepcidin-mediated iron sequestration, iron loss through gastrointestinal bleeding, and malabsorption, all of which limit iron availability for erythropoiesis and contribute to the characteristic hypoproliferative anemia [22,24]. The main mechanism of iron metabolism dysfunction in anemia associated with infectious diseases is hepcidin-mediated iron sequestration. In the context of infections, proinflammatory cytokines (especially IL-6) intensify hepatic synthesis of hepcidin, which binds to ferroportin on enterocytes and macrophages, inducing its internalization and degradation. Due to this, iron is no longer exported from cells to the plasma, leading to decreased intestinal iron absorption and iron retention in macrophages and hepatocytes, limiting its availability for erythropoiesis [24,25].

On top of that, iron loss can occur through gastrointestinal bleeding, common in infectious diseases with mucosal involvement (e.g. inflammatory bowel disease, severe infections), where inflammation and ulceration boost the risk of chronic hemorrhage. Malabsorption is another mechanism, present in intestinal infections or inflammation, where mucosal integrity is compromised and iron absorption is lowered both directly (by affecting

the absorption surface) and indirectly (by increasing hepcidin which blocks ferroportin) [26].

Pathogens

Plasmodium falciparum

Plasmodium falciparum is the main etiological agent of severe malaria, with a global partition basically in sub-Saharan Africa, where over 90% of cases and deaths occur. Incidence remains high in young children and pregnant women, along with in unimmunized travelers to endemic areas. In 2023, *P. falciparum* accounted for approximately 97% of malaria cases worldwide, with pronounced mortality, especially in Africa [27,28]. The main mechanisms responsible for anemia in *P. falciparum* infection cover:

- Iron dysregulation and hepcidin-mediated sequestration. Acute infection generates proinflammatory cytokines (IL-6), increasing hepatic synthesis of hepcidin, which blocks iron export from macrophages and intestinal absorption, restraining iron availability for erythropoiesis. Iron administration in the acute phase is ineffective because of elevated hepcidin levels [29-31].
- Hemolysis. The parasite destroys infected and uninfected erythrocytes by immunological and oxidative mechanisms, increasing splenic clearance [32].
- Bone marrow suppression. Inflammatory cytokines and parasitic factors inhibit the proliferation and differentiation of erythroid precursors, resulting in inadequate erythropoiesis and dyserythropoiesis [33].
- Iron loss. Gastrointestinal bleeding might possibly occur in severe cases, contributing to iron deficiency [34].
- Malabsorption. Intestinal inflammation correlated with malaria may decline iron absorption [29]. The clinical spectrum of *P. falciparum* malaria scales from asymptomatic infection to mild forms (fever, headache, myalgia, anemia, splenomegaly) to severe forms. It is described by: severe anemia, seizures, altered state of consciousness (cerebral malaria), acute renal failure, acidosis, hypoglycemia, pulmonary edema, shock, clinical bleeding [34]. Children more commonly present with severe anemia and seizures, and adults may actually develop pulmonary edema and renal failure. Anemia is a primary cause of mortality in children [35].

Parvovirus B19

Parvovirus B19 is a DNA virus with global distribution, with a seroprevalence of 50-80% in adults, transmitted predominantly by the respiratory route, but also

transplacentally or through blood. The infection is common in children and adolescents, with an increased incidence in spring and summer [36].

The main mechanism by which Parvovirus B19 causes anemia is direct bone marrow suppression. The virus has a limited tropism for erythroid precursors in the bone marrow, where it binds to the P antigen (globoside) and generates cytolysis, apoptosis and cell cycle arrest through the NS1 protein, inhibiting erythroblast proliferation and differentiation [37]. This leads to reticulocytopenia and a rapid reduction in erythrocyte formation. In patients with chronic hemolysis (e.g. spherocytosis, thalassemia, sickle cell disease), this effect precipitates severe aplastic crises [38]. In immunocompromised individuals, persistent infection causes pure red blood cell aplasia and chronic anemia.

Parvovirus B19 does not induce anemia through mechanisms of hepcidin-mediated iron dysregulation, gastrointestinal bleeding, or malabsorption. Unlike other infections, anemia is not the result of iron sequestration or loss, but rather of direct destruction of erythroid precursors [39]. However, in the context of concomitant infections (e.g., malaria), the severity of anemia may be amplified [40].

The clinical spectrum of Parvovirus B19 infection includes: erythema infectiosum (fifth disease) in children, with rash and fever; arthralgias/acute arthritis in adults; transient aplastic crisis in patients with chronic hemolysis [38,39]; pure red blood cell aplasia and chronic anemia in immunocompromised individuals [36]; hydrops fetalis and fetal death in pregnancy [39]; pancytopenia, hemophagocytic syndrome, acute bone marrow failure, rarely. There are no specific antiviral therapies approved by the FDA for Parvovirus B19.

Helicobacter Pylori

Helicobacter pylori infection is one of the most common bacterial infections worldwide, with a high prevalence in regions with low socioeconomic status. *H. pylori* is associated with chronic gastritis, gastric and duodenal ulcers, and gastric cancer [41].

The supreme mechanisms by which *H. pylori* causes anemia incorporate: iron dysregulation through decreased intestinal absorption (due to chronic gastritis and hypochlorhydria), hepcidin-mediated iron sequestration (*H. pylori*-induced inflammation increases IL-6 and hepcidin, limiting iron export and absorption), gastrointestinal bleeding (over gastric/duodenal ulcer or erosive gastritis), and malabsorption (atrophy of the

gastric mucosa impairs the absorption of iron and other micronutrients) [41].

Current literature specifies that *Helicobacter pylori* inhibit iron homeostasis through several complementary routes. The bacterium linearly consumes iron from the gastric environment, contradictory with the host for iron resources, and chronic infection induces rearrangement of the transferrin receptor on the surface of gastric epithelial cells, augmenting intracellular iron uptake and reducing systemic availability for erythropoiesis. In addition, *H. pylori* can induce a local inflammatory feedback with increased IL-6, which affects hepatic hepcidin synthesis, favoring iron sequestration in macrophages and reducing intestinal absorption [42,43].

Gastrointestinal bleeding is a powerful mechanism, markedly in patients with *H. pylori*-induced gastric or duodenal ulcers, where chronic blood loss can lead to iron deficiency anemia, even in the absence of total hemorrhage [44]. On the other hand, iron malabsorption occurs subsidiary to chronic gastritis and gastric mucosal atrophy, which covers hypochlorhydria and decreased solubilization of non-heme iron, affecting its efficient absorption [45].

The clinical spectrum of *H. pylori*-associated anemia diverges from mild, subclinical forms to iron deficiency anemia refractory to oral iron supplementation, with systemic manifestations such as fatigue, tachycardia, or cognitive damage in children [46]. Epidemiological studies and meta-analyses show a significant association between *H. pylori* infection and an increased risk of iron deficiency and iron deficiency anemia, with a more sizeable prevalence in children, adolescents, and populations in resource-limited settings [47]. Eradication of *H. pylori*, related to iron supplementation, results in a decisive increase in ferritin and hemoglobin, supporting the pathogenic role of the infection [48].

Hookworm infections (*Necator americanus* and *Ancylostoma duodenale*)

Hookworm infection (*Necator americanus* and *Ancylostoma duodenale*) affects over 500–700 million people across the globe and is endemic in tropical and subtropical regions with low socioeconomic status, explicitly in Asia, sub-Saharan Africa, and Latin America. Children, pregnant women, and rural populations are especially vulnerable groups [49].

The central mechanism by which hookworm causes anemia is chronic blood loss from the intestinal mucosa, caused by attachment and feeding of the parasites, which

devastate capillaries and release anticoagulants, leading to ongoing hemorrhage [50]. This is the reason for progressive iron deficiency, with drops in hemoglobin, ferritin, and protoporphyrin. The severity of anemia is in line with the intensity of the infection and the species involved (*A. duodenale* causes greater blood loss than *N. americanus*) [51]. Unlike other infections, hookworm does not induce significant systemic inflammation, does not increase hepcidin, and does not directly affect iron absorption or utilization, so the anemia is not mediated by iron sequestration or bone marrow suppression, but by chronic blood loss and iron deficiency [52].

The clinical spectrum of hookworm-associated anemia ranges from asymptomatic forms to microcytic hypochromic iron deficiency anemia with fatigue, dyspnea, pica, cognitive impairment in children, growth retardation, decreased work capacity in adults, and maternal-fetal complications in pregnant women (prematurity, low birth weight, increased maternal mortality). In severe infections, edema, hypoproteinemia, and skin manifestations (tropical chlorosis) may occur [53]. Anemia is directly correlated with the intensity of infection and the nutritional status of the host [54].

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a common cause of atypical pneumonia in children and adolescents, with global transmission, predominantly by aerosols, and with an increased incidence in communities (schools, families) where children act as reservoirs and vectors of transmission. The prevalence is higher in children and young people, but the infection can occur at any age, including adults, with clinical forms varying from mild respiratory infections to community-acquired pneumonia [55].

The main mechanism of anemia associated with *Mycoplasma pneumoniae* is immunologically mediated hemolysis, especially by cold agglutinin autoantibodies (IgM anti-I), which cause extravascular or intravascular hemolysis. This process is triggered by molecular mimicry between bacterial antigens and erythrocyte antigens, generating an autoimmune response. In rare cases, anemia may be part of a pancytopenic pattern or may be associated with complement activation and microangiopathy [56,57]. Unlike *Helicobacter pylori* or hookworm infections, anemia is not caused by iron loss, malabsorption, or bone marrow suppression, but by destruction of red blood cells by autoimmune mechanisms.

The clinical spectrum of anemia ranges from mild, subclinical forms to acute hemolytic anemia with jaundice, fatigue, tachycardia, splenomegaly, and, in severe cases, acute renal failure or pancytopenia. Extrapulmonary manifestations may include renal, neurological, cutaneous, or cardiovascular involvement, and hemolytic anemia may precede, accompany, or follow respiratory symptoms [58].

Babesia

Babesiosis is an emerging parasitic disease transmitted primarily by the bite of the *Ixodes scapularis* tick, with an increasing incidence in the northeastern and midwestern regions of the United States but also reported in Europe and Asia. Transmission can also occur by blood transfusion, organ transplantation, or vertically (congenital). The incident is seasonal (summer), in general affecting oldest, immunocompromised, or splenectomized adults, where the threat of severe disease is high [59,60].

The upmost mechanism of anemia in babesiosis is intravascular and extravascular hemolysis, initiated by capture and lysis of erythrocytes by *Babesia* spp. The parasite grows intraerythrocytically, impelling direct destruction of erythrocytes. In patients with immunosuppression or asplenia, clearance of infected erythrocytes is impaired, going for persistent parasitemia and severe anemia. In addition, autoimmune hemolytic anemia (WAHA) may occur, especially in asplenic patients, through molecular mimicry mechanisms and postinfectious autoantibody formation [61]. Other mechanisms include complement activation, proinflammatory cytokines (TNF- α , IL-6), rarely bone marrow suppression, or pancytopenia.

The clinical spectrum ranges from asymptomatic or mild forms (fever, fatigue, chills, headache, myalgia) to severe hemolytic anemia with jaundice, splenomegaly, renal failure, DIC, heart failure, shock, or death. Complications are common in the elderly, immunocompromised, and splenectomized. Thrombocytopenia and hepatic cytolysis are common. Anemia may persist or recur, especially in immunocompromised hosts [62].

Human Immunodeficiency Virus (HIV)

HIV infection has a high global prevalence, with approximately 38 million people affected worldwide, being endemic in sub-Saharan Africa, but also present in the United States, Europe and Asia. Transmission occurs through sexual contact, blood (including injection drug

use) and vertical (mother-to-child). Incidence is higher in vulnerable groups: men who have sex with men, people of color, Hispanics and injection drug users, according to the CDC (Centers for Disease Control and Prevention) and recent epidemiological data [63,64]. The main mechanisms by which HIV causes anemia are:

- Bone marrow suppression induced by direct infection of hematopoietic stromal and progenitor cells, as well as by proinflammatory cytokines (IL-1, TNF- α , IFN- γ), which inhibit erythropoiesis and promote myelopoiesis [65,66]
- Anemia of inflammation (anemia of chronic disease), with imbalance of iron metabolism managed by hepcidin, constricting the availability of iron for erythropoiesis [67].
- Nutritional deficiencies (iron, folate, vitamin B12), persistent in patients with advanced HIV or malnutrition [68].
- Antiretroviral medication (e.g. zidovudine, but also other myelosuppressive drugs), which can induce anemia through bone marrow toxicity [69].
- Opportunistic infections (e.g., *Mycobacterium tuberculosis*, parvovirus B19, human Cytomegalovirus, Epstein-Barr virus and neoplasms), which can worsen bone marrow suppression or induce hemolysis [67].
- Hemolysis (autoimmune or drug/infection-induced), rarer than in babesiosis or *Mycoplasma pneumoniae*, but possible [65].

The clinical spectrum of anemia in HIV ranges from mild, asymptomatic forms to severe anemia with fatigue, dyspnea, tachycardia, cognitive impairment, jaundice (if hemolysis is present), pancytopenia, or bone marrow failure. Anemia is associated with disease progression, increased risk of mortality, and infectious complications, similar to the clinical spectrum seen in babesiosis (severe hemolytic anemia), hookworm (chronic iron deficiency anemia), and *Mycoplasma pneumoniae* (autoimmune hemolytic anemia) [69].

Mycobacterium tuberculosis

Tuberculosis remains one of the most prevalent infectious diseases globally, with approximately 10 million new cases annually and a high incidence in Africa, Southeast Asia and low-income regions. Mortality is significant, especially in patients with HIV co-infection, and men and people of low socioeconomic status are disproportionately affected [70]. The main mechanisms by which tuberculosis causes anemia are:

- Anemia of inflammation (anemia of chronic disease), generated by the systemic inflammatory response with increased IL-6 and hepcidin, which leads to iron sequestration in macrophages, decreased intestinal iron absorption and inhibition of erythropoiesis [71].
- Bone marrow suppression influenced by proinflammatory cytokines (IFN- γ , TNF- α), with direct inhibition of erythroid precursors and diminished erythrocyte duration of life [72].
- Nutritional deficiencies (iron, folate, vitamin B12), constant in patients with advanced TB or malnutrition [73].
- Chronic blood loss (hemoptysis, gastrointestinal bleeding) and coinfections (HIV, helminths) can multifactorially be part of anemia [73].

The clinical spectrum of anemia in tuberculosis varies from mild, asymptomatic forms to moderate or severe anemia, predominantly normocytic normochromic, but also microcytic hypochromic in case of associated iron deficiency [74]. Anemia is linked to severe forms of the disease (meningeal, disseminated TB), wasting, immune impairment, and longer-lasting clinical recovery under treatment [74]. The prevalence of anemia at diagnosis is high (60-70%), and the constancy of anemia under treatment expresses an unfavorable prognosis and requires further evaluation [75].

Compared to other infections (*Mycoplasma pneumoniae* – autoimmune hemolysis, babesiosis – parasitic hemolysis, HIV – bone marrow suppression and inflammation), tuberculosis is characterized by an anemia of inflammation with dysregulation of iron metabolism, bone marrow suppression and multifactorial nutritional deficiencies. Screening and monitoring of anemia are essential to optimize management and prognosis [75,76].

Leishmania infections

Visceral leishmaniasis (VL) is a severe parasitic disease transmitted by the bite of sandflies, endemic in tropical and subtropical areas of South Asia (India, Bangladesh, Nepal), East Africa (Ethiopia, Sudan, Kenya), Latin America (Brazil) and the Mediterranean region. The disease predominantly affects young children and young adults, with a higher incidence in males and in rural areas, but also in some periurban areas. VL remains a major public health problem, with high mortality in the absence of treatment [77,78].

The main mechanisms of anemia in VL are multifactorial: hemophagocytosis mediated by splenic and marrow macrophages (destruction of erythrocytes), suppression of

erythropoiesis by chronic inflammation (proinflammatory cytokines, IFN- γ , TNF- α), dysfunction of the medullary erythropoietic niche (erythroblast apoptosis, alteration of the stromal microenvironment), hypersplenism with increased sequestration and destruction of figured elements, nutritional deficiency (iron, folate, B12) and, less frequently, anti-erythrocyte autoantibodies [79]. Unlike babesiosis (acute parasitic hemolysis), HIV (bone marrow suppression, inflammation, nutritional deficiency) and tuberculosis (anemia of inflammation, bone marrow suppression), VL combines hemolysis, bone marrow suppression and hypersplenism.

The clinical spectrum of anemia in VL is wide, from moderate to severe forms, with hemoglobin frequently below 8 g/dl. Anemia is associated with pancytopenia, massive splenomegaly, hepatomegaly, chronic fever, fatigue, pallor, susceptibility to secondary infections and increased risk of mortality if specific treatment is not initiated. Anemia improves significantly after antiparasitic treatment. In HIV coinfection, anemia may be more severe and have an atypical course [80,81].

Management approaches

Precision management approaches and targeted therapies for anemia associated with the abovementioned infectious diseases involve specific treatment of the pathogen, correction of contributing factors, and, where appropriate, additional hematological interventions (table 1).

1. Malaria. First-line is specific antimalarial therapy (artemisinins, atovaquone-proguanil, mefloquine, chloroquine, depending on species and resistance). Blood transfusion is reserved for severe forms with profound anemia. Iron supplementation is not recommended in the acute phase due to the risk of increased parasitemia [82].

2. Parvovirus B19 infection. Management consists of transfusional support in patients with severe aplastic crisis. In immunocompromised patients, intravenous immunoglobulins may be useful. There is no approved specific antiviral therapy [83].

3. *Helicobacter pylori*. Eradication of the bacterium with triple therapy (PPI + clarithromycin + amoxicillin/metronidazole) is essential, associated with oral iron supplementation. Eradication of *H. pylori* increases the effectiveness of iron treatment in patients with refractory iron deficiency anemia [83].

4. Hookworm infections. First-line therapy is with anthelmintics (albendazole 400 mg once or mebendazole 100 mg/day for 3 days), associated with iron

supplementation. Repeated deworming and public health interventions are essential in endemic areas [1].

5. *Mycoplasma pneumoniae*. Hemolytic anemia is treated with antibiotics (macrolides in adults), and in severe cases with corticosteroids or immunoglobulins. Transfusion is restricted for life-threatening appearances [83].

6. Babesiosis. First-line therapy is the combination of atovaquone + azithromycin for mild-moderate forms, and clindamycin + quinine for severe forms or in immunocompromised patients. Exchange transfusion is indicated in parasitemia >10% or organ failure [84].

7. HIV. Optimization of antiretroviral therapy (ART) is fundamental. Correcting nutritional deficiencies, treating opportunistic infections, as well as adjusting myelosuppressive medication is crucial. Recombinant human erythropoietin (epoetin alfa) is indicated in refractory anemia, according to the Anemia in HIV Working Group consensus [66,85].

8. Tuberculosis. Standard antituberculosis treatment (INH, RIF, PZA, EMB) minimizes anemia of inflammation. Iron supplementation is suggested only after inflammation has dropped, monitoring iron biomarkers (hepcidin, ferritin) to avoid deterioration of the disease [71].

9. Visceral leishmaniasis. Antiparasitic treatment (liposomal amphotericin B, antimonials, miltefosine) is vitally important. Improving of nutritional deficiencies and, if necessary, blood transfusion finish the management [83].

Management of anemia should be individualized, combining etiological treatment, correction of deficiencies, and hematological interventions, with close surveillance of therapeutic feedback and complications.

Future perspective and directions

Future directions in the prevention, diagnosis and management of anemia associated with infectious diseases aim at integrating mechanism-specific biomarkers and implementing precision medicine, complementing community interventions such as sanitation, vaccination and screening.

The use of biomarkers such as hepcidin, ferritin, soluble transferrin receptor, CRP and inflammation markers allows differentiation between absolute iron deficiency anemia, anemia of inflammation and hemolytic anemia, facilitating rapid etiological diagnosis and guiding personalized treatment, including in contexts with coinfections (malaria, HIV, tuberculosis, hookworm) or

chronic inflammation [14]. The development of point-of-care platforms for the detection of these biomarkers, including portable and multiplex technologies, will allow rapid and inexpensive diagnosis in endemic areas, reducing the dependence on centralized laboratories [86]. Precision medicine involves adapted interventions to the local etiological profile of anemia, using consolidated surveillance data (biomarkers, nutritional status, prevalence of infections) to select targeted therapies: antimalarials, anthelmintics, ART, antituberculosis treatment, *H. pylori* eradication, iron or micronutrient supplementation main in patients with well-known deficiency [87]. This approach reduces the risk of

inadequate treatment (e.g., iron supplementation in patients with active inflammation or acute infection) and optimizes resources.

These innovations complement public health policies: improving sanitation and access to clean water (prevention of hookworm, *H. pylori*, leishmaniasis), vaccination (tuberculosis, HIV, parvovirus B19 when available), community screening for anemia and infections, mass deworming, and food fortification [88]. Integrating these strategies, with biomarker-based monitoring, will allow more effective and sustainable interventions in areas with a high burden of infectious anemia [89].

Pathogen	Mechanism(s) of Anemia	First-Line Therapy
<i>Plasmodium falciparum</i> (malaria)	Hemolysis (infected/uninfected RBC destruction), bone marrow suppression, hepcidin-mediated iron sequestration, GI bleeding, malabsorption	Artemisinin-based combination therapy (ACT: artemether-lumefantrine, artesunate-amodiaquine, etc.); transfusion in severe anemia; avoid iron in acute phase
Parvovirus B19	Direct bone marrow suppression via infection of erythroid precursors (P antigen tropism), reticulocytopenia, aplastic crisis in chronic hemolysis	Supportive care (transfusion in severe cases); IVIG in immunocompromised; no approved antivirals
<i>Helicobacter pylori</i>	Iron dysregulation (hepcidin ↑, bacterial iron consumption), decreased absorption (gastritis, hypochlorhydria), GI bleeding (ulcer), malabsorption	Eradication therapy (PPI + clarithromycin + amoxicillin/metronidazole) + oral iron supplementation
Hookworms (<i>Necator americanus</i> , <i>Ancylostoma duodenale</i>)	Chronic intestinal blood loss from mucosal attachment, iron deficiency	Anthelmintics: albendazole (400 mg single dose) or mebendazole (100 mg BID × 3 days) + iron supplementation
<i>Mycoplasma pneumoniae</i>	Autoimmune hemolysis via cold agglutinin IgM antibodies (anti-I), complement-mediated lysis	Macrolides (azithromycin, clarithromycin); doxycycline/fluoroquinolones in adults; corticosteroids/IVIG if severe hemolysis
<i>Babesia</i>	Intravascular/extravascular hemolysis (intraerythrocytic parasite), impaired clearance in asplenia, autoimmune hemolysis (rare)	Atovaquone + azithromycin (mild-moderate); clindamycin + quinine (severe); exchange transfusion if parasitemia >10% or organ failure
HIV	Bone marrow suppression (direct & cytokine-mediated), anemia of inflammation (hepcidin ↑), nutritional deficiencies (iron, folate, B12), ART toxicity (e.g. zidovudine), opportunistic infections	Optimized ART; correct nutritional deficiencies; treat OIs; switch myelosuppressive ART; epoetin alfa in refractory anemia
<i>Mycobacterium tuberculosis</i>	Anemia of inflammation (IL-6/hepcidin-mediated iron sequestration), marrow suppression (cytokine-driven), nutritional deficiency, chronic blood loss (hemoptysis, GI)	Standard anti-TB regimen (INH, RIF, PZA, EMB); iron supplementation only after inflammation subsides (guided by biomarkers)
<i>Leishmania</i> spp. (visceral leishmaniasis)	Hemophagocytosis (splenic/marrow macrophages), bone marrow suppression, hypersplenism, nutritional deficiencies, autoantibodies (rare)	Liposomal amphotericin B (first-line in many regions); alternatives: antimonials, miltefosine; nutritional correction; transfusion if severe

Table 1. Infectious Pathogens, Mechanisms of Anemia, and First-Line Therapy

Conclusion

Anemia of infectious origin represents a major global health challenge, principally in resource-limited settings where infectious diseases and nutritional deficiencies coexist. The pathogens discussed induce anemia through distinct but often overlapping mechanisms, alongside hemolysis, bone marrow suppression, iron dysregulation, blood loss, and hypersplenism. These mechanisms not only endanger hematopoiesis and red blood cell survival but also boost the systemic burden of infection, thereby contributing to morbidity and mortality. Precision medicine approaches, integrating biomarker-driven

diagnostics with context-specific interventions, are expected to lift resource allocation and improve outcomes, majorly in resource-limited and high-burden settings.

Conflict of Interest Disclosures

Conflict of interest: No known conflict of interest correlated with this publication.

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