Brief: Anemia and Coexisting Infection and Inflammation

Anemia, Infection, and Inflammation

Anemia is a condition with multiple causes. Prominent among these is infection and concomitant inflammation. Addressing these conditions demands a comprehensive approach that recognizes the interactions between a complex biological system (humans) and their internal (biology, genetics, health, developmental stage) and external (physical, social, economic, home, community) environments. In other words, anemia prevention and control require an ecological approach.

The intersection between anemia and infection/inflammation exemplifies the complexity of this ecology as each potentially affects, and is affected, by the other. Pre-existing anemia affects susceptibility to infection while infections may induce anemia through various mechanisms including inflammation, hemolysis (i.e., rupturing of red blood cells, RBCs), blood loss, impaired absorption of nutrients, and defective RBC development). Therefore, anemia is both consequence and cause of disease. Moreover, the reality that multiple causes, such as different types of infections, nutritional deficiencies, genetics, and environmental factors contribute to anemia in individuals or populations compromises our ability to make a differential diagnosis.

Infections account for a large proportion of anemia, especially in regions with a high anemia burden such as sub-Saharan Africa and Oceania (Kassebaum et al. 2014). Infections strongly associated with anemia include parasitic infections such as malaria, hookworm and schistosomiasis; bacterial infections such as tuberculosis (TB) and non-typhoidal Salmonellae; and viruses such as human immunodeficiency virus (HIV) (WHO 2017a, 2017b, 2018a, 2018b, 2019a, 2019b, 2019c, 2020a, 2020b; Vos et al. 2017; Wang et al. 2016; Stanaway et al. 2019) (table 1). Other viral infections associated with anemia include hepatitis C and the novel coronavirus of 2019, SARS-CoV-2 (COVID-19).

Infection, Anemia Assessment, and Anemia Control

Complex interactions between the biochemical markers of iron biology, infection, and inflammation hinder our ability to accurately estimate the prevalence of iron deficiency (both absolute and functional, as described below), which is still a major cause of anemia. Acute phase responses to infection and inflammation, including elevated levels of ferritin, an iron-storage protein in the blood that serves as a biomarker of iron stores, may give a false indication of replete iron status (Daru et al. 2017; Suchdev et
Al. 2017). In addition to compromising the interpretation of commonly used biomarkers, a practical implication of the iron/inflammation interface is that iron-containing interventions may be less effective and therefore less cost-effective in settings of endemic infections such as malaria (Pasricha et al. 2021).

A critical biological aspect of this effect is the role of hepcidin in iron biology, as the expression of this liver-derived hormone during infection is a principal mechanism leading to the anemia of inflammation. Hepcidin binds to ferroportin, the sole iron exporter at the cell membrane, resulting in decreased intestinal iron absorption and transference to the circulatory system, iron sequestration in macrophages and hepatocytes and hence reducing iron recycling, and reduced erythropoiesis (Nemeth et al. 2004).

Absolute iron deficiency is a deficit in total body iron with absent or reduced iron stores that cannot meet iron requirements. Under conditions of infection/inflammation, functional iron deficiency prevents meeting iron requirements even with sufficient or increased body iron stores because of iron withholding by increased hepcidin. The two types of iron deficiency may coexist in the same individual, and may be difficult to distinguish using traditional biomarkers of iron status.

Making this distinction enables us to not only improve precision of diagnosis but also to make decisions about the safety and efficacy of intervention options. For example, interventions such as iron fortification and supplementation may be less effective where the infection burden is high, as elevated hepcidin limits iron absorption and mobilization (Prentice 2017; Prentice et al. 2017; Cercamondi et al. 2010; Glinz et al. 2015).

The intersection of malaria, iron metabolism, and anemia exemplifies the need for the ecological approach. In malaria-endemic areas, the prevalence of iron deficiency may be further underestimated, as malaria increases ferritin levels independently of inflammation (Muriuki et al. 2020). Malaria may cause iron deficiency through hemolysis but also through impaired iron absorption (Muriuki et al. 2021). Strategies for anemia prevention through malaria control include the use of vector control, deployment of insecticide-treated bed nets, prompt and accurate diagnosis of illness, and appropriate use of effective anti-malarial drugs (Hershey et al. 2017).

### Table 1. Infections and Mechanisms for Anemia Development

<table>
<thead>
<tr>
<th>Infection</th>
<th>Mechanism(s) Fostering Anemia Development</th>
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<tbody>
<tr>
<td><strong>Parasitic</strong></td>
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<tr>
<td>Malaria</td>
<td>Increased breakdown (hemolysis) of infected and uninfected RBCs, defective RBC production in the bone marrow, iron maldistribution; Upregulation of hepcidin production → Reduced dietary iron absorption and transport to the circulatory system, and decreased iron recycling of RBCs</td>
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<tr>
<td>Hookworms</td>
<td>Hookworm infection results in anemia through blood loss but does not influence hepcidin concentrations or decrease iron absorption.</td>
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<td>Schistosomiasis</td>
<td>Anemia may be caused by extracorporeal (i.e., outside the body) blood loss due to translocation of eggs across the bladder or intestinal walls, defective RBC development, autoimmune hemolysis, or elevated pressures in the portal venous system due to granulomas in the liver (Friedman, Kanzaria, and McGarvey 2005; Mahmoud and Woodruff 1972).</td>
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<tr>
<td><strong>Viral</strong></td>
<td></td>
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<td>HIV</td>
<td>Wide range of mechanisms including—</td>
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Infection:

Mechanism(s) Fostering Anemia Development:

- infection of hematopoietic (i.e., related to the production of blood) precursor cells
- immune-mediated cytopenia (i.e., reduced number of blood cells) and anemia of inflammation
- opportunistic infections (e.g., Epstein Barr virus, cytomegalovirus)
- the direct effect of antiretroviral drugs (Marchionatti and Parisi 2021).

Hepatitis C
Induction of autoimmune hemolytic anemia; the precise mechanism is unknown.

COVID-19
Dysregulation of iron homeostasis: reduced hemoglobin concentration, increased plasma ferritin, and decreased iron levels (Zhou, Yu, and Du 2020; Shah et al. 2020).

Bacterial

TB
Chronic inflammation characterized by increased levels of C-reactive protein and proinflammatory cytokines (Minchella, Donkor, et al. 2015; Gil-Santana et al. 2016). Other causes include nutritional deficiencies, such as folate and vitamin B12 deficiencies, autoimmune hemolytic anemia, and bone marrow fibrosis and dysfunction (Oyer and Schlossberg 2011). Treatment is associated with resolution of anemia in approximately two thirds of patients (Minchella, Donkor, et al. 2015; Lee et al. 2006).
References


