Journal of Infection (2014) 69, S23—S27

BIAMM British Infection Association

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Anaemia, iron deficiency and susceptibility to infections

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Available online 26 September 2014

KEYWORDS
Anaemia;
Iron deficiency;
Iron supplementation;
Infection risk;
Immune system;
Children

Summary Anaemia, iron deficiency and infections are three major causes of childhood morbidity and mortality throughout the world, although they predominantly occur in resource limited settings. As the three conditions may have the same underlying aetiologies, they often occur simultaneously and may interact. Being an essential component in erythropoiesis, iron is also essential for proper functioning of the host immune system as well as an essential nutrient for growth of various pathogens, including non-typhoid salmonella. This has resulted in a treatment dilemma in which iron is needed to treat the iron deficient anaemia and improve the immune system of the host (child), but the same treatment may also put the child at an increased, potentially fatal, infection risk.

Introduction

Anaemia, iron deficiency and infections are three major causes of childhood morbidity and mortality throughout the world, although they predominantly occur in resource limited settings such as sub-Saharan Africa. As the three conditions may have the same underlying aetiologies, they often occur simultaneously and may interact. For example, iron deficiency can lead to anaemia and may also increase susceptibility to infection by suppressing the immunological response to pathogens.[1] Conversely, treatment of iron deficiency has also been associated with an increased incidence of infection.[2—7] After a short introduction on childhood anaemia, iron deficiency and infection risk, this chapter will highlight some outstanding research questions which arise from their complex interaction.

Anaemia

Anaemia is defined as a reduction in the amount of circulating haemoglobin[8] resulting in a decrease in oxygen carrying capacity. Anaemia in children is a global public health problem especially affecting young children with a prevalence rate that can be as high as 70% in some communities.[8] In sub-Saharan Africa severe anaemia is a major contributor to under 5 years mortality rates.[9]

Three mechanisms may lead to the development of anaemia, namely: an increased red blood cell destruction;

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http://dx.doi.org/10.1016/j.jinf.2014.08.007

an impaired red blood cell production, and/or acute or chronic blood loss. Anaemia may have multiple aetiologies and should be considered as a syndrome rather than a specific disease. Since iron is essential for synthesis of haemoglobin, iron deficiency is often considered the primary cause of anaemia. As a consequence the terms *anaemia*, *iron deficiency* and *iron deficiency anaemia* are often interchanged. Besides confusing definitions, this approach is incorrect as anaemia can occur with sufficient iron stores and iron deficiency does not necessarily lead to anaemia, as in the initial stages of iron deficiency erythropoiesis is not restricted. For this reason anaemia and iron deficiency should be considered as distinct conditions. The possible aetiologies important in the development of anaemia are multiple, including: infections such as malaria,[10] hookworm[8] and HIV[8]; drugs such as antibiotics,[11] tuberculostatics[12] and antiretroviral drugs[13]; genetic disorders such as G6PD, alpha-thalassaemia and sickle cell disease[14]; and micronutrient deficiencies (iron, vitamin B12, folic acid and vitamin A). Despite the fact that multiple aetiologies contribute to the development of childhood anaemia in resource limited settings, the management of anaemia in these settings is often only focused on treatment and prevention of malaria and iron deficiency.

Iron deficiency

Iron is essential for many biochemical processes including electron transfer reactions, gene regulation, binding and transport of oxygen, and regulation of cell growth and differentiation. Iron deficiency is defined as a state in which there are no available iron stores due to disturbance of the normally stable cycle of iron metabolism.[15] Iron deficiency is considered to be the most common nutritional disorder worldwide, with children and pregnant women most at risk. As it may cause anaemia, affect the immune system and delay cognitive development, iron deficiency is a critical problem in child health.[1,15]

There are different factors and pathways that may disturb iron homeostasis and induce iron deficiency (Fig. 1). Physiological causes of iron deficiency include periods of increased demand during periods of rapid growth as during the first years of life, as well as inadequate supply (nutritional iron deficiency) or both so that diet does not cover physiological requirements.[16] This is an important cause of iron deficiency in sub-Saharan Africa, where limited bioavailability of iron from staple foods is common.[8] Pathological iron deficiency can follow increased blood loss (e.g. gastrointestinal blood loss) due to enteric parasitic infections including hookworm.[17,18] In addition to actual iron shortage, normal physiological systems for transporting iron to target tissues may be impaired in the presence of adequate iron stores.[19] During the acute phase of an infection a pro-inflammatory cytokine response causes a decrease in intestinal iron absorption and decreased release from body iron stores.[20] Such *functional iron deficiency* is discussed further below. High pressure of infection contributes to the high prevalence of (functional) iron deficiency in sub-Saharan Africa.

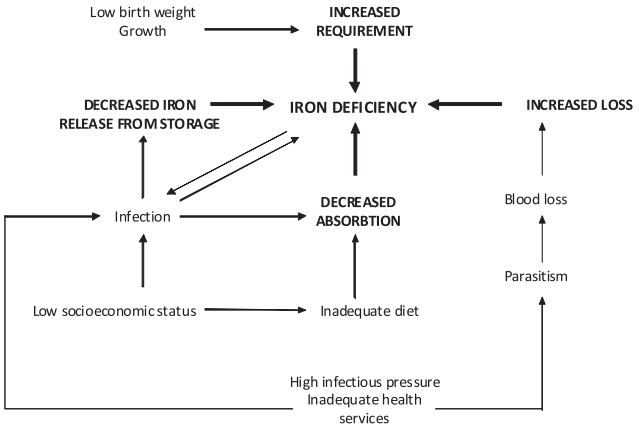

Figure 1 Aetiology of iron deficiency.

Iron deficiency and infection

Iron deficiency limiting immunity

Iron deficiency may increase risks of infection as iron is required for normal immune function including bactericidal activity of macrophages (iron is a critical component) of peroxide- and nitrous oxide-generating cellular enzymes[1] and also for T-cell numbers and function. In Malawian HIV-infected anaemic children receiving iron supplementation, an increase in circulating CD-4 positive T-cell numbers was observed.[21] Galan and colleagues (1992) reported reduced interleukin-2 production by activated lymphocytes in iron-deficient subjects.

Iron and pathogens

Iron is also an essential nutrient for many pathogens. The specific strategies microbes use to sequester iron from the host depend considerably on whether the pathogen adopts a predominately intracellular or extracellular lifestyle as well as its preferred iron source.[22] In a recent *in vitro* study, growth, adhesion, cellular invasion and epithelial translocation of *Salmonella typhimurium* were all increased in response to iron as was the growth of other pathogenic bacteria leading to the conclusion that the availability of iron may be correlated with virulence for several pathogens.[23]

Iron deficiency as an immune defence

The bacteriostatic effects of iron-binding proteins were first described in the mid-twentieth century.[24] This "hypoferremia of infection," a host-defence mechanism, is now known to be mediated largely by hepcidin a small 20—25 amino acid peptide predominantly expressed in hepatocytes in the liver.[25—27] Hepcidin is also produced by other cell types (at much lower levels), including renal tubular, myocardial, retinal, alveolar and pancreatic cells, monocytes, neutrophils, and adipocytes.[28—34] Through binding to the cellular iron transporter, ferroportin, in the small intestine, macrophages and bone marrow, hepcidin induces internalization and degradation of ferroportin and regulates cellular iron efflux.[35] There are several factors that down regulate hepcidin expression including reduced iron