Anemia: winning elbow room in the field of hematology and hemotherapy

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Anemia, one of the most common and widespread disorders in the world, is a public health problem in both industrialized and non-industrialized countries. In 2002, the WHO estimated that anemia resulting from iron deficiency was one of the ten most important factors contributing to the global burden of diseases and that it increases morbidity and mortality in preschool-aged children and pregnant women[1].

Anemia is defined as a decrease in the concentration of circulating red blood cells or in the hemoglobin (Hb) concentration and a concomitant impaired oxygen-carrying capacity in order to meet the body`s physiologic needs. Specific physiologic needs vary with a person's age, gender, altitude of residence, smoking behavior and in different stages of pregnancy[1].

Iron deficiency is by far the most common cause of anemia globally (causing approximately 75-80% of the total burden of anemias), but other nutritional deficiencies (including folate, and vitamins A and B_{12}), acute or chronic inflammation, parasitic infections, and inherited or acquired disorders that affect Hb synthesis, red blood cell production or red blood cell survival, can all cause anemia and can occur alone or together in the same individual[1].

Because iron metabolism disorders [particularly iron deficiency anemia (IDA) and anemia of chronic disease] make a large contribution to anemia, global efforts to reduce the anemia burden have largely been directed towards better programs for the assessment, prevention, diagnosis and management of these diseases around the world.

Iron deficiency and Iron deficiency anemia

IDA continues to be a major public health problem worldwide, with an estimated 3 billion people affected. The vast majority of cases of iron deficiency are acquired, resulting from blood loss, insufficient dietary iron intake, or both. Young children and menstruating women are disproportionately affected because their iron status is marginal to begin with. Recently it was rediscovered that infection by *H. pylori*, even in the absence of significant bleeding, can lead to severe IDA that is poorly responsive to oral iron therapy. This disorder is typically seen in young women, is associated with gastric atrophy, and can be associated with other autoimmune phenomena. Eradication of *H. pylori* infection can lead to the correction of the anemia[1,2].

Regarding iron deficiency, prophylactic measures should aim at restoring and maintaining an adequate iron status in the groups at highest risk for iron deficiency, i.e., preschool children, adolescent girls, reproductive-age women, pregnant women and postpartum lactating women.

A systematic review to verify the prevalence of IDA in under five-year-old Brazilian children showed that the median prevalence of anemia was 53% (mostly in under two-year-old children), which is considered a high prevalence rate by the WHO. Among the 53 analyzed studies, the age of the children was the variable most strongly associated with anemia[3].

Ideally, the most natural way of getting enough iron is through a diet with adequate iron content and good bioavailability of the iron. However, dietary iron intake is much less than ideal in almost all groups at high risk for iron deficiency.

In this regard, many countries have used iron fortification of foods and a follow-up analysis of iron status in many countries (including Brazil); this strategy showed minimal benefit for children while reproductive-age women had unchanged iron status. Moreover, general iron fortification of food would probably increase the prevalence of pre-existing iron overload conditions, particularly in the male population[3].

In countries with easy access to the health care system, it is easy to identify persons with iron deficiency and IDA by analyzing Hb and serum ferritin. According to the outcome, adequate treatment or prophylaxis with oral iron can be instituted. In areas where the health care is less efficient, especially in rural districts, with no facilities for the analysis of Hb or ferritin, but with a high prevalence of anemia, the finding of anemia should imply generous use of oral supplementation in order to benefit risk groups.

Due to the increase in the need for iron during childhood and pregnancy, the majority

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of children and pregnant women have a definitive need for iron supplements. The general recommendation in pregnancy is 60-100 mg of elementary iron daily from the 20th week of gestation. Some studies suggest that in order to be of optimum benefit for the outcome of pregnancy, iron supplements should be started when the woman decides to become pregnant in order to establish adequate iron reserves during pregnancy and postpartum. This approach is especially important in regions where iron deficiency and IDA are prevalent among reproductive-age women[2,3].

IDA should initially be treated with oral iron at doses of 100-300 mg/day and 3-6 mg/Kg/day of elementary iron for adults and children, respectively. It is essential to check the Hb concentration after 2-4 weeks to see if the treatment is working by inducing a increase in Hb. Iron should be continued for 3-6 months after Hb concentrations have reached normal levels in order to rebuild a minimum body reserve. In cases of severe anemia (Hb < 9 g/dL), intravenous iron should be considered[2].

It is very well known that oral iron is a less than ideal treatment mainly because of gastrointestinal adverse effects (particularly when using ferrous iron compounds), lack of adherence to therapy or insufficient length of therapy for the degree of iron deficiency, poor duodenal absorption due to concomitant gastrointestinal pathologies (inflammatory bowel disease, chronic kidney disease or any other cause of chronic inflammation, malignancy) and the long course of treatment needed to resolve anemia (1-2 months) and replenish body iron stores (another 3-6 months). Noncompliance to a prescribed course of oral iron is common and even in compliant patients, poor intestinal absorption fails to compensate for the iron need in the presence of ongoing blood losses or in inflammatory conditions[2].

In this scenario, new oral compounds containing either the ferric or ferrous salt forms have been developed as different preparations [amino-acid chelates, carbonyl iron, iron III polymaltose complex (IPC)] and approved for clinical use. Among these preparations, IPC is the most studied and used to treat IDA patients; it is not affected by food, milk or medicines which permits its ingestion during or after meals and the tolerability of IPC has proved to be much better, leading to higher compliance rates and improved effectiveness compared to ferrous sulfate[2].

In addition to that, modern formulations of intravenous iron have emerged as safe and effective alternatives for IDA management such as ferric gluconate, iron sucrose and, more recently, ferric carboxymaltose and iron isomaltoside. Both of these two new compounds potentially had better safety profiles than the more traditional IV preparations, particularly because these products may be given more rapidly and in larger doses than their predecessors with the possibility of complete replacement of iron in 15-60 minutes[4].

Anemia of chronic disease

Anemia of chronic disease (ACD), also called anemia of inflammation, is an acquired disorder of iron homeostasis. A common explanation for anemia in chronically ill patients, ACD was largely a diagnosis of exclusion in the past. This condition may be associated with many diverse systemic inflammatory conditions, including infection, rheumatologic disorders, inflammatory bowel disease, chronic kidney disease, malignancy, organ failure and trauma. The cause of ACD is multifactorial and includes a mildly decreased life span of erythrocytes, a direct inhibition of hematopoiesis coupled with a relative deficiency of erythropoietin, but the underlying iron etiology is evident: macrophages that normally recycle iron are found to sequester it, intestinal iron absorption is interrupted, and erythroid precursors respond very rapidly when iron-transferrin is made available. Research over the past decade has delineated the important role of inflammatory cytokines in each of these causes and the emerging role of the iron regulator hepcidin in the pathogenesis of ACD[5].

This type of anemia is typically mild to moderate and erythrocytes may not show any stigmata of iron deficiency. In a sense, anemia of chronic disease is the phenotypic opposite of hemochromatosis. Expression of hepcidin that is inappropriately high for body iron status results in the interruption of intestinal iron absorption and iron recycling. Consequently, decreased serum iron is available for erythropoiesis[5].

Treatment of ACD is unnecessary if the patient is asymptomatic. However, the anemia may be severe, and quality of life may be greatly improved with treatment, even in patients who believe they feel well with their anemia.

The first priority should be to correct any reversible contributors to the anemia (e.g., iron or vitamin B_{12} deficiency, absolute erythropoietin deficiency). Because the extent of ACD mirrors the activity of the underlying disease, all efforts should be made to treat the underlying disease[5].

Although transfusion is the fastest way to reverse ACD, many studies have shown responses to erythropoietin (20,000 to 40,000 units given subcutaneously each week). More recently, many studies have used high dose infusions of intravenous iron with good results in terms of efficacy and safety, which should be considered (together with erythropoietin or not) in the treatment of patients with ACD[5].

But, what is the underlying mechanism? It is postulated that the marrow requires 20-30 mg/day for erythropoiesis. In ACD patients, a small proportion of the infused iron is delivered in the ferric form into the plasma and taken up by transferrin. According to data from *in vitro* studies, approximately 45 mg of iron can be sustained in the plasma after the administration of 1000 mg IV iron. Meanwhile, most of the administered iron dose is taken up by the macrophages. The iron overload of the macrophages in the reticuloendothelial system may cause a 'by-pass' of the hepcidin block by over-expressing ferroportin and allowing a flow to the bone marrow, transported by transferrin (increased transferring saturation), to sustain erythropoiesis. In addition, in autoimmune diseases, macrophage iron loading may inhibit pro-inflammatory immune effector pathways, thus reducing disease activity (anti-inflammatory effect)[4].

Additional controlled studies are required to better delineate the management of ACD, to clearly reveal the impact of the correction of anemia on quality of life, medical outcomes, and survival of patients with ACD, particularly in those not undergoing chemotherapy; this may provide insight into the role of hypoxia on tumors and other diseases.

Anemia is a vast field and, therefore, there are important areas that I have neglected in this editorial. My choice of topics

should not be viewed as a judgment of what is most important; rather, it simply reflects the areas or diseases that have only recently become understood or well understood.

In the last decade, molecular understanding of systemic iron regulation was greatly expanded by the physiological analysis of these processes studied in the preceding fifty years. With the current knowledge about hepcidin and its role in systemic iron homeostasis as well as about ferroportin and its regulators, we could not ignore the potential targets for the diagnosis and treatment of iron disorders and anemias[6].

We are in an unprecedented position to understand the genome/environment interactions that make some people particularly susceptible to iron deficiency. We will understand the "erythroid regulator" that communicates body iron needs to liver hepatocytes producing hepcidin, allowing for mobilization of all available iron when erythropoiesis accelerates. A new understanding of iron biology may have therapeutic benefits as well. Perhaps it will lead to novel methods for oral iron repletion, allowing it to be accomplished in days, rather than months. If this becomes possible, it will have huge implications around the world[6].

Our understanding of the ACD has progressed enormously over the past few years but certainly we still have much to learn about it. As we refine our understanding of hepcidin-related manifestations and other manifestations, it should become possible to stratify this disorder according to causes and effects. Undoubtedly there will be new treatment strategies based on our understanding of the biology of ACD. It is quite likely that this understanding will also lead to a better appreciation of the molecular pathology of the anemia of aging[5,6].

In addition to that, a better understanding of iron homeostasis may also enhance treatment of other disorders. We still have much to learn about iron homeostasis in neoplastic diseases (i.e. solid tumors, lymphoma, myeloma), in many neurodegenerative disorders, particularly in those caused by iron deposition in the central nervous system[6].

All the aforementioned helps us to explain the increased interest in the field of anemia around the world and, particularly, in Brazil. The number of Brazilian scientific publications is increasing exponentially, the number of colleagues interested in working with anemia is increasing slowly but surely, not only among hematologists, but also among gynecologists, pediatricians, nephrologists, surgeons and others.

Finally, anemia is beginning to receive the importance and the acknowledgement it deserves. All of this is good for the whole medical community, but even better for patients around the world.

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