EDITORIAL

Iron deficiency and infection: another pathway to explore in critically ill patients?

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Anaemia is a common pathology with a high prevalence and incidence in the general population worldwide and one of the leading causes of years lived with disability and of mortality in myriad chronic medical illnesses [1]. Aetiologies are different depending especially on age and geographical location. In a systematic analysis for the Global Burden of Disease, Kassenbaum et al. [2] reported that iron-deficiency anaemia, haemoglobinopathies and parasitic diseases were the most frequent causes of anaemia worldwide.

Moreover, anaemia is more frequently diagnosed in older patients, the aetiology of which ranges from bone marrow failure syndromes to chronic kidney disease with erythropoietin deficiency and to iron deficiencies due to occult bleeding, inadequate iron intake and chronic inflammatory diseases processes [3, 4].

More than just indispensable for the synthesis of heme, iron, an essential trace element, also modulates host defence, as iron content in macrophages regulates their production of cytokines [5].

Iron is a required cofactor for enzymes that mediate O₂-dependent prolyl and asparaginyl hydroxylation of hypoxia-inducible factor 1 α (HIF-1 α), which leads to proteasomal degradation of this transcription factor.

Iron depletion in macrophages could therefore mimic the effects of hypoxia, stabilizing HIF-1 α and promoting the transcription and synthesis of interleukin-1 β (IL-1 β) and perhaps other cytokines. IL-1 β mediates systemic inflammation and activates important host defence mechanisms [6, 7].

These links between low iron concentration and greater inflammation may explain the results observed by Mohus et al. [8] published in the *Journal*. In a cohort population of 61,852 individuals with a 15-year follow-up, these authors observed an increased risk of bloodstream infections in patients with low iron status. This study has some limitations precluding any firm conclusion. First, one of the primary end points of the study was mortality occurring within 30 days after bloodstream infection. This delay is arbitrary and long, and it does not exclude other causes of death unrelated to infection. Second, concerning the iron status, it was only assessed by iron levels, transferrin saturation and total iron-binding capacity. No measurement of ferritin or hepcidin was available.

Moreover, associations of iron deficiency and anaemia were not possible because of the lack of haemoglobin measurements. The presence of a characteristic hyporegenerative microcytic hypochromic anaemia suggests a profound and chronic iron depletion. The value of haemoglobin could give additional information on the severity of iron deficiency. In this study [8], it is not possible to know if iron deficiency alone is the problem or if it was both that were predictive of bloodstream infections.

Measurements of iron status were made once, but follow-up lasted for 15 years. What happens during this length of time? We do not know whether the patients were supplemented with iron or if the iron status evolved. To answer this question, the authors looked at the iron prescriptions in the general population during the study period and reported that the daily intake of iron was lower than the recommendations, suggesting probably a persistence of iron deficiency in the population studied [8]. This indirect evidence is supported by another report showing that iron deficiency is often underestimated in the general population [9].

Lastly, iron status was measured only once, remotely from bloodstream infection. Looking at iron status at the

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Fig. 1 U-shaped relationship between iron concentrations and risks of infection. The red, orange and green colours respectively suggest high, moderate and very few susceptibilities to infections related to iron metabolism. Iron overload includes: red blood cell transfusion and iron supplementation

time of bloodstream infection is likely to be more informative and relevant to studying mortality after infection.

To limit this bias, the authors performed adjustments for comorbidities and excluded patients who developed bloodstream infections during the first 2 years of follow-up, with chronic illnesses that can lead to inflammatory anaemia (cancer, rheumatic illness or inflammatory bowel disease) and they observed the similar associations, suggesting a possible important role of iron status.

Finally, aetiologies of anaemia observed in critically ill patients are multifactorial and different from the general population included in the study of Mohus et al. [8]. This includes blood loss (surgery, gastrointestinal bleeding and blood sampling) but also decreased erythrocyte production (real or functional iron deficiency due to inflammation, decreased synthesis in erythropoietin) and a decrease of red blood cells lifespan [1, 10]. Since the adoption of a more restrictive transfusion policy nowadays in ICU patients, other treatments for anaemia have been advocated, such as iron administration in those patients found to have iron (real or functional) deficiency.

This topic is under investigation in ICU patients. First, several studies have reported the time course of iron metabolism in relation to inflammation, as observed in critically ill patients [11, 12].

Recently, the complex role of hepcidin in inflammation has been better defined: administration of hepcidin or a hepcidin agonist protects against lethal sepsis in mice by clearing non-transferrin-bound iron [13, 14] and, in contrast, blocking hepcidin, which limits iron sequestration by the reticuloendothelial system to reverse inflammatory anaemia [15].

Second, clinical trials of iron administration have shown a reduction in the severity of anaemia as would be expected, but also few effects on the risk of infection [16, 17]. If iron overload increases the risk of infection [14], the study of Mohus et al. [8] shows that indices of severe iron deficiency are also associated with an increased risk of bloodstream infection! This suggests a U-shaped relationship between iron status and susceptibility to infection (Fig. 1). What is against us as clinicians and as yet unknown is the optimal dose of intravenous iron

necessary to stimulate the bone marrow and reduce the requirement for red blood cell transfusion without risks of infection!

Therefore, this study opens the door to in-depth studies exploring the links between iron status and inflammation in ICU patients. It's time to investigate!

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Compliance with ethical standards

Conflicts of interest

The authors declare that there is no conflict of interest.

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