EDITORIAL

Micronutrient Changes in Critically Ill: Elusive Answers for Evaluation and Management

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Micronutrient (vitamins, trace elements, and electrolytes) research in critically ill suggests that lower levels, or deficiency are associated with increased mortality and morbidity.[1] Though there are few randomized trials in this regard, majority of the research is observational and conflicting. Identified deficiency is not true but is a consequence of illness. Clarity on acute or acute or chronic forms of deficiency is difficult to define.[2]

Iron is one of the key micronutrients essential for various biologic needs including synthesis of hemoglobin, transport of oxygen, energy production and immune functions. Iron is a critical nutrient for the replication and survival of most bacterial pathogens. The free iron (commonly called non-transferrin bound iron) is a heterogenous form of iron not bound to the plasma proteins (ferritin and/or transferrin) and is an essential nutrient for bacterial multiplication.[3,4] The pathogenic organisms are capable of extracting the free iron from plasma/tissue by various complex mechanisms. The humans have sailed successfully through thousands of years on the earth battling various pathogens thanks to the innate and acquired immune mechanisms that provide antibacterial properties to tissue fluids including phagocytic capabilities to certain immune cells. Research has shown that for the above systems to work optimally, there is a need for a virtually iron-free environment, and free-iron or free heme abolishes the bactericidal or bacteriostatic effects of serum resulting in increased virulence and multiplication of invading organisms. Sequestration of iron with decreased availability even for critical functions has been noted as a host response to sepsis as a part of the host defense mechanism against pathogens. Excessive sequestration can lead to anemia, and altered immune functions predisposing to secondary infections.[5] Both high as well as low iron status increase the risk of infections, and Mendelian randomization studies have shown that iron homeostasis set point changes increase the risk for sepsis, and have also correlated genetically predicted iron levels with increased risk of sepsis, and severe COVID-19.[6,7]

Iron studies use has expanded from their community evaluation of chronic anemia to use in the evaluation of various acute anemias in hospitalized and critically ill. Iron studies in critically ill septic patients have been noted for some time to be specific to the severity of illness or inflammation in the majority (analogous to anemia of chronic disease) and not due to acute loss (new bleeding) or acute on chronic loss (new bleeding or loss from other causes with pre-existing illness). This comes to be known as anemia of inflammation (AI), though has traditionally been discussed in chronic inflammatory states; of late has increasingly been documented and described in acute inflammatory states like sepsis.[8] The AI is different from iron deficiency anemia with its near normal mean corpuscular volume (MCV), high ferritin, and inflammatory markers apart from low hemoglobin. In essence, the AI is typically characterized by hypoferremia and hyperferritinemia.[9] Critical illness and resulting inflammation irrespective of the insult, affects the hemopoietic system at multiple sites and in particular the recycling of iron and the accelerated sequestration of red blood cells.[10]

In this issue of IJCCM, Jatteppanavar et al. have published a cross-sectional study on 142 patients with sepsis or septic shock whose iron profile (iron, ferritin, and transferrin saturation) and vitamin D levels were measured at admission using radioimmunoassay kits, and compared these values between survivors ($n = 60$) and non-survivors ($n = 82$).[11] They found a significant correlation between low iron levels, high ferritin levels, and low transferrin saturation levels at admission with the 28-day mortality. The vasopressor support, length of intensive care unit (ICU) stay, and the APACHE II and SOFA scores were also correlated significantly with increased mortality. The conclusions of this study noted some aspects of the iron profile but not the vitamin D level to be associated with increased mortality. Looking at the iron profile data of the study, the hypoferremia and hyperferritinemia are noted, and one could have used more information regarding hemoglobin level and MCV to assist with a diagnosis of underlying pre-existing anemia of chronic inflammation. Here again, the ferritin levels showed clear demarcation between survivors and non-survivors, and confirming the hyperinflammatory state in the latter. Vitamin D failed to be associated with the outcome given that both survivors and non-survivors had very low levels, but not to a level that was used as a threshold for supplementation in the VITdAL-ICU study.[12] This single-center cross-sectional study by Jatteppanavar et al. on a small number of patients warrants validation by further large studies in this patient population. It is difficult to comment if there were any

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underlying deranged iron profiles including iron deficiency in the non-survivors (as not uncommon in India), and to document the start of the septic process in the patients to find out if duration of septic process had affected the iron profile at admission. Going through the medical literature, results of various available studies on iron profile and sepsis outcomes have not yielded straight-forward or consistent results or answers. There have been studies that match the author's findings based on certain parameters, and contradict the results partially or completely.[8,13–17] The study by Brandtner et al. showed a positive correlation between high iron levels and high ferritin levels at ICU admission with the SOFA and mortality. Also, high iron, high ferritin, high transferrin saturation, and low transferrin concentration were associated with decreased survival.[17]

It is very difficult to correlate and associate the relation between iron status and sepsis mortality in view of heterogenous study protocols in different populations and in view of complex evidence with conflicting results. We need to be aware that ferritin is a positive acute phase reactant that is elevated in many acute infections. It is also elevated in chronic infections, and non-infectious conditions such as autoimmune disorders, chronic kidney disease, and malignancies. The acute phase reaction is mediated by cytokines including tumor necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6). The ferritin elevation results in the sequestration of iron and can be perceived as the body's defense mechanism against severe infection thereby depriving the free available iron in the body. Another key regulator of the inflammation-associated anemia is hepcidin which decreases iron levels by preventing intestinal iron absorption and by downregulating ferroportin in intestinal mucosae and macrophages.[8]

The change in iron profile could have made the person much more susceptible to sepsis as has been shown in the above Mendelian randomization studies or the inflammatory cascade in sepsis might have triggered the rapid changes in iron profile presenting at admission. Both high as well as low levels of iron have been known to worsen the outcome in a given patient.

The low iron in our study might have been the result of the natural defense mechanism of increased iron sequestration in ferritin stores. The transferrin is the iron-binding protein that gets saturated 20–30% with iron and makes non-transferring bound free iron undetectable in the internal milieu.[3] The low transferrin saturation probably denotes a relative deficiency of iron with or without anemia. It may also hypothetically denote the inability of transferrin to bind adequately to the normally available iron (because of sepsis cascade) thereby increasing the free non-transferrin bound iron which has got potential to cause oxygen radical injury resulting in multiorgan failure. The unbound iron is difficult to measure, and it would have been interesting if it was possible to measure the non-transferrin bound iron to correlate with the mortality.[3] It is difficult to explain the contradiction in Brandtner study where high iron and high transferrin saturation were associated with increased mortality without obtaining a detailed and reliable prior history.[17]

In common practice, evaluation and replacement of micronutrients are done with decreasing frequencies in the order of electrolytes, vitamins, and lastly, the trace elements. Studies into supplementation and in relation to levels deemed normal or supranormal levels vary. The current practice of using vitamin and trace element replacement in patients with preexisting nutritional deficiencies or those having prolonged ICU stays is common. Apart from this reactionary and often empirical practice (not advised by micronutrient levels), research into using micronutrients proactively with a hypothesis that their replacement to normal or supranormal levels may reduce inflammation or disease burden has been taking place over the years. A recent example of the same is the use of vitamin C, thiamine, and steroids in sepsis studies with conflicting results which finally failed to confirm the hypothesis in bigger studies.

There has been much interest in vitamin D in general practice and in recent decades in critically ill too. Though levels are noted to be consistently low, replacement is only noted to be associated with altered outcomes in severely depleted in a randomized trial.[12] Studies have not been able to identify characteristics and proportions of critically ill that have severe and non-severe forms of vitamin D deficiency. Through decades, single to multi-micronutrient evaluation and replacement in ICU for an improved outcome have largely been unsuccessful. The fact remains that in critically ill, the micronutrient levels alter, and the severity of alteration is associated with the severity of illness and replacement produces negative outcomes.[18]

To conclude, tests required to understand pre-existing and critical illness-related micronutrient changes or deficiencies are evolving. Currently, anemia of inflammation superseding pre-existing iron deficiency is common in septic patients. The severity of the illness corresponds with anemia. Vitamin D is consistently low in the ICU population and unlike anemia; replacement is possible in those with severe deficiency for outcome benefit. An extended iron profile with or without assessment of other micronutrients with a view to correlate levels and outcomes apart from finding avenues for intervention could only be facilitated by a large well designed studies in diverse critically ill patients.

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References

1. Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN micronutrient guideline. Clin Nutr 2022;41(6):1357–1424. DOI: 10.1016/j.clnu.2022.02.015.
2. Koekkoek WAC, Hettinga K, de Vries JHM, van Zanten ARH. Micronutrient deficiencies in critical illness. Clin Nutr 2021;40(6): 3780–3786. DOI: 10.1016/j.clnu.2021.05.003.
3. Patel M, Ramavataram DV. Non transferrin bound iron: Nature, manifestations and analytical approaches for estimation. Indian J Clin Biochem 2012;27(4):322–332. DOI: 10.1007/s12291-012-0250-7.
4. Bullen J, Griffiths E, Rogers H, Ward G. Sepsis: The critical role of iron. Microbes Infect 2000;2(4):409–415. DOI: 10.1016/s1286-4579(00)00326-9.
5. Darveau M, Denault AY, Blais N, Notebaert E. Bench-to-bedside review: Iron metabolism in critically ill patients. Crit Care 2004;8(5):356–362. DOI: 10.1186/cc2862.
6. Hamilton F, Mitchell R, Ahmed H, Ghazal P, Timpson N. Causal associations between iron status and sepsis: A Mendelian randomisation analysis. MedRxiv; 2022. DOI: 10.1101/2022.04.29.22274435.
7. Mohus RM, Flatby H, Liyanarachi KV, DeWan AT, Solligård E, Damås JK, et al. Iron status and the risk of sepsis and severe COVID-19: A two-sample Mendelian randomization study. Sci Rep 2022;12(1):16157. DOI: 10.1038/s41598-022-20679-6.
8. Jiang Y, Jiang FQ, Kong F, An MM, Jin BB, Cao D, et al. Inflammatory anemia-associated parameters are related to 28-day mortality in patients with sepsis admitted to the ICU: A preliminary observational study. Ann Intensive Care 2019;9(1):67. DOI: 10.1186/s13613-019-0542-7.

9. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood 2019;133(1):40–50. DOI: 10.1182/blood-2018-06-856500.
10. Muckenthaler MU, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. Cell 2017;168(3):344–361. DOI: 10.1016/j.cell.2016.12.034.
11. Bairwa M, Jatteppanavar B, Kant R, Singh M, Choudhury A. Impact of iron profile and vitamin D levels on clinical outcomes in patients with sepsis and septic shock: A cross-sectional analysis at a tertiary care center. Indian J Crit Care Med 2024;28(6):569–574.
12. Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: The VITdAL-ICU randomized clinical trial. JAMA 2014;312(15):1520–1530. DOI: 10.1001/jama.2014.13204.
13. Gupta D, Jain A, Chauhan M, Dewan S. Inflammatory markers as early predictors of disease severity in covid-19 patients admitted to intensive care units: A retrospective observational analysis. Indian J Crit Care Med 2022;26(4):482–486. DOI: 10.5005/jp-journals-10071-24171.
14. Fang YP, Zhang HJ, Guo Z, Ren CH, Zhang YF, Liu Q, et al. Effect of serum ferritin on the prognosis of patients with sepsis. Emerg Med Int 2022;2022:2104755. DOI: 10.1155/2022/2104755.
15. Vardi M, Hogerat T, Cohen S. Significance of extremely elevated ferritin level in medical inpatients. Cent Eur J Med 2014;9(1):115–120. DOI: 10.2478/s11536-013-0256-4.
16. Israel A, Bornstein G, Gilad L, Shechtman L, Furie N, Ben-Zvi I, et al. Clinical and prognostic significance of elevated ferritin levels in hospitalised adults. Postgrad Med J 2022;98(1162):622–625. DOI: 10.1136/postgradmedj-2021-139832.
17. Brandtner A, Tymoszuk P, Nairz M, Lehner GF, Fritsche G, Vales A, et al. Linkage of alterations in systemic iron homeostasis to patients' outcome in sepsis: A prospective study. J Intensive Care 2020;8:76. DOI: 10.1186/s40560-020-00495-8.
18. Costa NA, Pereira AG, Sugizaki CSA, Vieira NM, Garcia LR, Paiva SARd, et al. Insights into thiamine supplementation in patients with septic shock. Front Med 2022;8:805199. DOI: 10.3389/fmed.2021.805199.