



Individualized parenteral nutrition guideline: the challenge of trace elements

Claudio de Lima Barbosa^{1,2}

¹ Santa Genoveva Mater Dei Hospital, Uberlândia, Minas Gerais, Brazil.

² Faculty of Medicina of São José do Rio Preto, São Paulo, Brazil.

*Corresponding Author: Claudio de Lima Barbosa.

Santa Genoveva Mater Dei Hospital, Uberlândia, Minas Gerais, Brazil;

and Faculty of Medicina of São José do Rio Preto, São Paulo, Brazil.

E-mail: drclb2010@gmail.com

DOI: <https://doi.org/10.54448/ijn24208>

Received: 03-15-2024; Revised: 05-22-2024; Accepted: 05-28-2024; Published: 05-31-2024; IJN-id: e24208

Editor: Idiberto José Zotarelli Filho, MSc., Ph.D., Post-Doctoral.

Abstract

Parenteral nutrition (PN) is one of the pharmacological therapies that makes it possible to save lives previously condemned to death. PN entered clinical practice in the mid-1960s and was one of the most important advances in medicine after the discovery of anesthetics, antibiotics, and antisepsis methods. PN, however, is not without risks, as it is considered a high-alert medication that involves a significant risk of harm when used incorrectly. PN is the most complex existing pharmacological preparation with 20 to 40 active ingredients, the process of its application being transdisciplinary and its safety dependent on individual competence and reliable performance in each of its stages. The correct, individualized, and safe prescription of trace elements represents one of the biggest challenges in this process.

Keywords: Individualized nutrition. Parenteral nutrition. Trace elements.

Guideline

Indication of Trace Elements (TE) in Internal Medicine

The indication of supplementation of trace elements or TE in Internal Medicine is basically due to 3 situations [1-4]:

- Conditions associated with loss of bodily fluids;
- Increased oxidative stress;
- Situations in which insufficient oral/enteral nutrition does not reach your Dietary reference intakes (DRI).

Conditions in intensive care units associated with micronutrient depletion include severe burns, surgical or traumatic wounds, enterocutaneous fistulas, refractory diarrhea, or intestinal resections, resulting in decreased

absorptive area and when undergoing Renal Replacement Therapy (RRT) which causes loss of TE and proteins by the dialysate bath. Several harmful consequences have been associated with TE deficiency, such as poor wound healing, muscle weakness, inadequate immune response, and organic dysfunction, with special prevalence for the lack of zinc (Zn), iron (Fe), and selenium (Se). TE deficiencies are widespread and not only compromise the immune system but also hinder children's growth and development.

TE deficiency is a worldwide problem, as demonstrated by research including 22 countries demonstrating that globally 372 million preschool-aged children and 1.2 billion non-pregnant women of reproductive age (15-49 years) had one or more TE deficiencies [5]. Low levels of Vitamin D, Vitamin B12, folate, Vitamin A, iron, and zinc can be seen, and these deficiencies are often combined. Such a deficiency is associated with the exacerbation of existing diseases, especially infectious diseases, but also impairs physical and mental development. Among TE, selenium, iron, zinc, and vitamins A, C, and D are the first line of defense, as the body's physical barriers, that is, in the skin and respiratory epithelium, which are dependent on these TE for their integrity. Therefore, it is not surprising that TE supplementation, particularly vitamins C and D, reduces the risk of respiratory infections, as demonstrated in several meta-analyses, and may even shorten an active respiratory tract infection when used as a treatment [5].

In COVID-19

TE and vitamins play a fundamental role in modulating the immune response and their deficiency can influence the course of the disease, such as Se, Zn, Cu, vitamins D, C, E, and A [6]. Several studies have

reported that nutritional interventions can significantly improve the host immune response against RNA virus infections. Micronutrient supplementation in COVID-19 should not be confused with its administration in cases of deficiencies.

Nutritional deficiencies weaken the immune response in research models as well as in humans. These findings highlight the importance of assessing nutritional status to identify potential risk factors for viral infections. The evidence, however, on the individual effect of TE on COVID-19 has limitations. First, some micronutrients have not yet been shown to have a direct effect on SARS-CoV-2, so the available data has predominantly been from studies on related viruses such as SARS and MERS. Second, most clinical trials to evaluate these micronutrients are still ongoing, and results are not yet available. The results of these clinical trials are therefore necessary to determine the direct impact of micronutrients on SARS-CoV-2 and establish safe doses [7].

The GERIA-COVID Study carried out with seventy-seven patients hospitalized for COVID-19 in the ICU of a French university hospital concluded that regular vitamin D3 supplementation was associated with less severe COVID-19 and a better survival rate. Vitamin D3 supplementation may represent an effective, affordable, and well-tolerated adjuvant to the treatment of COVID-19 [8,9]. TE deficiency has a clinical impact, but excessive supplementation is also harmful, as shown in Table 1.

Table 1. Recommendations and Monitoring of TE in Parenteral Nutrition.

Recommendations and Monitoring of TE in Parenteral Nutrition		
TE	DRI/UL	Effect of deficiency
Zn	2.5-5 mg (12-18/L of diarrhea; in Short Bowel Syndrome/40 mg)	Dermatitis, alopecia, decreased wound and immunological healing, gonadal atrophy
Observe for signs of deficiency every 1 to 3 months of PN. A reliable interpretation of Zn deficiency in acute phase disease can only be made if serum CRP levels are <20 mg/L. Deficient levels <50% of reference values should be considered a suspected deficiency.		
Cu	300-450 µg (0.3-0.5mg)/10,000µg/d	Anemia, bone demineralization, gray hair
If the PN bag does not contain copper (Cu), watch for deficiency symptoms once a month. Check cupremia every 6 m if cholestasis, liver dysfunction, or suspected deficiency occurs. Large fluid losses, such as in massive diarrhea, may require 400-995 mcg/day, as well as gastric drainage and severe burns. Negative balance occurs in long-term Renal Replacement Therapy with Cu losses of up to 6.5 µmol/24 h in the dialysate bath. The risk of toxicity occurs in cases of cholestasis associated with long-term PN when Cu accumulates in the liver, kidneys, and brain: reduce, in these cases, the Cu intake to 150 µg/day (or 0.15 mg). Ceruloplasmin increases with oral contraceptives and in the acute inflammation phase: assess by PCR. The decrease in serum Cu leads to a decrease in ceruloplasmin.		

Mn	60-100 µg (0.06-0.1 mg)/11 mg	Bleeding, deterioration in wound healing.
If manganese (Mn) is included in the bag, watch for signs of toxicity every 1-3 months. Check serum Mn level if symptoms of toxicity present every 3-4 months, or monthly for patients with significant cholestasis. There is no need for brief PN supplementation. 110 µg can already bring harmful levels of Mn to the Magnetic Resonance Imaging of the cerebral globus pallidus, which ceases with the interruption of intravenous Mn. Most patients are asymptomatic, but some have Parkinson 's-like symptoms, confusion and irritability.		
Cr	10-15 µg (0.01-0.015 mg)/ND	Glucose intolerance, peripheral neuropathy, hyperlipidemia
If chromium (Cr) is included in the bag, check serum Cr every 6 months in patients with renal failure. There are few cases of Cr deficiency in long-term Parenteral Nutrition not increased by 6 months Cr 2 years after its initiation. There was no intoxication even when serum Cr levels were elevated or with Cr contamination due to metal hip implants or in those with Cr in PN.		
Se	60-100 µg/400 mcg	Hypothyroidism, cardiomyopathy, asthenia, arthritis, myositis, weak nails and hair
Pay attention to signs of deficiency every 1-3 months. Measure serum Se if deficiency is suspected or symptoms are present. Deficiency is a complication that is sometimes observed in patients with prolonged PN, as Se is not included in the bag. Serum levels should be monitored in patients receiving PN and it should be supplemented intravenously (IV) if levels fall. There are negative Se balances in RRT with losses of up to 1 µmol/24 h. Only very low Se values (<80% of the reference value) should be considered a deficiency in the acute phase of the disease.		
Fe	0.5-1.5 mg/45 mg/d	Anemia
Monitor serum ferritin and iron every 3 months		
Mo	10-50 µg / 2000 µg/d	Amino acid intolerance, Increased heart, and respiratory rate, headache, night blindness, and lethargy.
In deficiency, there is an increase in plasma methionine and a decrease in serum uric acid levels.		
Iodine: if patients with PN have reasonable stores of Iodine in the thyroid, it is sufficient for glandular metabolism for about 3 months. There is no need for PN supplementation when the duodenum is functional (site of absorption) or swallowing is viable. Pregnant women with PN need Iodine , due to the increased neurocognitive development needs of the fetus.		

Source: Own Authorship.

Legend: Dietary reference intakes (DRI); UL: Tolerable Upper Intake Level.

An important concept to be highlighted refers to the Tolerable Upper Intake Level/UL, which is the highest value of continued daily intake of a nutrient that does not have any adverse effect on health in almost all individuals in a given life stage or gender. As intake increases beyond the UL the potential risk of adverse effects also increases. This is a major challenge for the prescribing physician when calculating the dose of TE as the presentations available in the country are limited and combined (Table 2).

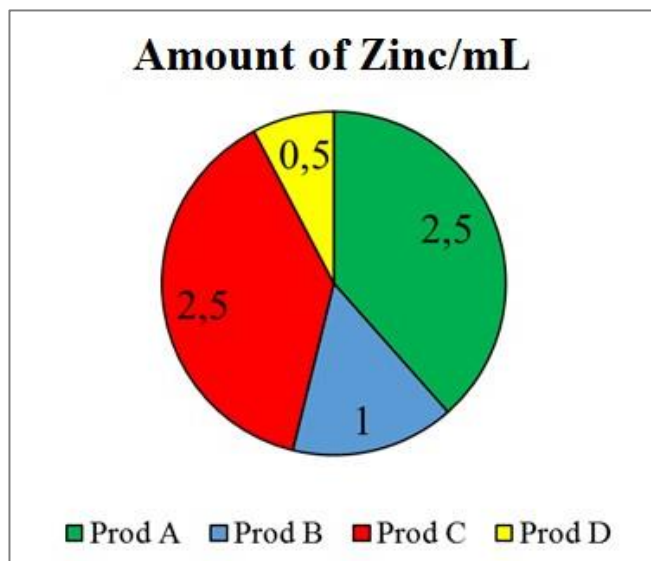
Table 2. Commercial presentation of TE ampoules available in the country.

Adult TE Solution (each mL contains)				
TE	Product A Hosppharma®	Product B Farmoterapica®	Product C OligTrat	Product D Addaven®
Zn	2.5 mg: 5 mg/amp	1 mg (1000 µg): 5 mg/amp	2.5 mg: 5 mg/amp	500 µg: 5 mg/amp
Cu	0.8 mg=800 µg: 1600 µg/amp	0.1 mg (100 µg): 500 µg/amp	0.8 mg: 1.6 mg/amp	38 µg: 380 µg/amp
Mn	0.4 mg=400 µg: 800 µg/amp	0.02 mg (20 µg): 100 µg/amp	0.4 mg: 0.8 mg/amp	5.5 µg: 55 µg/amp
Cr	10 µg: 20 µg/amp	2 µg: 10 µg/amp	10 mcg: 20 µg/amp	1 µg: 10 µg/amp
Se	--	--	--	7.9 µg: 79 µg/amp
I	--	--	--	13 µg: 130 µg/amp
Mo	--	--	--	1.9 µg: 19 µg/amp
F	--	--	--	95 µg: 950 µg /amp
Fe	--	--	--	110 µg: 1.1 mg/amp
	Standard dose: 2 mL	Standard dose: 5 mL	Amp-2 mL	Standard dose: 10 mL

Source: Own Authorship.

It is observed that the quantity of each TE differs depending on the company supplying PN. The Zinc in the TE ampoule from the Product C represents only 40% of Product A and C. The dose of Copper is 8 times lower in Product B than in the others, that is, 12.5% concerning the others (Figure 1).

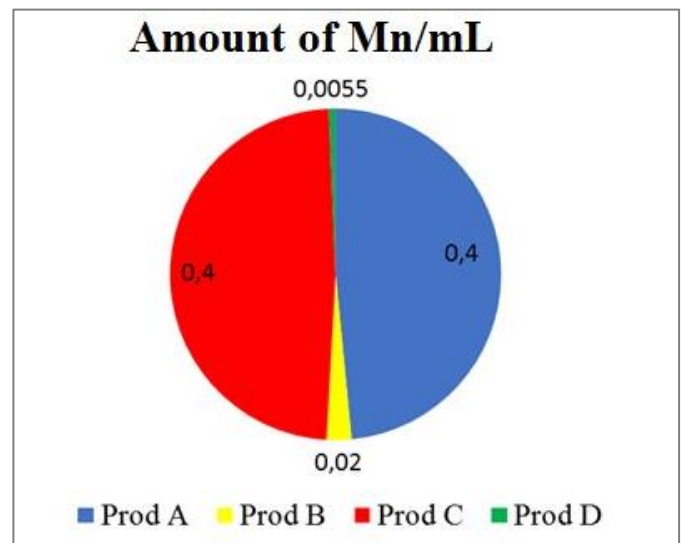
Figure 1. Amount of Zn in products available on the market.



Source: Own Authorship.

The Manganese in Product B therapy contains a concentration/mL of just 5% of that contained in other competitors, that is, 20 times lower (Figure 2).

Figure 2. Amount of Mn in products available on the market.



Source: Own Authorship.

Finally, the chromium in Product B is in the same concentration as the ampoules from the two other TE suppliers in the country.

Clinical Implication

This has a relevant impact depending on whether you want to replace one or another micronutrient in a dose that could exceed the UL of one or more TE. Some examples:

- Case 1 - patient with massive diarrhea, when Zn replacement is indicated, at a dose of 12 to 18 mg/day per liter of evacuation. To reach this amount, it would be very difficult not to extrapolate the UL of other TE and this could be harmful in hepatopathies (hepatic toxicity of Cu and Mn, which are excreted through bile [8]), neuropathies (cerebral toxicity of Mn and Cu) and in chronic kidney patients (Cr and Cu toxicity).
- Case 2 – patient on renal replacement therapy, receiving a ready-made bag of PN, not added TE and therefore needing replacement due to its loss due to the dialysate bath.
- Case 3 – A patient with high-output ileostomy secondary to radiotherapy for colon adenocarcinoma requires Zn replacement at a dose of 12 to 18 mg/day per liter of evacuation. To reach this amount, it would be very difficult not to extrapolate the UL of the other TE and this could be harmful, in this case, with liver metastases, that is, the TE could, above the UL, harm liver function.

It is therefore important that the pharmaceutical industry makes trace elements available separately for these cases so that their replacement is effective and safe. Furthermore, the standardization of TE ampoules in the country would also be beneficial.

Conclusion

Replacing micronutrients intravenously constitutes a unique challenge when considering the complexity of patients and their pathologies. There may be a deficiency of one or more Trace Elements (trace elements) but also their excess and consequent toxicity. A challenge to be overcome by the industry is the availability of isolated trace elements that allow the physician's prescription to be customized, especially in the most ill.

CRedit

Author contributions: **Conceptualization** - Claudio de Lima Barbosa; **Data curation** - Claudio de Lima Barbosa; **Formal Analysis** - Claudio de Lima Barbosa; **Investigation** - Claudio de Lima Barbosa; **Methodology** - Claudio de Lima Barbosa; **Project administration** - Claudio de Lima Barbosa; **Supervision** - Claudio de Lima Barbosa; **Writing - original draft** - Claudio de Lima Barbosa; **Writing-review & editing** - Claudio de Lima Barbosa.

Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed consent

Not applicable.

Funding

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

Peer review process

It was performed.

About the license©

The author(s) 2024. The text of this article is open access and licensed under a Creative Commons Attribution 4.0 International License.

References

1. Stawny M, Olijarczyk R, Jaroszkiewicz E, Jelińska A. "Pharmaceutical Point of View on Parenteral Nutrition" The Scientific World Journal 2013: 415310.
2. Boullata J. Overview of the parenteral nutrition use process. JPEN J Parenter Enteral Nutr 2012;36:10S-13S.
3. Barbosa CL. Heart Rate Variability in predicting mortality in patients undergoing Parenteral Nutrition. Master's Thesis – Faculty of Medicine of São José do Rio Preto-SP (FAMERP). São José do Rio Preto-SP, p. 102, 2016.
4. Blaauw R et al. Parenteral Provision of Micronutrients to Adult Patients: An Expert Consensus Paper. JPEN J Parenter Enteral Nutr 2019;43:S5-S23. <https://doi.org/10.1002/jpen.1525>.
5. Berger MM et al. The science of micronutrients in clinical practice – Report on the ESPEN symposium. Clinical Nutrition 2024;43(1):268-283.
6. Fedele D et al. Obesity, malnutrition, and trace element deficiency in the coronavirus disease (COVID-19) pandemic: An overview. Nutrition 2021; 81:111016.
7. Junaid K et al. Effective Immune Functions of Micronutrients against SARS-CoV-2. Nutrients 2020;12: 2992; doi:10.3390/nu12102992.
8. Annweiler G et al. Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID QuasiExperimental Study. Nutrients 2020; 12:3377; doi:10.3390/nu12113377.
9. Food and Nutrition Board IoM. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press; 2001.



<https://zotarellifilhoscientificworks.com/>