



Contents lists available at ScienceDirect

Clinical Nutrition

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ESPEN Guideline

ESPEN practical short micronutrient guideline

Mette M. Berger ^{a,*,1}, Alan Shenkin ^{b,1}, Oguzhan Sitki Dizdar ^c, Karin Amrein ^d, Marc Augsburg ^e, Hans-Konrad Biesalski ^f, Stephan C. Bischoff ^g, Michael P. Casaer ^h, Kursat Gundogan ⁱ, Hanna-Liis Lepp ^j, Angélique M.E. de Man ^k, Giovanna Muscogiuri ^{l,m}, Magdalena Pietka ⁿ, Loris Pironi ^{o,p}, Serge Rezzi ^q, Anna Schweinlin ^g, Cristina Cuerda ^r



^a Faculty of Biology & Medicine, Lausanne University, Lausanne, Switzerland

^b Institute of Aging and Chronic Disease, University of Liverpool, Liverpool, UK

^c Department of Internal Medicine and Clinical Nutrition Unit, University of Health Sciences Kayseri City Training and Research Hospital, Kayseri, Turkey

^d Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria

^e University Centre of Legal Medicine Lausanne-Geneva, Lausanne University Hospital and University of Lausanne, Geneva University Hospital and University of Geneva, Lausanne-Geneva, Switzerland

^f Institute of Nutritional Science, University of Hohenheim, Stuttgart, Germany

^g Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany

^h KU Leuven, Department of Cellular and Molecular Medicine, Laboratory of Intensive Care Medicine, Leuven, Belgium

ⁱ Division of Intensive Care Medicine, Department of Internal Medicine, Erciyes University School of Medicine, Kayseri, Turkey

^j North Estonia Regional Hospital, Tallinn, Estonia

^k Department of Intensive Care Medicine, Research VUmc Intensive Care (REVIVE), Amsterdam Cardiovascular Science (ACS), Amsterdam Infection and Immunity Institute (AI&II), Amsterdam Medical Data Science (AMDS), Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands

^l Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università di Napoli (Federico II), Naples, Italy

^m United Nations Educational, Scientific and Cultural Organization (UNESCO) Chair for Health Education and Sustainable Development, Federico II University, Naples, Italy

ⁿ Pharmacy Department, Stanley Dudrick's Memorial Hospital, Skawina, Poland

^o Department of Medical and Surgical Sciences, University of Bologna, Italy

^p Centre for Chronic Intestinal Failure, IRCCS AOUBO, Bologna, Italy

^q Swiss Nutrition and Health Foundation, Epalinges, Switzerland

^r Departamento de Medicina, Universidad Complutense de Madrid, Nutrition Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain

ARTICLE INFO

Article history:

Received 10 January 2024

Accepted 27 January 2024

Keywords:

Trace elements	Iron
Vitamin	Selenium
Deficiency	Zinc
Prescription	Thiamin
Diagnosis	B-vitamins
Monitoring	Vitamins-A- C-D- E- K
Copper	

SUMMARY

Background: Trace elements and vitamins, named together micronutrients (MNs), are essential for human metabolism. The importance of MNs in common pathologies is recognized by recent research, with deficiencies significantly impacting the outcome.

Objective: This short version of the guideline aims to provide practical recommendations for clinical practice.

Methods: An extensive search of the literature was conducted in the databases Medline, PubMed, Cochrane, Google Scholar, and CINAHL for the initial guideline. The search focused on physiological data, historical evidence (for papers published before PubMed release in 1996), and observational and/or randomized trials. For each MN, the main functions, optimal analytical methods, impact of inflammation, potential toxicity, and provision during enteral or parenteral nutrition were addressed. The SOP wording was applied for strength of recommendations.

Results: The limited number of interventional trials prevented meta-analysis and led to a low level of evidence for most recommendations. The recommendations underwent a consensus process, which resulted in a percentage of agreement (%): strong consensus required of >90 % of votes. Altogether the

* Corresponding author.

E-mail addresses: Mette.Berger@unil.ch (M.M. Berger), shenkin@liverpool.ac.uk (A. Shenkin), oguzhansitki.dizdar@sbu.edu.tr (O.S. Dizdar), karin.amrein@medunigraz.at (K. Amrein), Marc.Augsburger@chuv.ch (M. Augsburg), hans-k.biesalski@uni-hohenheim.de (H.-K. Biesalski), bischoff.stephan@uni-hohenheim.de (S.C. Bischoff), michael.casaer@uzleuven.be (M.P. Casaer), kursatgundogan@gmail.com (K. Gundogan), liis.lepp@gmail.com (H.-L. Lepp), ame.deman@amsterdamumc.nl (A.M.E. de Man), giovanna.muscogiuri@gmail.com (G. Muscogiuri), maggpietka@gmail.com (M. Pietka), Loris.pironi@unibo.it (L. Pironi), serge.rezzi@nutritionhealthfoundation.ch (S. Rezzi), anna.schweinlin@uni-hohenheim.de (A. Schweinlin), cuerda.cristina@gmail.com (C. Cuerda).

¹ Shared first authors.

<https://doi.org/10.1016/j.clnu.2024.01.030>

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guideline proposes 3 general recommendations and specific recommendations for the 26 MNs. Monitoring and management strategies are proposed.

Conclusion: This short version of the MN guideline should facilitate handling of the MNs in at-risk diseases, whilst offering practical advice on MN provision and monitoring during nutritional support.

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Abbreviation list

25(OH)D	25-hydroxyvitamin-D	ICU	intensive care unit
AA	ascorbic acid	IM	intramuscular
AI	adequate intake	IV	intravenous
AKI	acute kidney injury	MADD	multiple acyl-Coenzyme A dehydrogenase deficiency
CoQ10	Coenzyme Q10	MN	micronutrient
CRP	C-reactive protein	NAD	nicotinamid adenine dinucleotide
DFE	dietary Folate Equivalents	PLP	pyridoxal phosphate
DHAA	dehydroascorbic acid	PN	parenteral nutrition
DRI	dietary reference intake	RBC	red blood cells
EAR	estimated average requirement	RCT	randomized controlled trial
EN	enteral nutrition	RDA	recommended dietary allowances
FAD	flavin adenine dinucleotide	ROS	reactive oxygen species
FSMP	foods for special medical purposes	ThDP	thiamine diphosphate
GPX-3	plasma glutathione peroxidase	TPP	thiamine pyrophosphate
		UL	tolerable Upper Intake Level

1. Introduction

Micronutrients, a generic term for trace elements and vitamins, are essential components of nutrition in health and disease. For the general population, international recommendations are available in the form of recommended dietary allowances (RDA), or more recently, as DRI (Dietary Reference Intakes). However, there are yet no standardized procedures for the determination of requirements or recommendations for intake for patients with acute and chronic diseases. To assist clinicians, the recent ESPEN guideline [1] provides practical recommendations for the assessment of the micronutrient (MN) status in adult patients and information about basic or increased amounts, covering the fields of enteral and parenteral nutrition.

Status assessment is based on the patient's history, clinical assessment, and laboratory investigations. The guideline emphasizes the difficult interpretation of low micronutrient levels in the presence of inflammation, with the necessity to assess the magnitude of a concomitant inflammatory response [2,3].

The original document is very long since it includes extensive biochemistry physiology and advice on each of the MN. Therefore, the present abbreviated guideline is a summary focusing on the recommendations and clinical practice applications. The iteration of the guideline is of even higher importance after the publication by the World Health Assembly (WHA) of their resolution to accelerate efforts regarding micronutrient provision with safe supplementation.

2. Methods

The ESPEN micronutrient-working group attempted to apply the 2015 standard operating procedures for ESPEN guidelines and consensus papers with PICO questions (patient, intervention, comparator, outcome) [4], but failed due to a lack of intervention trials, resulting in structured reports for each MN based on systematic review. The literature was searched for evidence regarding

1) different diseases (see § 3), 2) therapeutic interventions (enteral nutrition, parenteral nutrition, renal replacement therapy), and 3) special periods of life (pregnancy, elderly).

The SIGN evaluation system (Scottish Intercollegiate Guidelines Network) [4] was applied to the available interventional trials. The recommendations were created and graded into the four listed classes (A/B/O/GPP). When solid evidence coming from biochemistry and physiology was extrapolated to clinical settings, it allowed the upgrading of recommendations to an A or B level, enabling the use of “shall” or “should” in the recommendation formulation. Dose recommendations based on existing RDA are attributed a level A as they are based on internationally validated evidence, whereas those based on DRI are given a level B.

As many recommendations are supported by limited evidence, they underwent a consensus process, which resulted in a percentage of agreement (%). The “strong consensus” qualification required >90 % of agreement, and “consensus” was defined as an agreement of 75–90 % of the experts and participants [5]. There were two rounds of votes. In case of agreement <90 % during the first Delphi vote, the recommendations were thoroughly reviewed and -if necessary-reformulated. All recommendations with substantial changes were voted on again. Recommendations with less than 75 % agreement were discarded.

For further details on methodology of the original guideline development, see the full version of the ESPEN guideline [1] and the ESPEN standard operating procedures (SOP) [4].

When transforming the original guideline to the practical version, the texts were reduced to the basic principles, and information on toxicity. The analytical aspects detailed in the main document were deleted, with focus mainly on the clinical aspects of deficiency and eventual toxicities. Please refer to the initial guideline for more detailed information.

The meaning of the recommendations has not been changed. In a few cases, it was necessary to adapt the wording because feedback from users since the publication of the original version showed that some of the recommendations were worded

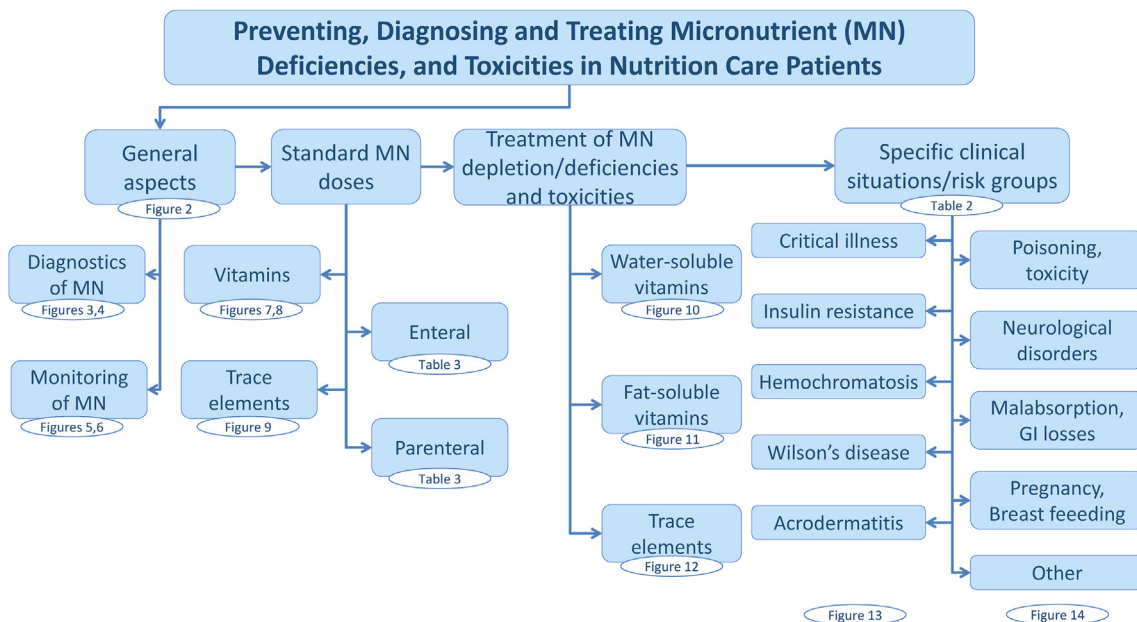


Fig. 1. Structure of the practical Guideline of Micronutrients; Carnitine, Choline and Co-10 have no defined DRIs (they are covered in full version of MN guideline). Abbreviation: MN, micronutrients.

ambiguously. The wording of these recommendations has been made more precise. The recommendations concerned are 2, 4.1, 4.6, 5.3, 7.4, 7.7, 12.6, 15.5, 16.1, 18.1, 20.2, 21.3, 23.3. The transformation to a practical version includes a graphical presentation as flow charts (Figs. 1 and 2). In these flow charts, the recommendations are rearranged according to the topic diagnostics (Figs. 3 and 4), monitoring (Figs. 5 and 6), standard doses for enteral and parenteral nutrition (Figs. 7–9), depletion, deficiency, and toxicity (Figs. 10–12), as well as special situations (Figs. 13 and 14) for which some additions were made for completeness. The respective position in the flow charts is indicated for each recommendation in brackets. The literature recommendations with grade A, B, or O are based on is cited directly below the respective recommendations.

3. Micronutrients status

Defining precisely suboptimal or deficient status is the basis for therapeutic intervention. The term “deficiency” has been used too broadly, being often used as soon as the laboratory returns blood values below the local or international reference range. The new Table 1 provides the definitions that are proposed to qualify the status and the therapeutic interventions. Particular attention is drawn to the definitions of ‘deficiency’ and ‘depletion’.

3.1. Requirements, dosage and treatment considerations

The DRIs are fundamental to inform national nutrition policies and regulations. We have therefore used the definitions of the Food

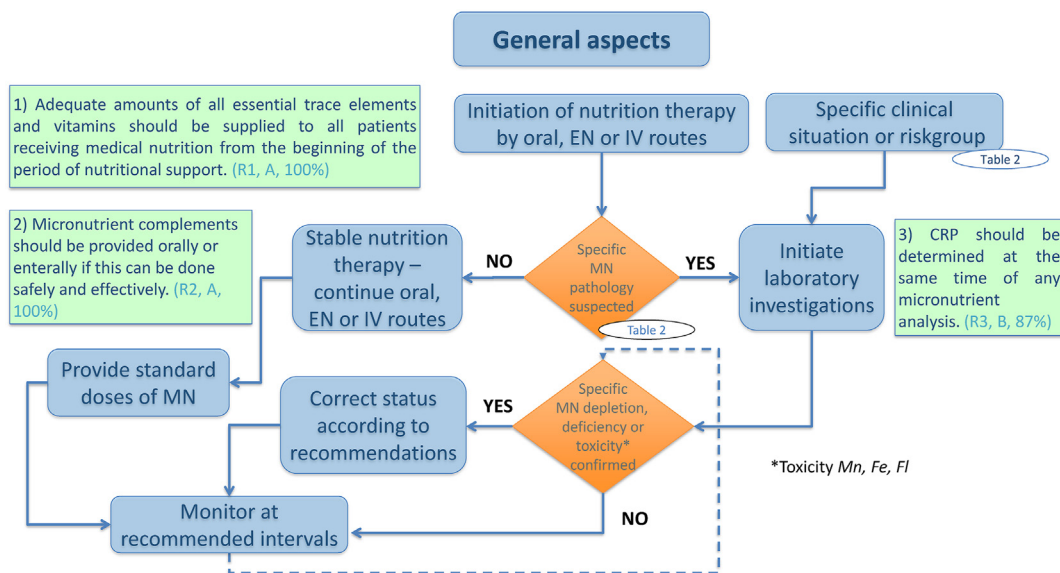


Fig. 2. General strategy for micronutrient handling in clinical practice. Abbreviation: CRP, C-reactive protein; EN, enteral nutrition; MN, micronutrients; IV, intravenous.

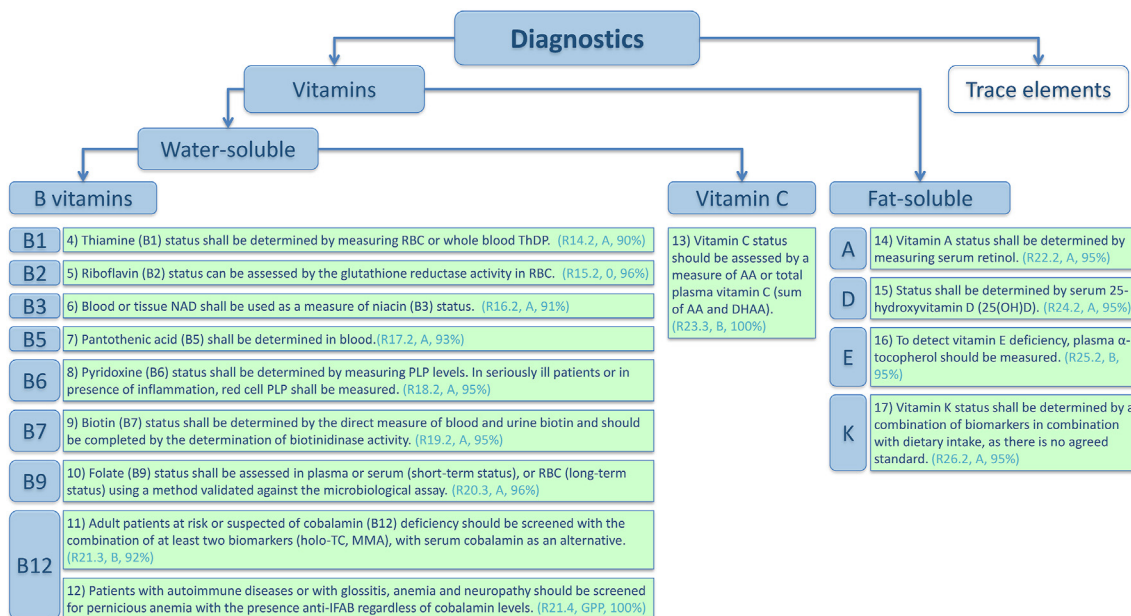


Fig. 3. Diagnostics of vitamins deficiencies. Abbreviations: AA, ascorbic acid; DHA, dehydroascorbic acid; holo-TC, holo-transcobalamin; MMA, methyl malonic acid; NAD, nicotinamid adenine dinucleotide; PLP, pyridoxal phosphate; RBC, red blood cell; ThDP, thiamine diphosphate.

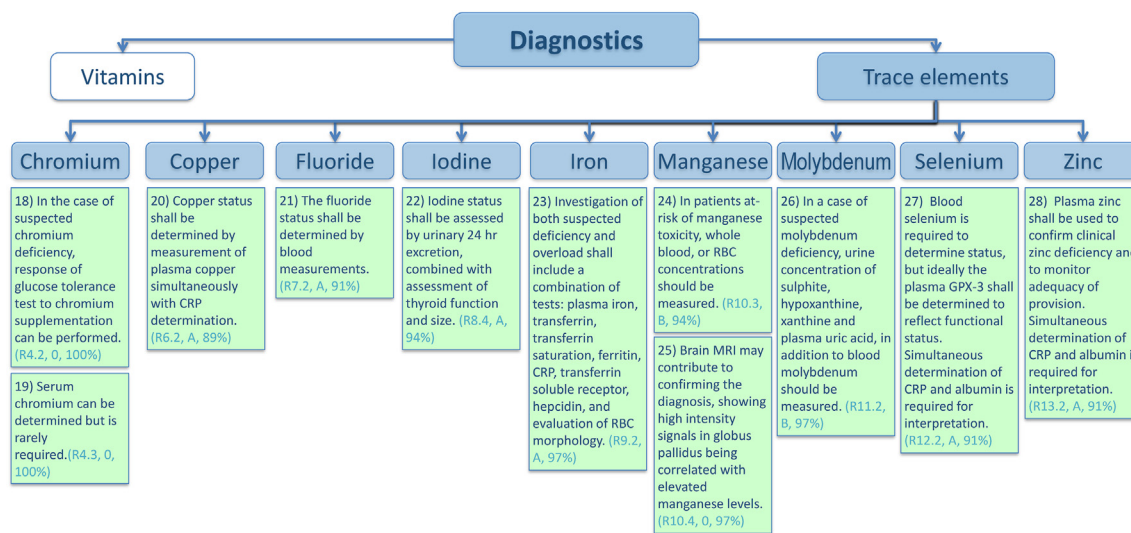


Fig. 4. Diagnosis of trace element disorders. Abbreviations: CRP, C-reactive protein; GPX-3, glutathione peroxidase; PVP-I, povidone iodine; RBC, red blood cell.

and Nutrition Board and the values that are available in clinical settings (Table 1). Whether treating out- or inpatients, there comes a point where MNs need to be prescribed, and a precise wording should be used to characterize it (repletion, complementation, supplementation).

In enteral nutrition (EN), all MN are included in the specific feeding mixtures in a fixed combination, although different commercial preparations may contain different amounts. By choosing a specific enteral product, clinicians can change to some extent the amount of MN provided. The enteral feeding solutions generally deliver all MNs. The ESPEN recommendations are formulated for 1500 kcal/day because this is the most common energy target. But international surveys show that feed delivery is generally below the prescribed target, resulting in lower amounts being frequently delivered [6]. In patients receiving less than 1500 kcal, an additional enteral or intravenous provision of MNs at the start of feeding may

be considered, especially if there is a recent history of poor intake [7,8] (Figs. 7–9).

Parenteral nutrition (PN) is different, as the intestine is bypassed, thereby increasing the risk of both insufficiency (absence of MN) and toxicity, if high doses are delivered by the intravenous (IV) route. Follow-up of patients on long-term PN generated knowledge about the minimal doses to deliver to stable patients [9]. The parenteral nutrition patient population is heterogeneous and fixed doses may not fit individual requirements. In numerous non-European countries, many pre-mixed multi-trace element combinations are incomplete, providing only 4 or 6 trace elements, and still contain doses that are not in keeping with the current knowledge, potentially providing inadequate or excessive quantities of different MNs [10]. This report summarizes our recommendations for input during PN and situations where different amounts may be required (Figs. 7–9).

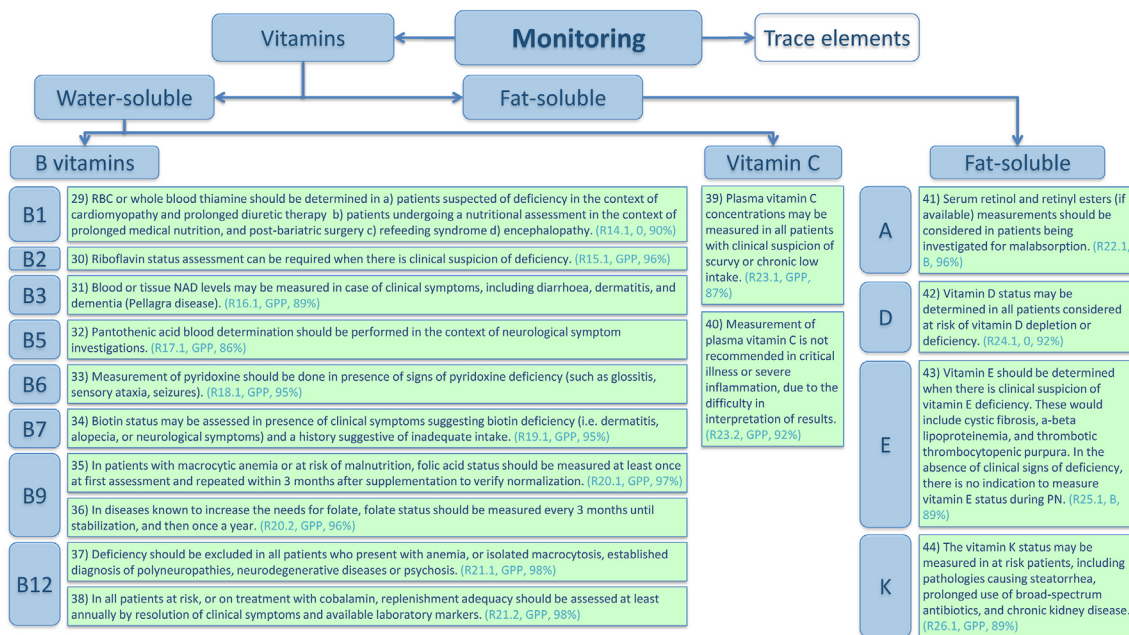


Fig. 5. Monitoring of vitamins. Abbreviations: NAD, nicotinamid adenine dinucleotide; RBC, red blood cell.

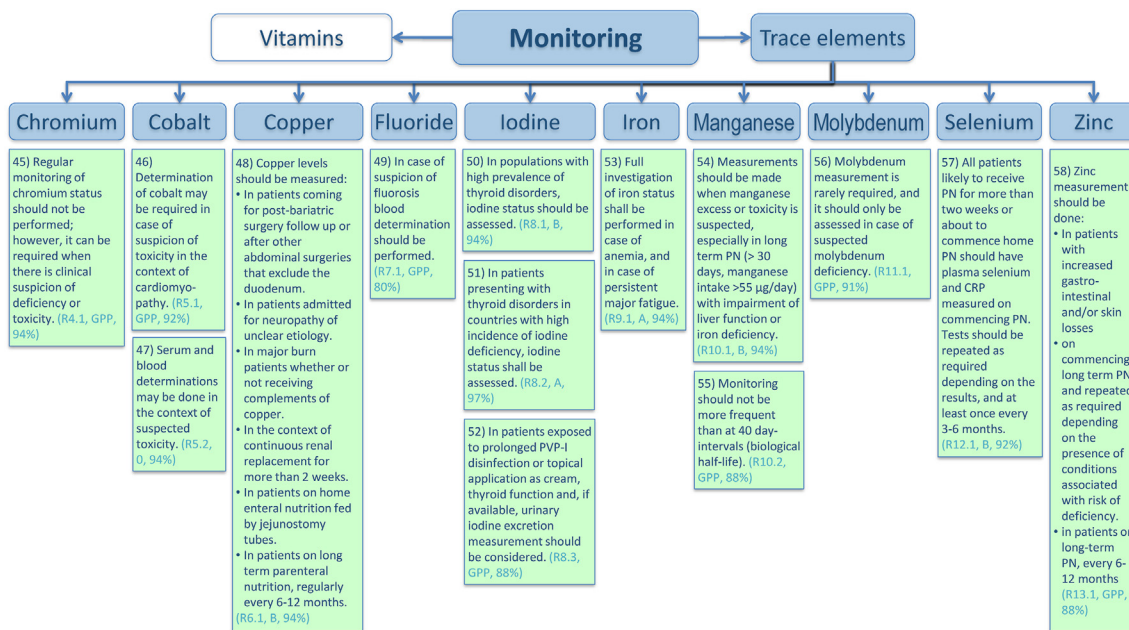


Fig. 6. Monitoring of trace elements. Abbreviations: CRP, C-reactive protein; PVP-I, povidone iodine.

3.2. General comments on provision of micronutrients

Some patients will benefit from “oral nutrition supplements” to complete insufficient oral food intake, whilst not receiving either enteral or parenteral nutrition. Such supplements contain a blend of trace element and/or vitamin preparations, contributing to covering DRI.

An important concept for the water-soluble vitamins is that they have low toxicity and hence most of the recommendations are for a minimal level of supply but increased amounts of all of them would

be safe and effective, although possibly wasteful. As summarized in the ASPEN position paper on MN requirements already in 2012 [10], the rationale for providing higher doses than the minimum calculated to be required IV is that many patients have higher vitamin requirements due to malnutrition, baseline deficiencies, and metabolic changes secondary to illness. Moreover, there is likely to be increased excretion of water-soluble vitamins when provided IV. These considerations remain valid a decade later. Hence for some vitamins, the parenteral recommendation is higher than the enteral as shown in Table 2 [1].

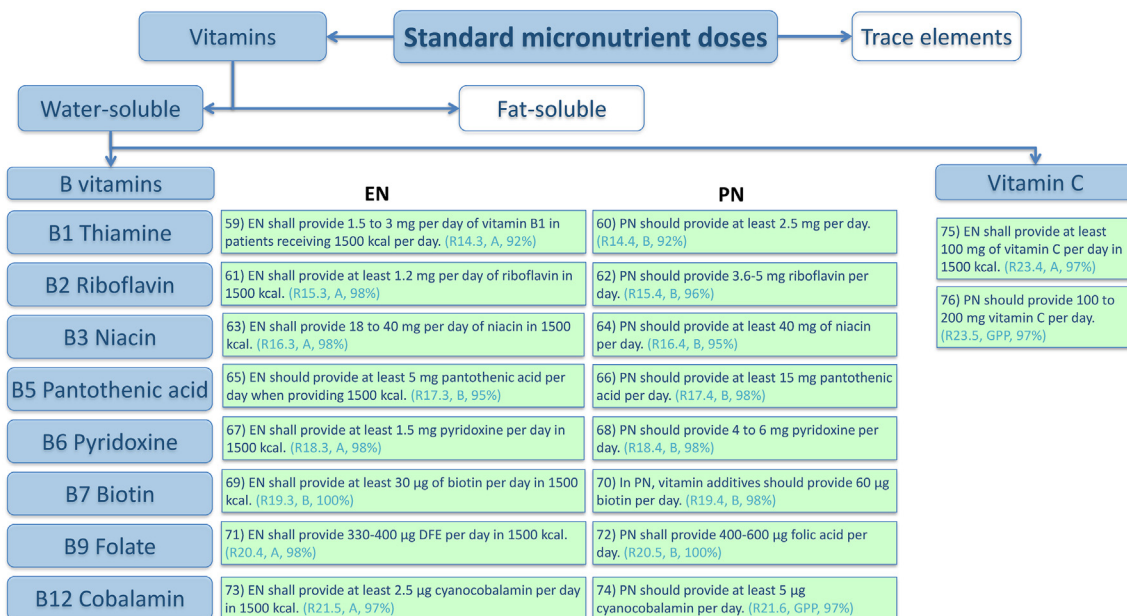


Fig. 7. Standard water-soluble vitamin doses in enteral and parenteral nutrition (for 1500 kcal standard EN and PN). Abbreviation: DFE, dietary folate equivalent.

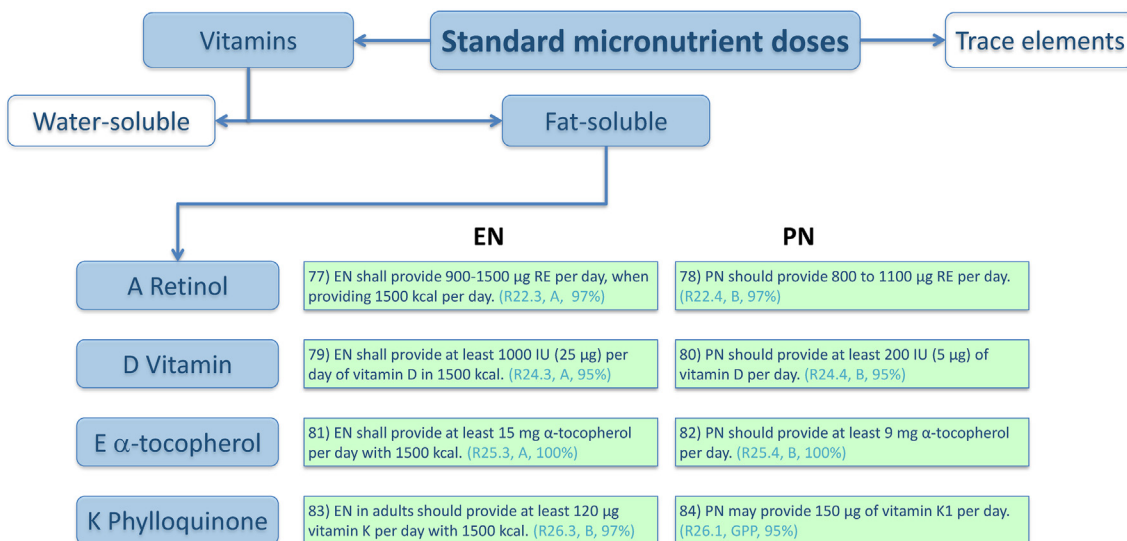


Fig. 8. Standard fat-soluble vitamin doses in enteral and parenteral nutrition (for 1500 kcal standard EN and PN). Abbreviation: RE, retinyl ester.

3.3. Pathologies at risk

The present guidelines deliver MN specific recommendations. Nevertheless, for background, the below Table 3 presents a non-exhaustive list of diseases for which specific MNs deficiencies have been demonstrated. This table aims at raising awareness about some often-overlooked aspects of the different diseases, and at considering a combination of MN determinations.

Finally for certain clinical situations the guideline recommends laboratory measuring of blood MN or biomarker concentrations (Figs. 3 and 4). However, this may not be available promptly in all

centers which may delay clinical decisions. In such cases, whilst awaiting laboratory results, increasing MN intake, or using a multi-MN preparation, with enhanced clinical monitoring for deficiency symptoms and their resolution upon treatment could be the best option.

Independent of MN specificities, the 3 first general recommendations apply to all MN (Fig. 2).

Recommendation 1 (Flowchart N°1)

Adequate amounts of all essential trace elements and vitamins should be supplied to all patients receiving medical nutrition from the beginning of the period of nutritional support.

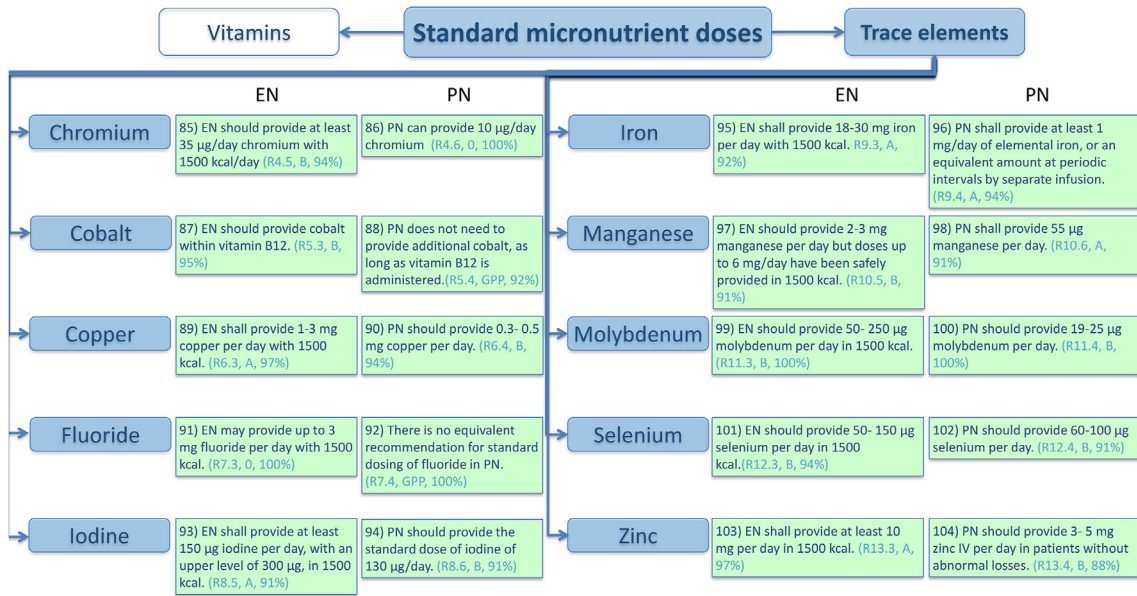


Fig. 9. Standard trace element doses in enteral and parenteral nutrition (for 1500 kcal standard EN and PN). Abbreviation: IV, intravenous.

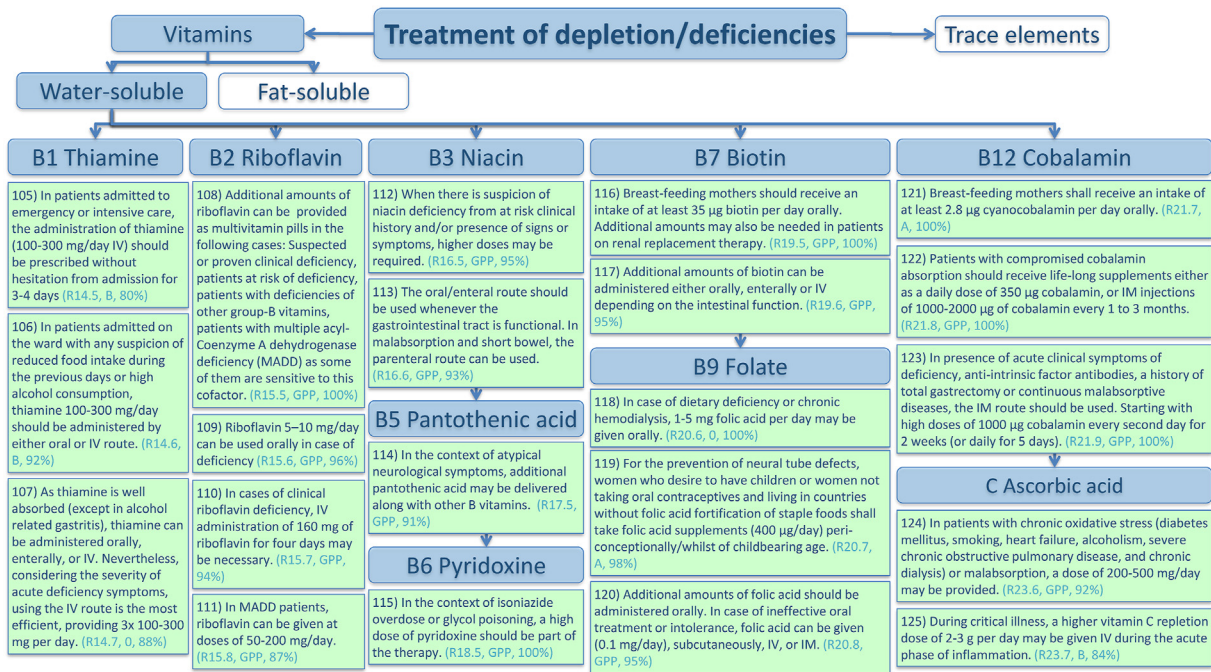


Fig. 10. Treatment guidance of insufficient status of water-soluble vitamins. Abbreviations: IM, intramuscular; IV, intravenous; MADD, multiple acyl-Coenzyme A dehydrogenase deficiency.

Grade of recommendation A – Strong consensus 100 %
Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 2 (Flowchart N°2)

Micronutrient complements should be provided orally or enterally if this can be done safely and effectively.

Grade of recommendation A – Strong consensus 100 %
Grade A awarded based on physiology/biochemistry, not clinical trials.

3.4. Impact of inflammation

The presence of inflammation in the context of surgery, trauma, infection or other acute or chronic diseases, complicates the assessment of the status based on blood levels. Using the surrogate biomarker C-reactive protein (CRP) as an indicator of its intensity, it has been clearly shown that inflammation induces a redistribution of many MNs from the circulating compartment to other organs, resulting in low levels for most MNs [2]. Low blood levels therefore do not necessarily indicate deficiency or even depletion. Within

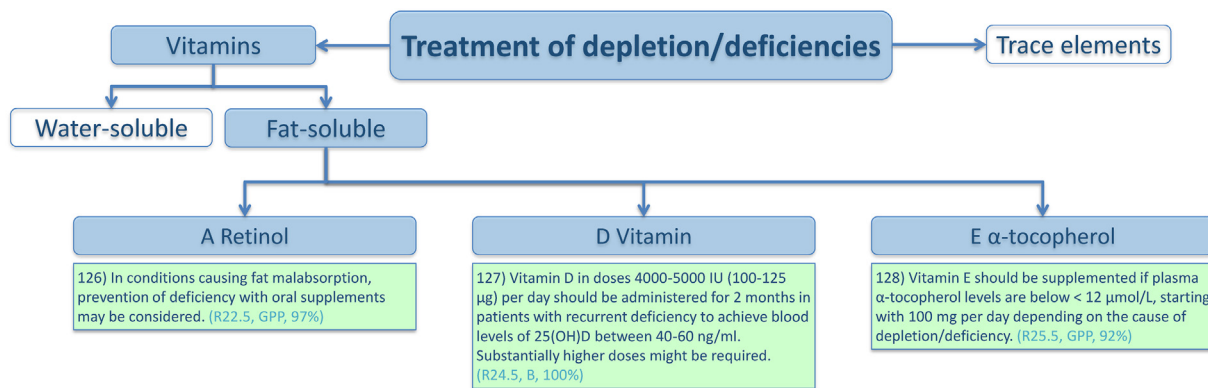


Fig. 11. Treatment of insufficient status of fat-soluble vitamins.

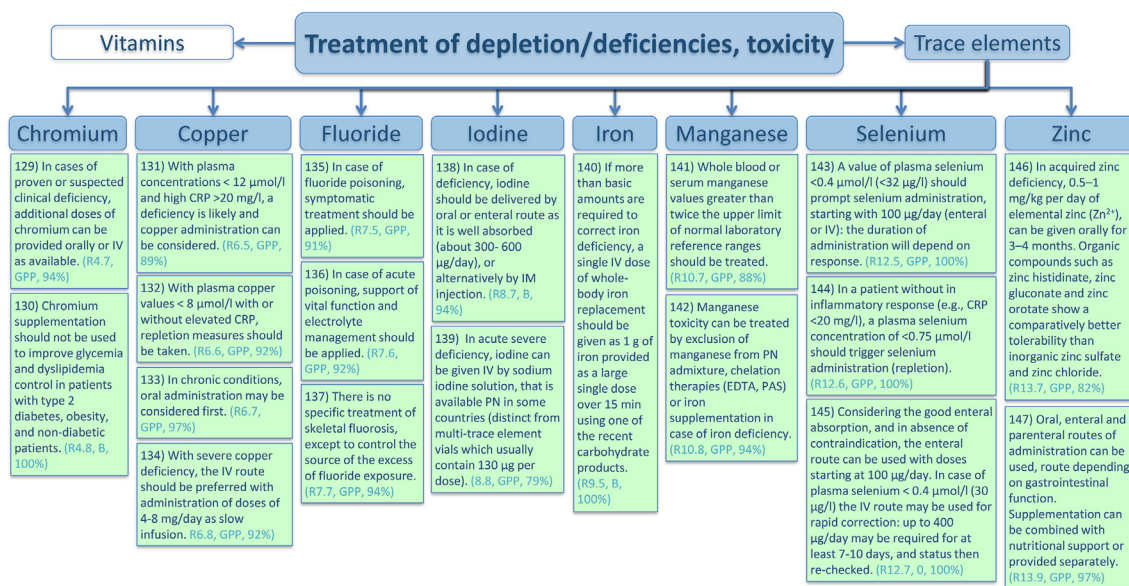


Fig. 12. Treatment guidance including route for insufficient and excess status of trace elements. Abbreviations: CRP, C-reactive protein; IM, intramuscular; IV, intravenous.

24 h of elective surgery in otherwise healthy individuals, plasma concentrations of many trace elements and vitamins have fallen markedly, without any change in whole body MN status [11]. The effects of inflammation in response to acute trauma or infection is usually rapid but may also be prolonged in chronic illness. There are some variations across diseases, and these are discussed with each MN.

Recommendation 3 (Flowchart N° 3)

C-reactive protein should be determined at the same time as any micronutrient analysis.

Grade of recommendation B – Consensus 87 %
Grade A awarded based on physiology, not clinical trials [2,12]

Comment: Single MNs are rarely determined alone. The impact of inflammation usually appears with CRP levels >20 mg/l [3]: therefore high-sensitivity CRP (hs-CRP), which aims at detecting mild inflammation, is not appropriate. Interleukin-6 may be used but is not widely available in clinical settings. Albumin is a carrier protein for many MNs. Its level may be influenced by dilution, and by inflammation, being a negative acute phase protein [11]. Therefore, albumin determination is

also desirable whenever MNs are assessed, as it is the carrier of most MNs.

The availability of optimal analytical methods is essential for diagnosis. The recommended methods are provided in the below Table 4 for trace elements, and in Fig. 3 of the flowchart for vitamins.

4. Chromium

Chromium (Cr) exists in several valence states. While Cr IV, V and VI are carcinogenic, the trivalent chromium is the biologically active, stable form. Insufficient intakes are frequent in industrial countries, and are associated with alterations of glucose metabolism, especially in older adults [13]. Also, at risk of deficiency are patients with acute illness due to metabolic stress (burns, trauma, infection), or patients with decreased absorption/intake (short bowel syndrome and PN without chromium supplementation). Chromium deficiency has been reported in adults with chronic intestinal failure after massive bowel resection receiving long-term PN without chromium [14–17]. The clinical manifestations were glucose intolerance, weight loss, elevated plasma free fatty acids and neuropathy that were reversed by

Specific clinical situations/risk groups – Part 1				
Critical illness	Insulin resistance	Hemochromatosis	Wilson's disease	Acrodermatitis
B1 Thiamine	Chromium	Iron overload	Copper toxicity	Zinc deficiency
148) In patients admitted to emergency or intensive care, the administration of thiamine (100-300 mg/day IV) should be prescribed without hesitation from admission for 3-4 days. (R14.5, B, 80%)	152) Chromium (200-250 µg/day for 2 weeks) can be given parenterally in patients on PN suspected to be deficient in chromium based on insulin-resistance: reassess insulin-resistance after 2 weeks. (R4.8, 0, 100%)	156) In hemochromatosis, and in iron overload conditions, iron stores should be reduced by repeated venesection. (R9.7, B, 94%)	The administration of oral zinc is a validated strategy in Wilson's disease, where blood levels are low, since copper is sequestered in the liver.	158) In acrodermatitis enteropathica, a life-long oral intake of 3 mg/kg per day of elemental zinc (Zn ²⁺) may be provided, with the dosage adjusted accordingly to plasma or serum zinc levels. (R13.8, 0, 94%)
B2 Riboflavin			In acute toxicity, treatment with oral D-penicillamine (250 to 500 mg/day) may be required.	
149) Additional amounts of riboflavin can be provided as multivitamin pills in the following cases: Suspected or proven clinical deficiency, patients at risk of deficiency, patients with deficiencies of other group-B vitamins, patients with multiple acyl-Coenzyme A dehydrogenase deficiency (MADD) as some of them are sensitive to this cofactor. (R15.5, GPP, 100%)	153) In insulin-resistant critically ill patients, chromium with doses ranging from 3–20 µg/h IV for 10 hours and up to 4 days may be required. (R4.9, 0, 100%)		157) Molybdenum may be used to treat copper overload in Wilson's disease as tetrathiomolybdate. (R11.5, GPP, 94%)	
Iron deficiency	154) In the case of suspected chromium deficiency, response of glucose tolerance test to chromium supplementation can be performed. (R4.2, 0, 100%)			
150) In anemic critically ill patients, with iron deficiency confirmed by low hepcidin levels, 1 g of iron provided as one of the recent carbohydrate products should be delivered. (R9.6, B, 100%)	155) In case of severe insulin resistance and hyperglycemia in critically ill patients, a therapeutic trial with IV chromium can also be used to reduce insulin requirements. (R4.8, 0, 100%)			
Zinc in major burns patients				
151) Patients with major burns > 20% body surface area have increased requirements due to exudative losses: 30-35 mg/day IV for 2-3 weeks should be provided. (R13.6, G, 91%)				

Fig. 13. Measurement and/or treatment guidance for micronutrients in risk groups and in special clinical situations. Recommendations in white boxes have not been formally agreed upon: for further explanation see text). Abbreviations: IV, intravenous; MADD, multiple acyl-Coenzyme A dehydrogenase deficiency.

Specific clinical situations/risk groups – Part 2				
Poisoning, toxicity	Neurological disorders	Malabsorption, GI losses	Pregnancy, Breast feeding	Other
Fluoride	B5 Pantothenic acid	B12 Cobalamin	B7 Biotin	E α-tocopherol
159) There is not a specific treatment of skeletal fluorosis, except to control the source of the excess of fluoride exposure. (R7.7, GPP, 94%)	163) In the context of atypical neurological symptoms, additional pantothenic acid may be delivered along with other B vitamins. (R17.5, GPP, 91%)	164) Patients with compromised cobalamin absorption should receive life-long supplements either as a daily dose of 350 µg cobalamin, or IM injections of 1000-2000 µg of cobalamin every 1 to 3 months. (R21.8, GPP, 100%)	167) Breast-feeding mothers should receive an intake of at least 35 µg biotin per day orally. Additional amounts may also be needed in patients on renal replacement therapy. (R19.5, GPP, 100%)	169) Vitamin E should be determined when there is clinical suspicion of Vitamin E deficiency. These would include cystic fibrosis, α-beta lipoproteinaemia, and thrombotic thrombocytopenic purpura. In the absence of clinical signs of deficiency, there is no indication to measure vitamin E status during PN. (R25.1, B, 89%)
Iodine	Copper	A Retinol	B9 Folate	
160) In patients exposed to prolonged PVP-I disinfection or topical application as cream, thyroid function and, if available, urinary iodine excretion measurement should be considered. (R8.3, GPP, 88%)	If ataxia occurs in patients at risk consider Cu deficiency and determine blood levels, and replete if required	165) Serum retinol and retinyl esters (if available) measurements should be considered in patients being investigated for malabsorption. (R22.1, B, 96%)	168) For the prevention of neural tube defects, women who desire to have children or women not taking oral contraceptives and living in countries without folic acid fortification of staple foods shall take folic acid supplements (400 µg/day) periconceptionally/whilst of childbearing age. (R20.7, A, 98%)	
B6 Pyridoxine	Manganese	Zinc		K Phylloquinone
161) In the context of isoniazide overdose or glycol poisoning, a high dose of pyridoxine should be part of the therapy. (R18.5, GPP, 100%)	If Parkinson's like symptoms occur during HPN, manganese levels and delivery should be checked, and adjusted.	166) In patients on PN who have gastrointestinal losses (fistulae, stomas, and diarrhea), while nil per mouth, IV doses up to 12 mg per day can be used and are usually sufficient to maintain the status: this addition will be required for as long as gastrointestinal losses persist. (R13.5, 0, 100%)		170) The vitamin K status may be measured in at risk patients, including pathologies causing steatorrhea, prolonged use of broad-spectrum antibiotics, and chronic kidney disease. (R26.1, GPP, 89%)
Manganese				
162) Manganese toxicity can be treated by exclusion of manganese from PN admixture, chelation therapies (EDTA, PAS) or iron supplementation in case of iron deficiency. (R10.8, GPP, 100%)				

Fig. 14. Measurement and treatment guidance for micronutrients in risk groups and in special clinical situations (recommendations in white boxes have not been formally agreed upon, for further explanation see text).

daily chromium supplementation in the PN solution [18,19]. Chromium insufficiency has been hypothesized to contribute to the development of type 2 diabetes and some studies have revealed a negative relationship between serum chromium and HbA_{1c} levels.

Toxicity depends on the valency: Cr (VI) is carcinogenic, nephrotoxic and causes dermatitis [20]. Both Cr (VI) and Cr (III) are capable of producing ROS (reactive oxygen species) [20]. Ingested trivalent chromium has a low level of toxicity due partially to its poor absorption [14]. Parenteral Cr (III) may have a higher potential

toxicity. Data points to a need to lower the recommended amount of parenteral chromium. It has been suggested that it is not necessary to give extra chromium in patients on PN, due to the widespread contamination in PN components [10,14].

4.1. When and what to measure

Recommendation 4.1: Regular monitoring of chromium status should not be performed; however, it can be required when there is clinical suspicion of deficiency or toxicity.

Table 1
Some important definitions and terminology related to assessment, requirements, and prescription of MN.

	ESPEN Definition	Comments
Definition of the words related to assessment of status		
Depletion	Presence of an objective loss of a MN in body fluids, or intake below standard recommendation with blood/plasma concentrations below reference range (see below).	Clinical signs or symptoms are not present at this stage
Deficiency	Evidence of objective loss of a MN in body fluids, or intake below standard recommendation AND EITHER: Presence of clinical signs or symptoms, compatible with a micronutrient deficiency OR Blood/plasma concentrations below reference range together with metabolic effects of inadequacy	Intake is not meeting losses Depending on the body stores, which vary for each MN, clinical signs of deficiency generally may require many weeks to become visible. Therefore, they are absent in acute conditions, such as intensive care. For example: B1 deficiency can occur in a very short period, whereas B12 deficiency can take months or years to appear
Established terms used to describe micronutrient requirements		
DRI = Dietary reference intake	Set of reference values including EAR, AI, RDA, UL, that, when adhered to, predict a low probability of nutrient inadequacy or excessive intake	DRIs are intended for the general population and will be used to indicate proportions of MNs used particularly in enteral nutrition
PN-DR = PN Daily recommended doses	The doses used in PN are extrapolated from RDAs, bioavailability studies and long-term follow up of patients on home PN. They aim at covering basal needs in most patients. Individual patients may have increased or decreased needs.	The commercially available preparations contain variable amounts of MNs. Growing data indicates that many are outdated providing either too much or too little of particular MNs.
Wording used to describe the type of prescription		
Complement	Complementation will be used to indicate the delivery of micronutrients to cover basal needs (e.g. to complete enteral feeds [8] or PN).	This action is likely to be needed to cover basal needs in case of progressive or insufficient EN
Repletion	Doses aiming to <i>restore a normal status</i> , and where the deficit is known. Sometimes called supplementation but term to be avoided as confusing	The term “Repletion” will be used when deficiency or losses are identified or presumed: the administration aims at restoring a normal status.
Supplementation	Term used when the aim is to deliver higher than standard doses (i.e. superior to DRI or parenteral nutrition recommendation) [122]. The term does not include pharmaco-nutrition but designates doses higher than basal requirements delivered in an attempt to correct depletion or deficiency.	This term is often applied without differentiation of amount whenever a MN is prescribed, which leads to confusion

Abbreviations: AI, adequate intake; EAR, estimated average requirement; EN, enteral nutrition; MN, micronutrient; PN, parenteral nutrition; RDA, recommended dietary allowance; UL, tolerable upper intake levels.

Grade or recommendation GPP – Strong consensus 94 % (No. 45)

Comment: Insufficient intakes are frequent in industrial countries, and are associated with alterations of glucose metabolism, especially in older adults [13].

Recommendation 4.2: In the case of suspected chromium deficiency, response of glucose tolerance test to chromium supplementation can be performed.

Grade of recommendation 0 – Strong consensus 100 % (No. 18, No. 154)
References [13,19]

Recommendation 4.3: Serum chromium can be determined but is rarely required.

Grade of recommendation 0 – Strong consensus 100 % (No. 19)
References [13,21–23]

Table 2
Disease-specific risks of depletion or deficiency in trace elements and vitamins.

Disease	Deficiency favouring disease development	Inadequacy or deficit worsening the condition	Deficiency as a result of disease
Alcoholism		B1, Fe	A, D, E, K, B1, B2, B6, B7, B9, B12, C, Zn
Alcoholic hepatitis	B6, Zn	Fe, Zn	
Anaemia	B1, B6, B9, B12, Fe, Cu, Co		
Cancer cachexia	D, Zn		
Cardiomyopathies/Heart failure	B1, B6, D, Se, Fe	Se	
Chronic obstructive pulmonary disease	D, Cu, Se, Mn, Zn		
Chronic intestinal failure			B2, B7, B9, B12, A, D, E, K, Cu, Fe, Zn
Atrophic gastritis			B9, B12, C, D, Fe
Diabetes mellitus	B9, Cr		
Inflammatory bowel diseases		Zn	B1, B6, B12, A, D, E, K, Fe, Se, Zn
Non-alcoholic fatty liver disease	Cu		
Liver diseases		Zn	B12, A, D, E, Se, Zn
Multiple sclerosis	B7		
Obesity	β-carotene, E, Se, Zn	B1, B9, D, Fe, Se, Zn	
Obesity Post Bariatric surgery			A, D, E, K, B1, B9, B12, C, Cu, Zn, Fe
Osteoporosis	B12, D, K, Cu, Fe, Zn, Mn, F, Bo		
Renal failure (chronic)			B1, B6, B9, K, D, Cu, Se, Zn
Sarcopenia	B1, B12, D, Zn, carnitine	D, Se, Zn	
Critical illness		B1, C, D, Cu, Fe, Se, Zn	B1, B12, Cr, D, Fe, Se, Zn

Note: the below list of diseases associated with known alterations of MNs is non-exhaustive (alphabetic order) and may in some cases be less fully supported by the evidence. These and other diseases may have further or still unknown associations with various MN inadequacies. For detailed references see original MN guideline [1].

Table 3
ESPEN Recommendations for daily trace element and vitamin intakes – 2022 (all values are per day).

	PN Home & long-term A	PN high requirements ^a B	EN in 1500 kcal ^b C	EN high requirements in 1500 kcal ^c	DRI per day Age 31->70 years	EC directive ^d : Min-max per 1500 kcal
Trace elements						
Chromium	10–15 µg	15 µg	35–150 µg	200 µg	20–35 µg	18.75–225 µg
Copper	0.3–0.5 mg	0.5–1.0 mg	1–3 mg	Same as C	0.9 mg	0.9–7.5 mg
Fluoride	0–1 mg	Same as A	0–3 mg	3–4 mg	3–5 mg (AI)	0–3 mg
Iodine	130 µg	Same as A	150–300 µg	Same as C	150 µg	97.5–525 µg
Iron	1.0 mg	Same as A	18–30 mg	30 mg	8 mg (18 mg F 19–50 yrs)	7.5–30 mg
Manganese	55 µg	Same as A	2–3 mg	Same as C	1.8–2.3 mg	0.75–7.5 mg
Molybdenum	19–25 µg	Same as A	50–250 µg	250 µg	45 µg	52.5–270 µg
Selenium	60–100 µg	150–200 µg	50–150 µg	200 µg	55 µg	37.5–150 µg
Zinc	3–5 mg	6–12 mg	10–20 mg	20 mg	8–11 mg	7.5–22.5 mg
Lipo-soluble vitamins						
A Retinole	800–1100 µg	1100 µg	900–1500 µg	1500 µg	700–900 µg	525–2700 µg
D3 Cholecalciferol	200 IU/5 µg	800–1000 IU/20–25 µg	25 µg	30 µg	15–20 µg	7.5–37.5 µg
E α-tocopherol	≥9 mg	20–25 mg	15 mg	40 mg	15 mg	7.5–45 mg
K2 menaquinone	150 µg ^f	1–10 mg ^g	120 µg	Same as C	90–120 µg	52.5–300 µg
Water-soluble vitamins						
B1 Thiamine	Provide at least ^h	100–200 mg	Provide at least ^h	100 mg	1.1–1.2 mg	0.9–7.5 mg
B2 Riboflavin	2.5 mg	10 mg	1.5 mg	10 mg	1.1–1.3 mg	1.2–7.5 mg
B3 Niacin	3.6 mg	Same as A	1.2 mg	40 mg	11–16 mg	13.5–45 mg
B5 Pantothenic acid	40 mg	Same as A	18 mg	7.5 mg	5 mg	2.25–22.5 mg
B6 Pyridoxine	15 mg	Same as A	5 mg	7.5 mg	1.5–1.7 mg	1.2–7.5 mg
B7 Biotin	4 mg	Same as A	1.5 mg	75 µg	30 µg (AI)	11.25–112.5 µg
B9 Folic acid	60 µg	Same as A	30 µg	500 µg	400 µg DFE	150–750 µg
B12 Cyanocobalamin	400 µg	600–1000 µg	330–400 µg DFE	7.5 µg	2.4 µg	1.05–10.5 µg
C Ascorbic acid	5 µg	Same as A	>2.5 µg	200 mg	7.5–90 mg	33.75–330 mg

Abbreviations: EN = enteral nutrition, FSMP = Foods for Special Medical Purposes, PN = parenteral nutrition, AI = Adequate Intake, DFE = dietary folate equivalent.

^a : Increased requirements may occur in patients with on-going increased losses such as gastrointestinal losses, continuous renal replacement therapy, those who are hypermetabolic or who are depleted before commencing PN, and in pregnancy.

^b : The 1500 kcal value has been chosen based on numerous studies confirming that this value seems to be a very common objective. In case of higher nutrient delivery (e.g. 2000 kcal per day or more), exceeding this recommendation is not exposing the patient to any risk considering upper tolerable levels.

^c : increased requirements during critical illness and in patients with acute admission with malnutrition (NRS ≥5); intended for max 15 days as repletion, to avoid requiring IV supply.

^d : The EC directive.

^e : Retinol includes retinol and retinyl ester.

^f : During PN, vitamin K requirements are usually provided by the lipid emulsions.

^g : High dose administered in case of coagulopathy (not nutrition-related).

^h : For water-soluble vitamins, amounts recommended are minimum amounts, and more can usually be safely delivered.

4.2. How much to provide in typical EN and PN

Recommendation 4.4: Enteral nutrition should provide at least 35 µg/day chromium with 1500 kcal/day.

Grade of recommendation B – Strong consensus 94 % (No. 85)

Grade B awarded based on DRI/RDA, not clinical trials

Recommendation 4.5 Parenteral nutrition can provide at least 10 µg per day

Grade of recommendation 0 – Strong consensus 100 % (No. 86)
References [16,17,24–26]

Comment: the requirement in PN is still debated, especially since absorption of chromium is low, and no trials have been

Table 4
Recommended analytical methods.

Chromium	Chromium status assessment is based on determination of serum and urine levels using ICP-MS. Serum chromium can be determined but is rarely required.
Copper	Several methods are available: the most precise and applicable to biological fluids is ICP-MS, although atomic absorption spectroscopy is also frequently used
Fluoride	Analytical methods use a fluoride-specific electrode (urine), flow injection analysis coupled with a fluoride-specific electrode (serum and urine) (FIA-FE), or by ion chromatography with conductivity detection (IC-CD)
Iodine	Iodine status is best determined by 24 h urine collections. Classically, deficiency diagnosis is based on urinary excretion of iodine <100 µg/24 h. Analytical methods consist in selective electrode (iodide), a chemical method (total iodine) or more recently on ICP-MS. Iodine may also be determined in serum by ICP-MS
Iron	Iron status assessment requires the simultaneous determination of hemoglobin, ferritin (storage form of iron), transferrin saturation and total Iron-binding capacity, and occasionally bone marrow iron staining. The most recent methods include the determinations of hepcidin, zinc protoporphyrin, and soluble transferrin receptor
Manganese	Manganese status is best assessed by whole blood or RBC concentration measured by ICP-MS or atomic absorption spectroscopy. Plasma or serum concentration can also be measured
Molybdenum	Molybdenum can be determined in blood, urine or hair by ICP-MS, and also by neutron activation analysis
Selenium	Selenium status is most commonly obtained from plasma or whole blood selenium measurement by CFAAS or ICP-MS. Selenoprotein P and plasma glutathione peroxidase (GPX3) are more accurate measures of whole-body status
Zinc	Total zinc can be measured in whole blood, plasma, serum, urine, or hair preferably by ICP-MS, or by atomic absorption spectroscopy

Abbreviations: CFAAS, carbon furnace atomic absorption spectrometry; FIA-FE, flow injection analysis coupled with a fluoride-specific electrode; GPX3, glutathione peroxidase; IC-CD, ion chromatography with conductivity detection; ICP-MS, inductively coupled plasma mass spectrometry; RBC, red blood cell.

performed with lower doses. The above doses have been used safely and effectively in adults for many years. More research on chromium is required.

4.3. When and how to provide additional amounts

Recommendation 4.6: In cases of proven or suspected clinical deficiency, additional doses of chromium can be provided orally or IV as available.

Grade of recommendation GPP – Strong consensus 94 % (No. 129)

Recommendation 4.7: Chromium supplementation should not be used to improve glycemia and dyslipidemia control in patients with type 2 diabetes, obesity, and non-diabetic patients.

Grade of recommendation B – Strong consensus 100 % (No. 130)
References [18,27–31]

Recommendation 4.8: In case of severe insulin resistance and hyperglycemia in critically ill patients, a therapeutic trial with IV chromium can also be used to reduce insulin requirements.

Grade of recommendation O – Strong consensus 100 % (No. 155)
References [21–23]

Comment: A low plasma chromium level is associated with hyperglycemia, insulin resistance, high inflammatory status and increased cardiovascular risk in humans [18,19]. These recommendations are not applicable to general diabetic patients, but only for critically ill patients, in case of increasing insulin doses (30–50 U/hour of insulin required to maintain blood glucose <10 mmol/l). Such a trial is limited to 4 days [21–23].

Recommendation 4.9: Chromium (200–250 µg/day for 2 weeks) can be given parenterally in patients on parenteral nutrition suspected to be deficient in chromium based on insulin-resistance: reassess insulin-resistance after 2 weeks.

Grade of recommendation O – Strong consensus 91 % (No. 152)
References [21–23].

Recommendation 4.10: In insulin-resistant critically ill patients, chromium with doses ranging from 3 to 20 µg/h IV for 10 h and up to 4 days may be required.

Grade of recommendation O – Strong consensus 100 % (No. 153)
References [21–23].

5. Cobalt

Cobalt is a rare element with properties like iron and nickel. It is essential for the formation of vitamin B12 [32]. All the essential functions of cobalt are covered in the chapter about vitamin B12.

5.1. When and what to measure

Recommendation 5.1: Determination of cobalt may be required in case of suspicion of toxicity in the context of cardiomyopathy.

Grade or recommendation GPP – Strong consensus 92 % (No. 46)

Recommendation 5.2: Serum and blood determinations may be done in the context of suspected toxicity.

Grade of recommendation O – Strong consensus 94 % (No. 47)
Grade O awarded based on biochemistry, not clinical trials [32]

Comment: Human beings may be exposed to cobalt through occupational contact (glass, inks, and paints), in processing plants, hard-metal industry, diamond polishing, and the manufacture of ceramics. In cases of suspected cobalt toxicity, the assessment of the status is based on determination of serum [33] and urine levels [34,35] using inductively coupled plasma mass spectrometry (ICP-MS).

5.2. How much to provide in typical EN and PN

Recommendation 5.3: Enteral nutrition should provide cobalt within vitamin B12.

Grade of recommendation B – Strong consensus 95 % (No. 87)
Grade B awarded based on physiology/biochemistry (no DRI), not clinical trials [36,37],

Recommendation 5.4: Parenteral nutrition does not need to provide additional cobalt, as long as vitamin B12 is administered.

Grade of recommendation GPP – Strong consensus 92 % (No. 88)

6. Copper

Copper exists in two different redox states: the oxidized cupric (Cu²⁺) and reduced cuprous (Cu⁺) forms. It serves as an essential catalytic cofactor in redox chemistry for proteins involved in growth and development [38], and as an essential cofactor for oxidation–reduction reactions involving copper-containing oxidases. Absorption occurs in the stomach and small intestine, primarily in the duodenum [39], and is highly regulated.

Copper depletion is observed in some acute conditions such as major burns, after gastric and bariatric surgery, and in patients requiring continuous renal replacement therapy, or in prolonged PN or EN without adequate copper [40–46]. Symptoms of deficiency require some weeks to develop and are not readily recognized. The acute symptoms include cardiac arrhythmias, myeloneuropathy, and delayed wound healing [45,47]. The chronic symptoms include microcytic anemia, neutropenia, osteoporosis, ataxia, and hair de-pigmentation [47].

Supra-normal blood levels are observed in inflammatory conditions, reflecting the increase in ceruloplasmin. Elevated copper levels exist in Alzheimer's disease [48], and are observed in pathologies such as infections, hemopathies, haemochromatosis, hyperthyroidism, liver cirrhosis and hepatitis, and physiologically, in pregnancy.

Intoxication is rare but may occur in an industrial context. Cholestasis can also affect the liver's ability to excrete copper, resulting in chronic copper toxicity [49]. It is also increased in genetic disorders such as Wilson's disease, and in Menke's syndrome [49]. Toxicity symptoms include hematemesis, hypotension, melena (black "tarry" feces), coma, headaches, behavioral changes, fever, diarrhea, abdominal cramps, brown ring-shaped markings in eyes (Kayser-Fleischer rings), and jaundice. Not included as a recommendation in the 2022 guideline, but considering its importance we include in Fig. 13 for completeness the first line therapy of Wilson's disease with hepatic neurological and symptoms, which is penicillamine and zinc salts [50]:

tetrathiomolybdate (R11.5) is a strong decoppering agent but remains an experimental therapy, as clinical experience is limited.

6.1. When and what to measure

Recommendation 6.1: Copper levels should be measured:

- In patients coming for post-bariatric surgery follow up or after other abdominal surgeries that exclude the duodenum.
- In patients admitted for neuropathy of unclear etiology.
- In major burn patients whether receiving, or not, complements of copper.
- In the context of continuous renal replacement for more than 2 weeks.
- In patients on home enteral nutrition fed by jejunostomy tubes.
- In patients on long term parenteral nutrition, regularly every 6–12 months.

Grade of recommendation B – Strong consensus 94 % (No. 48)

References [41,46,51–54]

Comment: If ataxia occurs in patients at risk (see R6.1), copper deficiency should be considered with determination of blood levels, followed by repletion if confirmed. The increasing number of reports of neurological symptoms after bariatric surgery made it important to insert it among MN related neurological disorders (Fig. 13).

Recommendation 6.2: Copper status shall be determined by measurement of plasma copper simultaneously with CRP determination.

Grade of recommendation A – Consensus 89 % (No. 20)

Grade A awarded based on biochemistry, not clinical trials.

Comment: Copper, a long-ignored trace element, is an essential catalytic cofactor in redox chemistry for proteins involved in growth and development [55], and as an essential cofactor for oxidation–reduction reactions involving copper-containing oxidases. Copper concentrations in plasma increase in the context of an inflammatory response since ceruloplasmin is a positive acute phase reactant [2]. A normal serum copper in the presence of an elevated CRP would suggest copper depletion or deficiency. In case of uncertainty, ceruloplasmin concentrations will assist diagnosis, as low values of the latter provide confirmation of deficiency.

6.2. How much to provide in typical EN and PN

Recommendation 6.3: Enteral nutrition shall provide 1–3 mg copper per day with 1500 kcal.

Grade of recommendation A – Strong consensus 97 % (No. 89)

Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 6.4: Parenteral nutrition should provide 0.3–0.5 mg copper per day.

Grade of recommendation B – Strong consensus 94 % respectively (No. 90)

Recommendations [42,43,56]

6.3. When and how to provide additional amounts

Recommendation 6.5: With plasma concentrations <12 $\mu\text{mol/l}$ and high CRP >20 mg/l, a deficiency is likely and copper administration can be considered.

Grade of recommendation GPP – Consensus 89 % (No. 131)

Recommendation 6.6: With plasma copper values < 8 $\mu\text{mol/l}$ with or without elevated CRP, repletion measures should be taken.

Grade of recommendation GPP – Strong consensus 97 % (No. 132)

Recommendation 6.7: In chronic conditions, oral administration may be considered first.

Grade of recommendation GPP – Strong consensus 94 % (No. 133)

Recommendation 6.8: With severe copper deficiency, the IV route should be preferred with administration of doses of 4–8 mg/day as slow infusion.

Grade of recommendation GPP – Strong consensus 92 % (No. 134)

7. Fluoride

Fluoride is an abundant element [57], occurring in soils, rocks, and water: it is therefore naturally present in the food and drink we consume. Its status as “essential” is debated. Reported unequivocal signs of fluoride deficiency are almost non-existent. Pharmacological doses prevent caries.

Chronic toxicity is most frequent, and may present as gastric complaints, anemia, osteomalacia, teeth problems, and neuromuscular and gastrointestinal symptoms. Chronic toxicity has been observed along with excessive water supplies and industrial exposures (excess of 2 mg/day) resulting in dental fluorosis and mottled enamel. Skeletal fluorosis is a rare toxic osteopathy characterized by massive bone fluoride fixation that occurs with doses 10–25 mg/day for many years. The disease is an endemic problem in some parts of the world [58,59]. In patients on home PN for chronic intestinal failure, high blood fluoride values due to high fluoride intakes from drinking water have been reported [60].

7.1. When and what to measure

Recommendation 7.1: In case of suspicion of fluorosis blood determination should be performed.

Grade of recommendation GPP – Consensus 88 % (No. 49)

Recommendation 7.2: The fluoride status shall be determined by blood measurements.

Grade of recommendation A – Strong consensus 91 % (No. 21)

Grade A awarded based on biochemistry, not clinical trials.

7.2. How much to provide in typical EN and PN

Recommendations 7.3: Enteral nutrition may provide up to 3 mg fluoride per day with 1500 kcal.

Grade of recommendation 0 – Strong consensus 100 % (No. 91)

Grade 0 awarded based on DRI/RDA, not clinical trials (absence of DRI).

Recommendations 7.4: There is no equivalent recommendation for standard dosing of fluoride in parenteral nutrition.

Grade of recommendation GPP – Strong consensus 100 % (No. 92)

Comment: There is no DRI. Fluoride is not essential in children nor in adults. Adults typically consume <0.5 mg of fluoride daily in food [61]. Nutritional intakes in adults are safe up to 4 mg/day in men and 3 mg/day in women. Although not essential in adult PN, 0.95 mg per day has been provided without any complication and may be continued. It is not provided in North America.

7.3. When and how to treat

Recommendation 7.5: In case of fluoride poisoning, symptomatic treatment should be applied.

Grade of recommendation GPP – Strong consensus 91 % (No. 135)

Recommendation 7.6: In case of acute poisoning, support of vital function and electrolyte management should be applied.

Grade of recommendation GPP – Strong consensus 97 % (No. 136)

Recommendation 7.7: There is not a specific treatment of skeletal fluorosis, except to control the source of the excess of fluoride exposure.

Grade of recommendation GPP Strong consensus 94 % (No. 137)

8. Iodine

Iodine plays a central role in thyroid physiology, being both a major constituent of thyroid hormones and a regulator of thyroid gland function. Importantly, healthy thyroid function depends also on an adequate provision of selenium (liver deiodination) and iron (metabolism) at any age.

Iodine deficiency disorders represent a global health threat to individuals and societies, including affluent countries in Europe, and impose a significant burden on public healthcare systems. Severe iodine deficiency causes goiter and hypothyroidism [62]. Iodine deficiency increases the risk of developing autonomous thyroid nodules that are unresponsive to TSH control [63].

Moreover, iodine deficiency during pregnancy and breastfeeding adversely affects the development of the child [64,65]. Even mild or moderate iodine deficiency in the mother affects the synthesis of thyroid hormones and may impair brain development. During pregnancy, women have a sharply increased need for iodine, which is frequently not covered by food sources and iodine supplements. Patients on long-term PN may be at risk of deficiency [66].

8.1. When and what to measure

Recommendation 8.1: In populations with high prevalence of thyroid disorders, iodine status should be assessed.

Grade of recommendation B – Strong consensus 94 % (No. 50) Reference [67]

Recommendation 8.2: In patients presenting with thyroid disorders in countries with high incidence of iodine deficiency, iodine status shall be assessed.

Grade of recommendation A – Strong consensus 97 % (No. 51) References [67–70]

Recommendation 8.3: In patients exposed to prolonged povidone iodine (PVP–I) disinfection or topical application as cream, thyroid function and, if available, urinary iodine excretion measurement should be considered.

Grade of recommendation GPP - Consensus 88 % (No. 52, No. 160)

Recommendation 8.4: Iodine status shall be assessed by urinary 24-h excretion, combined with assessment of thyroid function and size.

Grade of recommendation A – Strong consensus 94 % (No. 22) Grade A awarded based on biochemistry, not clinical trials.

Comment: Iodine deficiency is a persistent public health problem in Europe [71] and in the World. Classically, deficiency diagnosis is based on urinary excretion of iodine <100µg/24 h: the measurement is not usually available in hospitals. Iodine status evaluation can be considered in patients with hyperthyroidism or hypothyroidism and prolonged topical iodine exposure after having excluded other etiological factors. Serum thyroid stimulating hormone (TSH) is not a sensitive indicator of iodine status whether in children or adults, as concentrations are usually maintained within a normal range despite frank iodine deficiency [63].

8.2. How much to provide in typical EN and PN

Recommendation 8.5: Enteral nutrition shall provide at least 150 µg iodine per day, with an upper level of 300 µg, in 1500 kcal.

Grade of recommendation A – Strong consensus 91 % (No. 92) Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 8.6: Parenteral nutrition should provide the standard dose of 130 µg/day.

Grade of recommendation B – Strong consensus 91 % (No. 93) References [52,66–68,72]

8.3. How to provide additional amounts

Recommendation 8.7: In case of deficiency, iodine should be delivered by oral or enteral route as it is well absorbed (about 300–600 µg/day), or alternatively by IM injection.

Grade of recommendation B – Strong consensus 94 % (No. 138) Reference [73]

Recommendation 8.8: In acute severe deficiency, iodide can be given IV by sodium iodide solution, that is available for parenteral nutrition in some countries (distinct from multi-trace element vials which usually contain 130 µg per dose).

Grade of recommendation GPP – Consensus 79 % (No. 139)

9. Iron

Iron (Fe) is the most abundant trace element in the human body. The two most common iron states are the divalent ferrous (Fe²⁺) and the trivalent ferric (Fe³⁺). It is required for most, if not all, pathways for energy and substrate metabolism [74]. The main

function of iron is as a functional component of heme, participating in oxygen binding and transport (hemoglobin, myoglobin), oxygen metabolism (catalases, peroxidases), cellular respiration and electron transport (cytochromes) [74–76].

Worldwide, iron deficiency is the most common nutritional deficiency, affecting hundreds of millions of people [77,78]. It has economic consequences as it reduces working capacity, increasing sick leave, and being often incorrectly treated [79].

Iron depletion and deficiency progresses through several stages [80,81]. Storage depletion is characterized by decreasing serum ferritin concentrations and levels of iron in bone marrow. In Marginal deficiency, iron stores are depleted, iron supply to erythropoietic cells and transferrin saturation are reduced, but hemoglobin parameters remain within the normal range. When iron deficiency anemia develops, the stores are exhausted; hematocrit and levels of hemoglobin decline; and the resulting microcytic, hypochromic anemia is characterized by small RBC [79].

Iron overload: The most common causes are hereditary hemochromatosis (*HFE*-associated), and other rare genetic disorders, but it may develop secondary to transfusion (Thalassemia, etc). The signs and symptoms of overload are non-specific [82], and include chronic fatigue, joint pain, and diabetes: the disorder evolves towards end-organ failure, involving particularly the pancreas and liver [83].

9.1. When and what to measure

Recommendation 9.1: Full investigation of iron status shall be performed in case of anemia, and in case of persistent major fatigue.

Grade of recommendation A – Strong consensus 94 % (No. 53)
References [78–81]

Recommendation 9.2: Investigation of both suspected deficiency and overload shall include a combination of tests: plasma iron, transferrin, transferrin saturation, ferritin, CRP, transferrin soluble receptor, hepcidin, and evaluation of red blood cell (RBC) morphology.

Grade of recommendation A – Strong consensus 97 % (No. 23)
Grade A awarded based on biochemistry, not clinical trials.

9.2. How much to provide in typical EN and PN

Recommendation 9.3: Enteral nutrition shall provide 18–30 mg iron per day with 1500 kcal.

Grade of recommendation A – Strong consensus 94 % (No. 95)
Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 9.4: Parenteral nutrition shall provide at least 1 mg/day of elemental iron, or an equivalent amount at periodic intervals by separate infusion.

Grade of recommendation A – Strong consensus 92 % (No. 96)
References [84–86].

Comment: This recommendation is high for men and postmenopausal women, but the modestly higher doses provided are likely to be beneficial and not harmful considering the high prevalence of iron deficiency. While nutritional doses shall be provided to any patients whatever the inflammatory status, additional iron

high-dose supplementation to correct deficiency during infections and hemato-oncologic disease has been associated with a 1.16 RR of infection [87]: this risk shall be balanced against the consequences of deficiency. If countries do not have iron containing multi-trace element products the above alternative should apply. In patients with low body weight (<40 kg), the 1 mg per day dose should be adapted.

9.3. When and how to provide additional amounts

Recommendation 9.5: If more than basic amounts are required to correct iron deficiency, a single IV dose of whole-body iron replacement should be given as 1 g of iron provided as a large single dose over 15 min using one of the recent carbohydrate products.

Grade of recommendation B – Strong consensus 100 % (No. 140)
References [88,89]

Comment: When IV iron is required, risk minimization should be addressed: anaphylactoid reactions during iron infusions are rare (<1:250,000 administrations with recent formulation) but may be life threatening [90,91]. There are many forms of iron suitable for IV use. Iron sucrose and ferric gluconate are widely used but may require multiple administration. As iron is strongly bound to carbohydrates (carboxymaltose, ferumoxytol, isomaltoside, gluconate, sucrose, low molecular weight iron dextran), the amount of labile iron is low, allowing the rapid administration of large single doses [89,91–94]. The risk is highest with high molecular weight iron dextran. The best studied example is ferric carboxymaltose, infused over 15 min [88,95].

Recommendation 9.6: In anemic critically ill patients, with iron deficiency confirmed by low hepcidin levels, 1 g of iron provided as one of the recent carbohydrate products should be delivered.

Grade of recommendation B – Strong consensus 100 % (No. 150)
References [92–94,96]

Comment: considering the above-mentioned relative risk of infection, such repletion should be undertaken when inflammation abates, and patient is close to discharge.

9.4. When to provide reduced amounts

Recommendation 9.7: In hemochromatosis, and in iron overload conditions, iron stores should be reduced by repeated venesection.

Grade of recommendation B – Strong consensus 94 % (No. 156)
References [97,98]

10. Manganese

Manganese (Mn) is one of the most common metals in the human body, mainly present in the bone, liver, kidney, pancreas, and adrenal and pituitary glands [99]. Manganese is important for many physiological processes such as regulation of blood sugar and cellular energy, reproduction, digestion, bone growth, blood coagulation, and hemostasis, antioxidant defense, and proper immune function [100].

Toxicity is a greater concern than deficiency. The most common somatic effects are hypertension, increased heart rate due to blocking of calcium channels by manganese, and elevated cholesterol levels because of the reduced conversion of cholesterol to bile acids. Other symptoms are decreased fertility in men as well as increased fetal abnormalities [101]. Nevertheless, the

brain is the main target organ of manganese toxicity. Manganese overexposure results in compromised mitochondrial function, oxidative stress, protein misfolding and trafficking, and neuro-inflammation [102]. Neurological damage might be irreversible. In patients exposed to manganese, elevated whole-blood manganese has been shown to correlate with MRI signal intensity in globus pallidus. Manganese overload initially induces non-specific symptoms such as headache, asthenia, irritability, fatigue, and muscular pains, but later, a neurodegenerative syndrome with psychiatric symptoms, known as manganism. This condition is like the cognitive, motor, and emotional defects seen in Parkinson's disease. Considering the importance of checking undue Mn delivery, this problem has been included in Fig. 14, despite not being a formal recommendation.

10.1. When and what to measure

Recommendation 10.1: Measurements should be made when manganese excess or toxicity is suspected, especially in long term parenteral nutrition (>30 days, manganese intake >55 µg/day) with impairment of liver function or iron deficiency.

Grade of recommendation B – Strong consensus 94 % (No. 54)
References [103,104]

Recommendation 10.2: Monitoring should not be more frequent than at 40 day-intervals (biological half-life).

Grade of recommendation GPP – Consensus 88 % (No. 55)

Recommendation 10.3: In patients at-risk of manganese toxicity, whole blood, or RBC concentrations should be measured.

Grade of recommendation B – Strong consensus 94 % (No. 24)
Grade B awarded based on biochemistry, not clinical trials [103–105]

Recommendation 10.4: Brain magnetic resonance imaging (MRI) may contribute to confirming the diagnosis, showing high intensity signals in globus pallidus being correlated with elevated manganese levels.

Grade of recommendation 0 – Strong consensus 97 % (No. 25)
References [103,106]

10.2. How much to provide in typical EN and PN

Recommendation 10.5: Enteral nutrition should provide 2–3 mg manganese per day but doses up to 6 mg/day have been safely provided in 1500 kcal.

Grade of recommendation B – Strong consensus 91 % (No. 97)
Reference [7]

Recommendation 10.6: Parenteral nutrition shall provide 55 µg manganese per day.

Grade of recommendation A – Strong consensus 91 % (No. 98)
Reference [104]

Comment: The above recommended dose of Mn in adults treated with PN, are still frequently exceeded by the current multi-trace element products [107]

10.3. When and how to treat?

Recommendation 10.7: Whole blood or serum manganese values greater than twice the upper limit of normal laboratory reference ranges should be treated.

Grade of recommendation GPP – Consensus 88 % (No. 141)

Comments: Dietary intake does not lead to toxicity, because absorption is tightly regulated in the gut [99]. Toxicity has been observed in adults receiving IV > 500 µg/day and in pediatric patients receiving >40 µg/kg/day [102], but even as little as 110 µg/day to adults causes an elevation in whole blood manganese concentration [104]. Patients suffering from cholestasis, liver failure or hepatic encephalopathy can develop manganese toxicity, as manganese is excreted in the bile [103,108]. Due to neuronal cell death in basal ganglia structures, functional recovery, and effective treatment for manganism is currently limited [108].

Recommendation 10.8: Manganese toxicity can be treated by exclusion of manganese from PN admixture, chelation therapies (EDTA, PAS) or iron supplementation in case of iron deficiency.

Grade of recommendation GPP – Strong consensus 94 % (No. 142, No. 162)

11. Molybdenum

Molybdenum (Mo) is an essential trace element for enzymes of microorganisms, plants and animals. It is used in plants and mammals in amino acid and purine metabolism [109,110]

Clinically apparent nutritional deficiency induced by low dietary molybdenum has not been reported in humans [109]. Molybdenum deficiency may occur in long-term PN without added molybdenum. Deficiency leads to biochemically detectable high plasma methionine, low serum uric acid, and high urinary thiosulfate, xanthine and hypoxanthine [110].

There are no reports of acute toxicity of dietary molybdenum in humans. A controlled study in healthy young men found that molybdenum intakes, ranging from 22 µg/day to 1490 µg/day (almost 1.5 mg/day), elicited no serious adverse effects when molybdenum was given for 24 days [111]. A high concentration of molybdenum may act as an inhibitor in purine catabolism [112], and has been shown to cause copper deficiency in animals.

11.1. When and what to measure

Recommendation 11.1: Molybdenum measurement is rarely required, and it should only be assessed in case of suspected molybdenum deficiency.

Grade of recommendation GPP – Strong consensus 91 % (No. 56)

Recommendation 11.2: In a case of suspected molybdenum deficiency, urine concentration of sulphite, hypoxanthine, xanthine and plasma uric acid, in addition to blood molybdenum should be measured.

Grade of recommendation B – Strong consensus 97 % (No. 26)
Grade A awarded based on biochemistry, not clinical trials

11.2. How much to provide in typical EN and PN

Recommendation 11.3: Enteral nutrition should provide 50–250 µg Molybdenum per day in 1500 kcal.

Grade of recommendation B – Strong consensus 100 % (No. 99)
Grade B awarded based on DRI/RDA, not clinical trials

Recommendation 11.4: Parenteral nutrition should provide 19–25 µg molybdenum per day.

Grade of recommendation B – Strong consensus 100 % (No. 100)
Reference [113]

11.3. When to provide additional amounts

Recommendation 11.5: Molybdenum may be used to treat copper overload in Wilson's disease as tetrathiomolybdate.

Grade of recommendation GPP – Strong consensus 94 % (No. 157)

12. Selenium

Selenium (Se) is essential in mammals, being required for the synthesis of the amino acid selenocysteine, an essential component of at least 25 selenoproteins in human tissues [114]. The biochemical functions include antioxidant and redox activity, control of thyroid hormone metabolism, together with several proteins of uncertain function [115]. Selenium is well absorbed (56–81 %).

Deficiency is most often caused by insufficient intake, and is largely geography dependent (soil content is highly variable), and may lead to population deficiency and specific chronic pathologies such as the Keshan cardiomyopathy, and Kashin-Beck osteochondropathy in China [116]. Selenium deficiency is associated with increased incidence and virulence of viral infections [117,118]. Milder selenium depletion will cause effects on metabolism and tissue function [115].

Severe deficiency has been recognized during PN as cardiac and skeletal muscle myopathy, and as skin and nail effects [119]. A value of plasma selenium <0.4 µmol/l (<32 µg/l), should always trigger supplements provision, and other actions should be tailored to the combined data from plasma selenium and CRP [119], as inflammation causes a proportional decrease in plasma levels due to redistribution [2,120].

Upper limits for plasma selenium before toxicity symptoms occur are not clear, and range from $\cong 6$ µmol/l [121] to $\cong 12$ µmol/l [122]. Selenium toxicity outbreaks have occurred due to misformulation of dietary supplements resulting in clinical signs of selenosis [123]. The concern comes from recent awareness that selenium overexposure is positively associated with type 2 diabetes and high-grade prostate cancer.

12.1. When and what to measure

Recommendation 12.1: All patients likely to receive PN for more than two weeks or about to commence home PN should have plasma selenium and CRP measured on commencing PN. Tests should be repeated as required depending on the results, and at least once every 3–6 months.

Grade of recommendation B – Strong consensus 92 % (No. 57)
Reference [124]

Recommendation 12.2: Blood selenium is required to determine status, but ideally the plasma glutathione peroxidase (GPX-3) shall

be determined to reflect functional status. Simultaneous determination of CRP and albumin is required for interpretation.

Grade of recommendation A – Strong consensus 91 % (No. 27)
Reference [125].

Comment: In many patients there is an element of inflammation. This leads to a reduction in plasma selenium [2], related to redistribution out of the circulating compartment since plasma selenium returns to normal in many cases without supplementation [120]. Selenoprotein P has been shown to be a more selective indicator of status [126].

12.2. How much to provide in typical EN and PN

Recommendation 12.3: Enteral nutrition should provide 50–150 µg selenium per day in 1500 kcal.

Grade of recommendation B – Strong consensus 94 % (No. 101)
Grade B awarded based on DRI/RDA, not clinical trials.

Recommendation 12.4: Parenteral nutrition should provide 60–100 µg selenium per day.

Grade of recommendation B – Strong consensus 91 % (No. 102)
References [24,127,128]

12.3. When and how to provide additional amounts

Recommendation 12.5: A value of plasma selenium <0.4 µmol/l (<32 µg/l) should prompt selenium administration, starting with 100 µg/day (enteral or IV): the duration of administration will depend on response.

Grade of recommendation GPP – Strong consensus 100 % (No. 143)

Recommendation 12.6: In a patient without an inflammatory response (e.g., CRP <20 mg/l), a plasma selenium concentration of <0.75 µmol/l should trigger selenium administration (repletion).

Grade of recommendation GPP – Strong consensus 100 % (No. 144)

Comment: Patients who are depleted because of a recent reduced intake may require twice the normal daily amount (up to 200 µg/day), with monitoring of plasma selenium level. If the gastrointestinal tract is available, this can be given orally. Burn patients who have high losses of selenium, benefit from large IV supplies of around 375 µg/day, with more rapid healing and fewer infections [40]. Patients with other major trauma, and cardiac surgery may similarly benefit from a supplement of 275 µg/day [129]. Patients receiving renal replacement therapy have increased losses and oxidative stress and will require increased amounts [44].

Recommendation 12.7: Considering the good enteral absorption, and in absence of contraindication, the enteral route can be used with doses starting at 100 µg/day. In case of plasma selenium <0.4 µmol/l (30 µg/l) the IV route may be used for rapid correction: up to 400 µg/day may be required for at least 7–10 days, and status then be rechecked.

Grade of recommendation 0 – Strong consensus 100 % (No. 145)
References [125,130–132]

13. Zinc

More than 300 zinc metalloenzymes are present in biology, with essential roles in virtually all metabolic pathways [133–135]. Some examples in man include carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases and alcohol dehydrogenase. Zinc-finger proteins are central to the control of transcription of DNA into RNA. The key roles of zinc in protein and nucleic acid synthesis explain the failure of growth and impaired wound healing observed in individuals with zinc deficiency. Zinc is also part of several aspects of the antioxidant defense system.

Deficiency is caused by inadequate intake, increased requirements, malabsorption, increased losses and impaired utilization. Children, pregnant and lactating women have increased requirements and thus are at increased risk of depletion [136]. The clinical features of severe deficiency include alopecia, skin rash, growth retardation, delayed sexual development and bone maturation, impaired wound healing and immune function, diarrhea, and blunting of taste and smell [135,137].

Zinc deficiency affects both innate and adaptive immunity [138]. All immune cells are affected. T cell functions and the balance between the different T helper cell subsets are particularly susceptible to changes in zinc status. While acute zinc deficiency alters innate and adaptive immunity, chronic deficiency increases inflammation [138].

The clinical feature of zinc toxicity relates to the route and the dose of exposure and differs between acute and chronic exposure. Symptoms appear when ingestion exceeds 1 to 2 g of zinc. Toxic exposures can occur through gastrointestinal, dermal, respiratory, and parenteral routes through erroneously prepared parenteral nutrition [139].

13.1. When and what to measure

Recommendation 13.1: Zinc measurement should be done:

- In patients with increased gastrointestinal and/or skin losses
- on commencing long term PN and repeated as required depending on the presence of conditions associated with risk of deficiency.
- in patients on long-term PN, every 6–12 months

Grade of recommendation GPP – Consensus 88 % (No. 58)

Recommendation 13.2: Plasma zinc shall be used to confirm clinical zinc deficiency and to monitor adequacy of provision. Simultaneous determination of CRP and albumin is required for interpretation.

Grade of recommendation A – Strong consensus 91 % (No. 28)
Grade A awarded based on biochemistry, not clinical trials

13.2. How much to provide in typical EN and PN

Recommendation 13.3: Enteral nutrition shall provide at least 10 mg per day in 1500 kcal.

Grade of recommendation A – Strong consensus 97 % (No. 103)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 13.4: Parenteral nutrition should provide 3–5 mg zinc IV per day in patients without abnormal losses.

Grade of recommendation B – Strong consensus 88 % (No. 104)
References [24,140]

13.3. When and how to provide additional amounts

Recommendation 13.5: In patients on parenteral nutrition who have gastrointestinal losses (fistulae, stomas, and diarrhea), while nil per mouth, IV doses up to 12 mg per day can be used and are usually sufficient to maintain the status: this addition will be required for as long as gastrointestinal losses persist.

Grade of recommendation O – Strong consensus 100 % (No. 166)
Reference [140]

Recommendation 13.6: Patients with major burns >20 % body surface area have increased requirements due to exudative losses: 30–35 mg/day IV for 2–3 weeks should be provided.

Grade of recommendation B – Strong consensus 91 % (No. 151)
References [40,141]

Recommendation 13.7: In acquired zinc deficiency, 0.5–1 mg/kg per day of elemental zinc (Zn^{2+}), can be given orally for 3–4 months. Organic compounds such as zinc histidinate, zinc gluconate and zinc orotate show a comparatively better tolerability than inorganic zinc sulfate and zinc chloride.

Grade of recommendation: GPP – Consensus 82 % (No. 146)

Recommendation 13.8: In acrodermatitis enteropathica, a life-long oral intake of 3 mg/kg per day of elemental zinc (Zn^{2+}) may be provided, with the dosage adjusted accordingly to plasma or serum zinc levels.

Grade of recommendation O – Strong consensus 94 % (No. 158)
Reference [142]

Recommendation 13.9: Oral, enteral and parenteral routes of administration can be used, route depending on gastrointestinal function. Supplementation can be combined with nutritional support or provided separately.

Grade of recommendation GPP – Strong consensus 97 % (No. 147)

14. Thiamine (vitamin B1)

Thiamine is a water-soluble vitamin essential for carbohydrate metabolism and energy metabolism [143], being a cofactor of enzymes involved in the production of ATP and the synthesis of essential cellular molecules, synthesis of various neurotransmitters and nucleic acids, and control of oxidative stress. In humans, body stores are limited, resulting in dietary intake dependency.

Thiamine deficiency is a major public health concern in several countries [143]. Clinical thiamine deficiency may present with signs and symptoms involving the neurological, and cardiovascular systems [143,144]. The neurological symptoms range from mental changes such as apathy, decrease in short-term memory, confusion, and irritability to cognitive deficits and the Wernicke-Korsakoff encephalopathy, optic neuropathy, and central pontine myelinolysis [145]. The involvement of other organs manifests as in beriberi, congestive heart failure, or unexplained metabolic lactic acidosis [146]. Among the thiamine disorders, the refeeding syndrome is of particular concern in inpatients and is associated with increased mortality [147–150].

Thiamine is among the MNs at highest risk for deficiency [151,152]. Patients at risk are numerous and include malnutrition, poor oral intake and chronic alcohol consumption, malignancies,

and increased metabolic requirements (pregnancy) [146]. Reduced gastrointestinal absorption due to disease or intestinal resections, increased gastrointestinal or renal losses [153], obesity pre- and post-bariatric surgery [154], should also be considered. Critical illness is a risk condition with its multiple metabolic challenges: deficiency or depletion may be found in over 90 % of patients [155,156].

No toxicity. The only effect of high doses is increased urinary excretion [157,158].

14.1. When and what to measure

Recommendation 14.1: RBC or whole blood thiamine should be determined in

- patients suspected of deficiency in the context of cardiomyopathy and prolonged diuretic treatment
 - patients undergoing a nutritional assessment in the context of prolonged medical nutrition, and post-bariatric surgery
 - refeeding syndrome
 - encephalopathy
- Grade of recommendation 0 – Consensus 90 % (No. 29)
References [147–149,156,159,160]

Recommendation 14.2: Thiamine status shall be determined by measuring RBC or whole blood thiamine diphosphate (ThDP).

Grade of recommendation A – Consensus 90 % (No. 4)
Grade A awarded based on biochemistry, not clinical trials.

Comment: Thiamine is found under five forms: the active form is called thiamine diphosphate (ThDP or thiamine pyrophosphate (TPP) [1]. If RBC or whole blood ThDP determination is not available, measurement of red cell transketolase and its activation by thiamine may be considered. Thiamine status determination in erythrocytes may be more reliable in the presence of inflammation [161]. In patients on diuretic therapy, low TPP levels are present in 18 % on intensive care unit (ICU) admission [162].

14.2. How much to provide in typical EN and PN

Recommendation 14.3: Enteral nutrition shall provide 1.5 to 3 mg per day of vitamin B1 in patients receiving 1500 kcal per day.

Grade of recommendation A – Strong consensus 92 % (No. 59)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 14.4: Parenteral nutrition should provide at least 2.5 mg per day.

Grade of recommendation B – Strong consensus 92 % (No. 59)
References [72,163]

Comment: in “mild deficiency” or depletion, identified by low dietary intakes and low blood ThDP, but no clinical symptoms, an intake of 10 mg per day for one week should be prescribed [164].

14.3. When and how to provide additional amounts

Recommendation 14.5: In patients admitted to emergency or intensive care, the administration of thiamine (100–300 mg/day IV) should be prescribed without hesitation from admission for 3–4 days.

Grade of recommendation B – Consensus 80 % (No. 105, No. 148)
References [163,165–167]

Recommendation 14.6: In patients admitted on the ward with any suspicion of reduced food intake during the previous days or high alcohol consumption, thiamine 100–300 mg/day should be administered by either oral or IV route.

Grade of recommendation B – Strong consensus 92 % (No. 106)
Reference [168]

Recommendation 14.7: As thiamine is well absorbed (except in alcohol related gastritis), thiamine can be administered orally, enterally, or IV. Nevertheless, considering the severity of acute deficiency symptoms, using the IV route is the most efficient, providing 3 × 100–300 mg per day.

Grade of recommendation 0 – Consensus 88 % (No. 107)
Reference [149,168]

15. Riboflavin (vitamin B2)

Riboflavin (vitamin B2) is involved in redox reactions and antioxidant functions, metabolism of other B vitamins (niacin, B6, B12, and folate), immunity (antibody production and immunomodulation) [33] and energy production. Intracellular metabolism involves phosphorylation of riboflavin to form the cofactors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which account for most of riboflavin in plasma and tissues.

Deficiency is manifested with oral-buccal lesions, seborrheic dermatitis. Other manifestations are ocular and normochromic, normocytic anemia and marrow aplasia [169]. There is evidence that poor riboflavin status interferes with iron handling and contributes to the etiology of anemia when iron intakes are low [169]. Riboflavin deficiency is frequently associated with pyridoxine, folate, and niacin deficiencies [10,169].

Patients at risk of deficiency are those with, thyroid dysfunction, diabetes, renal disease, alcoholism, and in pregnancy, lactation, and in the elderly. Also, patients with surgery, trauma, burns, or fractures, and patients on psychotropic drugs, tricyclic antidepressants, or barbiturates [10]. Patients with anorexia nervosa who avoid dairy products area can be at risk for deficiency [10]. In old adult patients, low levels, and at-risk levels of riboflavin have been described probably due to decreased intake of dairy products and alteration in absorption and metabolism.

Toxicity: Riboflavin consumed orally from the diet or from most multivitamin supplements rarely causes side effects (eventually yellow-colored urine).

15.1. When and what to measure

Recommendation 15.1: Assessment of riboflavin status can be required when there is clinical suspicion of deficiency.

Grade of recommendation GPP – Strong consensus 96 % (No. 30)

Recommendation 15.2: The riboflavin status can be assessed by the glutathione reductase activity in RBC.

Grade or recommendation 0 – Strong consensus 96 % (No. 5)
Grade 0 awarded based on biochemistry, not clinical trials

Comment: Red blood cell flavin adenine dinucleotide (FAD) is another validated method of assessment, especially in the context of inflammation. Regular monitoring of riboflavin status is not

required. Deficiency is manifested with oral-buccal lesions and seborrheic dermatitis of the face, trunk, and scrotum. Other manifestations are ocular lesions and anemia and marrow aplasia.

15.2. How much to provide in typical EN and PN

Recommendation 15.3: Enteral nutrition shall provide at least 1.2 mg per day of riboflavin in 1500 kcal.

Grade of recommendation A – Strong consensus 98 % (No. 61)
Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 15.4: Parenteral nutrition should provide 3.6–5 mg riboflavin per day.

Grade of recommendation B – Strong consensus 96 % (No. 62)
Reference [170]

15.3. When and how to provide additional amounts

Recommendation 15.5: Additional amounts of riboflavin can be provided as multivitamin pills in the following cases:

- Suspected or proven clinical deficiency
- Patients at risk of deficiency
- In patients with deficiencies of other group-B vitamins
- In patients with multiple acyl-Coenzyme A dehydrogenase deficiency (MADD) as some of them are sensitive to this cofactor
Grade of recommendation GPP – Strong consensus 100 % (No. 108, No. 149)

Recommendation 15.6: Riboflavin 5–10 mg/day can be used orally in case of deficiency.

Grade of recommendation GPP – Strong consensus 96 % (No. 109)

Recommendation 15.7: In cases of clinical riboflavin deficiency, IV administration of 160 mg of riboflavin for four days may be necessary.

Grade of recommendation GPP – Strong consensus 94 % (No. 110)

Recommendation 15.8: In MADD patients, riboflavin can be given at doses of 50–200 mg/day.

Grade of recommendation GPP – Consensus 87 % (No. 111)

16. Niacin (vitamin B3)

Niacin is a collective term for nicotinic acid and nicotinamide. All tissues convert absorbed niacin into its main metabolically active form, the coenzyme NAD. More than 400 enzymes require NAD to catalyze reactions in the body. Niacin helps to convert nutrients into energy, create cholesterol and fats, create and repair DNA, and exert antioxidant effects [171,172].

Causes of niacin deficiency include inadequate oral intake, poor bioavailability from grains, defective tryptophan absorption, carcinoma tumors, metabolic disorders, and the long-term use of chemotherapeutic treatments [173]. Some secondary causes include chronic alcoholism and general malabsorptive states such as prolonged diarrhea [174].

Severe niacin and/or tryptophan deficiency leads to a variety of clinical symptoms, including diarrhea, dermatitis and dementia,

collectively known as “pellagra” or “the three D disease and even death (four D) if not recognized and treated promptly [175,176].

Toxicity: The well-known side effect of niacin is flushing (face, arms, and chest), which typically occurs within 30 min of ingestion and abates after 60 min [177]. Niacin can also cause serious hepatotoxicity that may evolve into multiple organ failure. Niacin associated hepatotoxicity is generally related to ingestion of around 3 g per day. In contrast, the more common symptom of flushing can occur at doses as low as 30 mg per day [178].

16.1. When and what to measure

Recommendation 16.1: Blood or tissue NAD levels may be measured in case of clinical symptoms, including diarrhoea, dermatitis, and dementia (Pellagra disease).

Grade of recommendation GPP – Consensus 89 % (No. 31)

Recommendation 16.2: Blood or tissue NAD shall be used as a measure of niacin status.

Grade of recommendation A – Strong consensus 91 % (No. 6)
Grade A awarded based on biochemistry, not clinical trials.

Comment: Since measurement may be difficult to organize, storing a blood sample and awaiting the effects of niacin supplements on symptoms may be a pragmatic alternative.

16.2. How much to provide in typical EN and PN

Recommendation 16.3: Enteral nutrition shall provide 18 to 40 mg per day of niacin in 1500 kcal.

Grade of recommendation A – Strong consensus 98 % (No. 63)
Grade A awarded based on DRI/RDA, not clinical trials.

Recommendation 16.4: Parenteral nutrition should provide at least 40 mg of niacin per day.

Grade of recommendation B – Strong consensus 95 % (No. 64)
Reference [170]

16.3. When and how to provide additional amounts

Recommendation 16.5: When there is suspicion of niacin deficiency from at risk clinical history and/or presence of signs or symptoms, higher doses may be required.

Grade of recommendation GPP – Strong consensus 95 % (No. 112)

Recommendation 16.6: The oral/enteral route should be used whenever the gastrointestinal tract is functional. In malabsorption and short bowel, the parenteral route can be used.

Grade of recommendation GPP – Strong consensus 93 % (No. 113)

Comment: recent evidence points to a relation between impaired NAD + biosynthesis and acute kidney injury (AKI) after major vascular and cardiac surgeries [179,180]. Tryptophan (precursor of NAD) or nicotinamide supplementation have been shown to diminish renal injury in ischemia-induced AKI, opening supplementation perspectives.

17. Pantothenic acid (vitamin B5)

Pantothenic acid is a constituent of the coenzyme A (CoA) and acyl carrier protein (ACP) and therefore is involved in numerous biochemical processes in oxidative respiration, lipid metabolism, synthesis of steroids, acetylated molecules (amino acids, carbohydrates) as well as prostaglandins [181].

Naturally occurring pantothenic acid deficiency is very rare and observed only in conditions of severe malnutrition. Severe deficiency can cause numbness and burning of the hands and feet, headache, extreme tiredness, irritability, restlessness, sleeping problems, stomach pain, heartburn, diarrhea, nausea, vomiting, and loss of appetite.

Toxicity of pantothenic acid is rare, and no Tolerable Upper-Level Intake (UL) has been established.

17.1. When and what to measure

Recommendation 17.1: Pantothenic acid blood determination should be performed in the context of neurological symptom investigations.

Grade of recommendation GPP – Consensus 86 % (No. 32)

Comment: Severe deficiency can cause numbness and burning of the hands and feet, headache, extreme tiredness, and multiple non-specific symptoms.

Recommendation 17.2: Pantothenic acid shall be determined in blood.

Grade of recommendation A – Strong consensus 93 % (No. 7)
Grade A awarded based on biochemistry, not clinical trials.

17.2. How much to provide in typical EN and PN

Recommendation 17.3: Enteral nutrition should deliver at least 5 mg pantothenic acid per day when providing 1500 kcal.

Grade of recommendation B – Strong consensus 95 % (No. 65)
Grade B awarded based on DRI/RDA, not clinical trials

Recommendation 17.4: Parenteral nutrition should deliver at least 15 mg pantothenic acid per day.

Grade of recommendation B – Strong consensus 98 % (No. 66)
Reference [182]

17.3. When and how to provide additional amounts

Recommendation 17.5: In the context of atypical neurological symptoms additional pantothenic acid may be delivered along with other B vitamins.

Grade of recommendation GPP – Strong consensus 91 % (No. 114, No. 163)

18. Pyridoxine (vitamin B6)

The name Vitamin B6 refers to a group of six water-soluble pyridine compounds (B6 vitamers) [183]. The biologically active form is pyridoxal phosphate (PLP), which serves as coenzyme for more than 160 enzymatic reactions. These reactions include transaminations, racemizations, decarboxylations and aldol

cleavage [183], affecting carbohydrate, protein, and lipid metabolism. The most important function of active, phosphorylated PLP in the cell is related to the biosynthesis as well as the degradation of amino acids, which is central to transamination reactions [184].

Deficiency can cause a variety of diseases [185], including seborrheic dermatitis with cheilosis and glossitis, microcytic anemia, epileptiform convulsions, confusion, and/or depression, and angular stomatitis.

Populations with the greatest risk for deficiency include alcoholics, renal dialysis patients [186,187], the elderly, post-operative, infections, critical illness [188], pregnancy, and people receiving medical therapies that inhibit vitamin activity (i.e., isoniazid, penicillamine, anti-cancer, corticosteroids, anticonvulsants). Deficiency has been observed during isoniazid therapy [189], HIV infection [190], severe alcoholic hepatitis [191], postoperative delirium, migraine attacks, and thymoglobulin immunosuppression [1].

Toxicity: No adverse effects due to high food intakes of pyridoxine have been reported. Clinical signs observed in case of excess pyridoxine are sensory neuropathy with ataxia or areflexia, impaired cutaneous and deep sensations, and dermatologic lesions.

18.1. When and what to measure

Recommendation 18.1: Measurement of pyridoxine should be done in presence of signs of pyridoxine deficiency (such as glossitis, sensory ataxia, seizures).

Grade of recommendation GPP – Strong consensus 95 % (No. 33)

Recommendation 18.2: Pyridoxine (B6) status shall be determined by measuring plasma pyridoxal phosphate (PLP) levels.

In seriously ill patients or in presence of inflammation, red cell PLP shall be measured.

Grade of recommendation A – Strong consensus 95 % (No. 8)
Grade A awarded based on biochemistry, not clinical trials.

18.2. How much to provide in typical EN and PN

Recommendation 18.3: Enteral nutrition shall deliver at least 1.5 mg pyridoxine per day in 1500 kcal.

Grade of recommendation A – Strong consensus 98 % (No. 67)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 18.4: Parenteral nutrition should deliver 4 to 6 mg pyridoxine per day.

Grade of recommendation B – Strong consensus 98 % (No. 68)
Reference [170]

18.3. When and how to provide additional amounts

Recommendation 18.5: In the context of isoniazide overdose or glycol poisoning, a high dose of pyridoxine should be part of the therapy.

Grade of recommendation GPP – Strong consensus 95 % (No. 115, No. 161)

19. Biotin (vitamin B7)

Biotin can be found in all cells of the human body. It plays an important role in the metabolism of fatty acids, glucose, and amino acids as it is a cofactor for five carboxylases that are critical for their metabolism [192]. Biotin sufficiency is essential for normal fetal development.

Biotin deficiency is rare in the general population due to its wide availability. Biotin deficiency leads to dermal (i.e. dermatitis, alopecia) as well as neurological complications such as ataxia [193,194]. Conditions at risk of developing deficiency include chronic alcohol consumption, malabsorption in the context of Crohn's disease and colitis, short bowel syndrome, celiac disease, severe malnutrition, smoking, and pregnancy. Long-term antibiotic use may destroy bacteria that produce biotin.

Toxicity of biotin is unlikely, and no UL has been established.

19.1. When and what to measure

Recommendation 19.1: Biotin status may be assessed in presence of clinical symptoms suggesting biotin deficiency (i.e. dermatitis, alopecia, or neurological symptoms) and a history suggestive of inadequate intake.

Grade of recommendation GPP – Strong consensus 95 % (No. 34)

Comment: Conditions at risk of developing deficiency include chronic alcohol consumption, malabsorption in the context of Crohn's disease and colitis, short bowel syndrome, celiac disease, severe malnutrition, smoking, and pregnancy. Long-term antibiotic use may destroy bacteria that produce biotin.

Recommendation 19.2: Biotin status shall be determined by the direct measure of blood and urine biotin and should be completed by the determination of biotinidase activity.

Grade of recommendation A – Strong consensus 95 % (No. 9)
Grade A awarded based on biochemistry, not clinical trials.

19.2. How much to provide in typical EN and PN

Recommendation 19.3: In enteral nutrition at least 30 µg of biotin per day should be provided in 1500 kcal.

Grade of recommendation B – Strong consensus 100 % (No. 69)
Grade A awarded based on biochemistry, not clinical trials

Recommendation 19.4: In parenteral nutrition, vitamin additives should provide 60 µg biotin per day.

Grade of recommendation B – Strong consensus 98 % (No. 70)
Reference [195]

19.3. When and how to provide additional amounts

Recommendation 19.5: Breast-feeding mothers should receive an intake of at least 35 µg biotin per day orally.

Additional amounts may also be needed in patients on renal replacement therapy.

Grade of recommendation GPP/0 – Strong consensus 100 % (No. 116, No. 167)
Reference [194]

Recommendation 19.6: Additional amounts of biotin can be administered either orally, enterally or IV depending on the intestinal function.

Grade of recommendation GPP – Strong consensus 95 % (No. 117)

20. Folate and folic acid (vitamin B9)

Folate is a generic term referring to a family of molecules [196], which include both the naturally occurring MN folates and synthetic forms (folic acid). Biologically active folate forms include folinic acid and 5-methyltetrahydrofolate (5-MTHF) [196].

Most symptoms of folate deficiency overlap with cobalamin deficiency, i.e. megaloblastic anemia, and pancytopenia, glossitis, angular stomatitis, oral ulcers, neuropsychiatric manifestations, including depression, irritability, insomnia, cognitive impairment, psychosis, anorexia, and fatigue [197]. Deficiency in one or both vitamins cause megaloblastic anemia [198].

Cases of isolated clinical folate deficiency are extremely rare. In patients with chronic kidney disease and/or on hemodialysis, folic acid and vitamin B12 metabolism are impaired, and it has long been known that their requirements are significantly higher than standard DRI [199]. Some patients, especially diabetics, may require as much as 15 mg per day [22]. Hyper-homocysteinemia is common, and folic acid together with vitamin B12 is critical for the conversion of homocysteine to methionine [200]. Folic acid has also been shown to improve endothelial function in chronic kidney disease [201].

Toxicity: Oral administration of folic acid in recommended dosage is considered non-toxic. Due to the proliferative effects, folic acid might increase cancer risk and progression. Moreover, it is said to cause insulin resistance in children, interact with epilepsy medication, mask a vitamin B12 deficiency, and be hepatotoxic [202]. Excess folic acid is excreted in the urine.

20.1. When and what to measure

Recommendation 20.1: In patients with macrocytic anemia or at risk of malnutrition, folic acid status should be measured at least once at first assessment and repeated within 3 months after supplementation to verify normalization.

Grade of recommendation GPP – Strong consensus 97 % (No. 35)

Recommendation 20.2: In diseases known to increase the needs for folate, folate status should be measured every 3 months until stabilization, and then once a year.

Grade of recommendation GPP – Strong consensus 96 % (No. 36)

Recommendation 20.3: Folate status shall be assessed in plasma or serum (short-term status), or RBC (long-term status) using a method validated against the microbiological assay.

Grade of recommendation A – Strong consensus 96 % (No. 10)
Grade A awarded based on biochemistry, not clinical trials.

Comment: The gold standard method of measuring folate is microbiological assay with *Lactobacillus rhamnosus*. Analysis of homocysteine at the same time improves the interpretation of laboratory measurements.

20.2. How much to provide in typical EN and PN

Recommendation 20.4: Enteral nutrition shall provide 330–400 µg Dietary Folate Equivalents (DFE) per day in 1500 kcal.

Grade of recommendation A – Strong consensus 98 % (No. 71)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 20.5: Parenteral nutrition should provide 400–600 µg per day folic acid.

Grade of recommendation B – Strong consensus 100 % (No. 72)
Grade B awarded based on DRI/RDA, not clinical trials

20.3. When and how to provide additional amounts

Recommendation 20.6: In case of dietary deficiency or chronic hemodialysis, 1–5 mg folic acid per day may be given orally.

Grade of recommendation 0 – Strong consensus 100 % (No. 118)
Reference [199]

Comment: In case of deficiency, the oral administration should last four months, or until the reason for the deficiency is corrected. In patients on chronic hemodialysis with hyperhomocysteinemia, increased amounts may be required for prolonged periods.

Recommendation 20.7: For the prevention of neural tube defects, women who desire to have children or women not taking oral contraceptives and living in countries without folic acid fortification of staple foods shall take folic acid supplements (400 µg/day) periconceptionally/whilst of childbearing age.

Grade of recommendation A – Strong consensus 98 % (No. 119, No. 168)
References [203,204]

Recommendation 20.8: Additional amounts of folic acid should be administered orally. In case of ineffective oral treatment or intolerance, folic acid can be given (0.1 mg/day), subcutaneously, IV, or intramuscular (IM).

Grade of recommendation GPP – Strong consensus 95 % (No. 120)

21. Cobalamin (vitamin B12)

Vitamin B12 (cobalamin) is an essential water-soluble MN synthesized by fungi and microorganisms, and in the stomach of ruminant animals. Humans are totally dependent upon animal sources or fortification [205,206]. Cobalamin absorption is complex, and depends on the gastric intrinsic factor and receptor-mediated endocytosis [207].

Cobalamin is a cofactor for two enzymes in humans: methionine synthase and methyl malonyl-CoA mutase [205]. These pathways are essential for mitochondrial metabolism, immune response, DNA integrity, neuronal myelin sheath integrity, and synthesis of neurotransmitters.

The prevalence of cobalamin deficiency is estimated to be around 10–26 % in the general population in Western countries, with old adults being at highest risk [208]. Deficiency is largely underdiagnosed and might reach 75 %–90 % of vegetarian or vegan diet communities [209,210].

Inadequate intake is the main cause of low status worldwide [208]. Absorption of cobalamin from food requires normal stomach, pancreas, and small intestine function [211]. The most prevalent

causes of deficiency are an autoimmune condition known as pernicious anaemia, resulting from a lack of intrinsic factor and, and food-bound cobalamin malabsorption. Both conditions are also common with chronic atrophic gastritis, which affects around 10–30 % of people over 60 years [209]. Long-term diabetic metformin treatment exposes to risk of deficiency [212,213]. Post-bariatric surgery patients are at high risk: symptoms manifest after a few months without adequate complementation: the requirements are far superior to DRI.

The manifestations of deficiency are primarily haematological or neuropsychiatric [209], with a variety of non-specific symptoms.

Toxicity: There is no upper toxicity limit for cobalamin and no reports of acute toxicity in oral or parenteral cobalamin supplementation or treatment.

21.1. When and how to measure or monitor

Recommendation 21.1: Cobalamin deficiency should be excluded in all patients who present with anaemia, or isolated macrocytosis, established diagnosis of polyneuropathies, neurodegenerative diseases or psychosis.

Grade of recommendation GPP – Strong consensus 98 % (No. 37)

Recommendation 21.2: In all patients at risk, or on treatment with cobalamin, replenishment adequacy should be assessed at least annually by resolution of clinical symptoms and available laboratory markers.

Grade of recommendation GPP – Strong consensus 98 % (No. 38)

Recommendation 21.3: Adult patients at risk or suspected of cobalamin deficiency should be screened with the combination of at least two biomarkers (holo-TC, methyl malonic acid (MMA)), with serum cobalamin as an alternative.

Grade of recommendation B – Strong consensus 92 % (No. 11)
Grade B awarded based on DRI/RDA, not clinical trials.

Recommendation 21.4: Patients with autoimmune diseases or with glossitis, anaemia and neuropathy should be screened for pernicious anaemia with the presence of anti-intrinsic factor antibodies regardless of cobalamin levels.

Grade of recommendation GPP – Strong consensus 100 % (No. 12)

21.2. How much to provide in typical EN and PN

Recommendation 21.5: Enteral nutrition shall provide at least 2.5 µg cyanocobalamin per day in 1500 kcal.

Grade of recommendation A – Strong consensus 97 % (No. 73)

Recommendation 21.6: Parenteral nutrition should provide at least 5 µg cyanocobalamin per day.

Grade of recommendation GPP – Strong consensus 97 % (No. 74)

21.3. When and how to provide additional amounts

Recommendation 21.7: Breast-feeding mothers shall receive an intake of at least 2.8 µg cyanocobalamin per day orally.

Grade of recommendation A – Strong consensus 100 % (No. 121)

Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 21.8: Patients with compromised cobalamin absorption should receive life-long supplements either as a daily dose of 350 µg cobalamin, or IM injections of 1000–2000 µg of cobalamin every 1 to 3 months.

Grade of recommendation GPP – Strong consensus 100 % (No. 122, No. 164)

Recommendation 21.9: In presence of acute clinical symptoms of deficiency, anti-intrinsic factor antibodies, a history of total gastrectomy or continuous malabsorptive diseases, the IM route should be used. Starting with high doses of 1000 µg cobalamin every second day for 2 weeks (or daily for 5 days).

Grade of recommendation GPP – Strong consensus 100 % (No. 123)

Comment: Intranasal and sublingual administration are alternative routes [54]. The conditions include, but are not limited to, short bowel syndrome, bariatric surgery, Crohn's diseases, gastrectomy, atrophic gastritis, and ileal resection. Treatment should be continued at least twice monthly until resolution of all clinical signs and/or etiopathogenetic factors (including resolution of macrocytosis). Monitoring blood potassium should be part of repletion therapy.

22. Vitamin A (retinol)

This liposoluble vitamin is a prohormone. The precursor Retinol is transformed into the active Retinoic acid and retinal. Retinol and retinal are responsible for vision and reproductive function. Retinoic acid controls cellular growth and differentiation [214]. The active metabolites, activate gene expression in more than 500 target genes [214]. Vitamin A plays an important role in the immune system [215]. Retinol binding protein (RBP) is a negative acute phase protein, which leads to a fall in serum retinol [216].

Vitamin A deficiency is a public health problem in most developing countries due to malnutrition, especially in children and pregnant women [217]. Before the well-known ophthalmic signs of deficiency (including night blindness, xerophthalmia), there is an increased susceptibility to infections, especially of the respiratory tract as the main symptom [218,219]. The intestinal immune and barrier function are also impaired [220].

Deficiency should be sought in liver diseases, chronic alcohol consumption, chronic kidney diseases, short bowel syndrome, and obesity.

Toxicity: Acute toxicity develops when quantities of natural vitamin A above 300,000 IU (adults) or > 60,000 IU (children) are ingested within a few hours or days [221]. Symptoms include increased intracranial pressure, nausea, headaches, pain in joints and bones. Chronic toxicity results from the ingestion of daily amounts of >25,000 IU for more than 6 years or >100,000 IU for more than 6 months, with a high inter-individual variability [222]. Above 14,000 µg/d for longer time periods may cause hepatotoxic effects.

22.1. When and what to measure

Recommendation 22.1: Serum retinol and retinyl esters (if available) measurements should be considered in patients being investigated for malabsorption.

Grade of recommendation B – Strong consensus 96 % (No. 41, No. 165)

Grade A awarded based on physiology, not clinical trials

Comment: Malabsorption/reduced binding protein/reduced storage may occur in the context of several diseases including persistent critical illness

Recommendation 22.2: Vitamin A status shall be determined by measuring serum retinol.

Grade of recommendation A – Strong consensus 95 % (No. 14)

Grade A awarded based on biochemistry, not clinical trials.

Comment: interpretation can be improved by also measuring CRP and retinol binding protein

22.2. How much to provide in typical EN and PN

Recommendation 22.3: Enteral nutrition shall provide 900–1500 µg retinyl esters (RE) per day, when providing 1500 kcal per day.

Grade of recommendation A - Strong consensus 97 % (No. 77)

Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 22.4: Parenteral nutrition should provide 800 to 1100 µg RE per day.

Grade of recommendation B– Strong consensus 97 % (No. 78)

Reference [85]

22.3. When and how to provide additional amounts

Recommendation 22.5: In conditions causing fat malabsorption, prevention of deficiency with oral supplements may be considered.

Grade of recommendation GPP – Strong consensus 97 % (No. 126)

23. Vitamin C (ascorbic acid)

Vitamin C has numerous functions, which are all based on electron donation [223–225]. It is the most potent water-soluble antioxidant, which directly scavenges radicals, mitigates the production of oxygen radicals, and recycles other antioxidants. Furthermore, vitamin C is an important cofactor/cosubstrate for the biosynthesis of neurotransmitters, cortisol, peptide hormones, and collagen. It promotes endothelial collagen synthesis, and maintains endothelial vasodilation and barrier function [226]. It limits the inflammatory response and ischemia-reperfusion injury, and improves immunity [227] and wound healing [1].

Clinical conditions with increased inflammation and oxidative stress, such as sepsis, trauma, cardiac arrest, major surgery, and burns are associated with a high risk of depletion. Very low plasma levels are observed in a substantial proportion of patients within hours of acute disease/injury [1,228–232]. In critically ill patients, low plasma concentrations are associated with severity of oxidative stress [233], organ failure, and mortality [230].

Chronic depletion is encountered in patients after bariatric surgery [234], alcohol abuse [235], chronic dialysis, smoking [236], chronic inflammation and oxidative stress, smoking, heart failure [237], severe chronic obstructive pulmonary disease (COPD), chronic dialysis, and malabsorption [1].

Symptoms of classical scurvy (such as anemia, poor wound healing, myalgia and bone pain, spongy and purplish gums that are prone to bleeding, loose teeth) are rarely seen in hospital settings, where deficiency easily goes unnoticed.

Toxicity: Supplements are contraindicated in blood disorders like thalassemia, G6PD deficiency, sickle cell disease, and hemochromatosis [238]. Adverse events include urinary calcium oxalate crystallization, renal stone formation and nephropathy due to increased oxalate excretion in susceptible patients receiving higher than repletion doses for longer periods of time.

23.1. When and what to measure

Recommendation 23.1: Plasma vitamin C concentrations may be measured in all patients with clinical suspicion of scurvy or chronic low intake.

Grade of recommendation GPP – Consensus 87 % (No. 39)

Recommendation 23.2: Measurement of plasma vitamin C is not recommended in critical illness or severe inflammation, due to the difficulty in interpretation of results.

Grade of recommendation GPP – Strong consensus 92 % (No. 40)

Recommendation 23.3: Vitamin C status should be assessed by a measure of L-ascorbic acid (AA) or total plasma vitamin C (sum of AA and dehydroascorbic acid (DHAA)).

Grade of recommendation B – Strong consensus 100 % (No. 13)
Grade B awarded based on biochemistry, not clinical trials

Comment: The determination of plasma ascorbic acid necessitates considerable logistical and analytical efforts [239]. The high susceptibility of vitamin C to degradation related to temperature, light, pH, dissolved oxygen, and the presence of oxidizing/reducing agents, requires specific pre-analytical precautions. But deficiency is widespread [1]. A clinical trial of vitamin C of about 1g/day for at least one week, should not be delayed in the presence of clinical symptoms.

23.2. How much to provide in typical EN and PN

Recommendation 23.4: Enteral nutrition shall provide at least 100 mg of vitamin C per day in 1500 kcal.

Grade of recommendation A– Strong consensus 97 % (No. 75)

Reference [240], additionally, grade A is awarded based on DRI/RDA, not clinical trials

Recommendation 23.5: Parenteral nutrition should provide 100 to 200 mg vitamin C per day.

Grade of recommendation GPP – Strong consensus 97 % (No. 76)

23.3. When and how to provide additional amounts

Recommendation 23.6: In patients with chronic oxidative stress (diabetes mellitus, smoking, heart failure, alcoholism, severe chronic obstructive pulmonary disease, and chronic dialysis) or malabsorption, a dose of 200–500 mg/day may be provided.

Grade of recommendation GPP - Strong consensus 92 % (No. 124)

Recommendation 23.7: During critical illness, a higher vitamin C repletion dose of 2–3 g per day may be given IV during the acute phase of inflammation.

Grade of recommendation 0 – Consensus 84 % (No. 125)

References [129,241–247]

Comment: The above 2–3 g/day dose is a metabolic concept distinct from the pharmacological doses used in sepsis trials. The recent large LOVIT-randomized controlled trial (RCT) in ICU septic patients receiving vasopressor therapy [248], showed that the high dose patients had a higher risk of death or persistent organ dysfunction at 28 days compared to placebo (44.5 vs 38.5 %; $p = 0.01$). Intriguing data pointing to the importance of the chemical form of vitamin C show that while sodium ascorbate (a base) seems effective in reducing shock symptoms and signs in ovine gram-negative sepsis model, ascorbic acid might not be due to its intense promotion of acidosis [249,250]. The chemical formulation of the vitamin C administered in the different ascorbic acid RCTs is under investigations and may provide helpful explanations for some of the outcomes [251].

24. Vitamin D (25-hydroxyvitamin D)

Vitamin D is not a classic vitamin but a steroid hormone precursor. Cutaneous endogenous production is possible from cholesterol with UV-B exposure, explaining the strong seasonal variation in vitamin D levels. Supply depends on food intake, but usually does not cover the needs. The vitamin D receptor is expressed in many body tissues including muscle (skeletal and cardiac), bone, immune system, skin, and endocrine organs, which is a major difference compared to other vitamins.

The only disease caused by vitamin D deficiency is rickets (osteomalacia in adults), which was first described in the 17th century. The definition and relevance of vitamin D deficiency, particularly in acute illness, remains debated, as the definition of deficiency is based on blood levels from studies on osteoporosis, a condition with no (or very limited) inflammation.

A level below 50–75 nmol/l (or 20–30 ng/ml) of serum/plasma 25(OH)D concentration is considered to define deficiency by the endocrine societies [1,252,253]. A cut-off <25 or <30 nmol/l (or 10/12 ng/ml) increases the risk for osteomalacia, and nutritional rickets dramatically and therefore is considered to determine severe vitamin D deficiency [253]. The risk of deficiency is elevated in patients with severe kidney or liver dysfunction, bed ridden and chronically ill patients [254]. Importantly, benefit from vitamin D supplementation can only be expected in deficiency, not in the general population [255].

Toxicity: Intoxication is rare, but has been described with 1) true overdoses, deliberate or accidental (typically single doses of millions IU or daily doses of >10,000 or even 100,000 IU), 2) manufacturing errors and 3) increased vitamin D sensitivity (i.e. CYP24A1 loss of function mutations, or idiopathic infantile hypercalcemia) [256]. Vitamin D toxicity symptoms are mediated by high calcium levels (hypercalcemia, hypercalciuria, dizziness, renal failure) [257].

24.1. When and what to measure

Recommendation 24.1: Vitamin D status may be determined in all patients considered at risk of vitamin D depletion or deficiency.

Grade of recommendation 0 – Strong consensus 92 % (No. 42)

Reference [254]

Recommendation 24.2: Status shall be determined by serum 25-hydroxyvitamin D (25(OH)D).

Grade of recommendation A – Strong consensus 95 % (No. 15)
Grade A awarded based on biochemistry, not clinical trials.

24.2. How much to provide in typical EN and PN

Recommendation 24.3: Enteral nutrition shall provide at least 1000 IU (25 µg) per day of vitamin D in 1500 kcal.

Grade of recommendation A – Strong consensus 95 % (No. 79)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 24.4: Parenteral nutrition should provide at least 200 IU (5 µg) of vitamin D per day.

Grade of recommendation B – Strong consensus 95 % (No. 80)
References [258,259]

Comment: Patients on EN frequently receive 400–800 IU/day. Although this may be adequate in some patients, the above dose is higher because patients receiving EN are likely to have higher requirements as a result of poor status due to prior illness. Some patients will have higher requirements, which should be checked by a blood determination.

24.3. When and how to provide additional amounts

Recommendation 24.5: Vitamin D in doses 4000–5000 IU (100–125 µg) per day should be administered for 2 months in patients with recurrent deficiency to achieve blood levels of 25(OH)D between 40 and 60 ng/ml. Substantially higher doses might be required.

Grade of recommendation B - Strong consensus 100 % (No. 127)
References [260,261]

Comment: Studies have suggested that these higher doses are required in patients who have recurrent deficiency with extremely low 25(OH)D levels [262]. Populations at risk include inflammatory bowel disease, obese adults, bariatric surgery, chronic liver disease, pancreatic insufficiency, chronic intestinal failure, pregnant women, and older adults. Patients with advanced and chronic kidney disease are a group requiring specialized care. Single ultra-high bolus doses are unphysiological: they upregulate catabolic processes and have been shown to be inefficient or even harmful and are therefore not recommended: Such doses may be needed upfront when time is critical (i.e. before initiation of potent osteoporosis treatment): such high bolus doses should be followed by maintenance doses (daily, weekly) to prevent vitamin D inactivation [263].

25. Vitamin E (α-tocopherol)

Vitamin E is a fat-soluble antioxidant. Alpha-tocopherol, the natural vitamin E with the highest biological activity, is a component of all biological membranes and is the most important lipid-soluble antioxidant. Its most important function is to protect membrane lipids, lipoproteins and depot fats from lipid peroxidation [264]. The activity of vitamin E is limited to the naturally occurring form, α-tocopherol, and the synthetic forms. As they are not converted to α-tocopherol by humans, the other naturally occurring forms of vitamin E (β, γ and δ-tocopherol and

tocotrienols) do not contribute toward meeting requirements [122,264].

Deficiency is rare and may appear in context of severe malnutrition. Patients with fat malabsorption are at risk of inadequate supply of fat-soluble MNs [265]. Genetic causes are rare but should be sought in case of resistant deficiency [266].

In adults with fat malabsorption, early vitamin E inadequacy is generally asymptomatic [267]. Neurological symptoms are associated with balance and coordination disorders, peripheral neuropathy, and muscle weakness. Instructions to reduce fat intake as part of weight management results in a 50 % reduction in vitamin E intake [268,269].

Toxicity: There are no reports regarding parenteral vitamin E toxicity. Toxic effects from high doses of vitamin E are rare even after a high intake for several years [270]. From numerous studies on the prophylactic and therapeutic use of vitamin E, even in large supplemental oral doses (3200 IU) per day, have shown no consistent adverse effects.

25.1. When and what to measure

Recommendation 25.1: Vitamin E should be determined when there is clinical suspicion of Vitamin E deficiency. These would include cystic fibrosis, α-beta lipoproteinaemia, and thrombotic thrombocytopenic purpura. In the absence of clinical signs of deficiency, there is no indication to measure vitamin E status during PN.

Grade of recommendation B – Consensus 89 % (No. 43, No. 169)
References [265–268]

Comment: In adults with fat malabsorption, early vitamin E inadequacy is generally asymptomatic [267]. Neurological symptoms are associated with balance and coordination disorders, peripheral neuropathy, and muscle weakness.

Recommendation 25.2: To detect vitamin E deficiency, plasma α-tocopherol should be measured.

Grade of recommendation B – Strong consensus 95 % (No. 16)
Grade B awarded based on biochemistry, not clinical trials

25.2. How much to provide in typical EN and PN

Recommendation 25.3: Enteral nutrition shall provide at least 15 mg α-tocopherol per day with 1500 kcal.

Grade of recommendation A – Strong consensus 100 % (No. 81)
Grade A awarded based on DRI/RDA, not clinical trials

Recommendation 25.4: Parenteral nutrition should provide at least 9 mg α-tocopherol per day.

Grade of recommendation B – Strong consensus 97 % (No, 82)
Reference [271]

25.3. When and how to provide additional amounts

Recommendation 25.5: Vitamin E should be supplemented if plasma α-tocopherol levels are below <12 µmol/l, starting with 100 mg per day depending on the cause of depletion/deficiency.

Grade of recommendation GPP – Strong consensus 92 % (No. 128)

26. Vitamin K (phylloquinone)

Vitamin K includes a group of lipid-soluble molecules that possess carboxylase enzyme cofactor activity necessary for the activation of vitamin K dependent-proteins [272]. These include the coagulation factor proteins C, S, M, Z, factors VII, IX, X and prothrombin. Vitamin K includes vitamers known as vitamin K1 (phylloquinone) and vitamin K2 (menaquinones). While phylloquinone is produced by plants, menaquinones are synthesized by human intestinal microbiota. Vitamin K3 (menadione) is a synthetic provitamin K that requires conversion to menaquinone-4 (MK-4) to be active [273].

The most common causes of vitamin K deficiency are conditions with fat malabsorption (celiac disease, cystic fibrosis, short bowel, etc.), malnutrition, antibiotic and anticoagulant (warfarin) treatments.

Vitamin K deficiency may contribute to significant bleeding, poor bone development, osteoporosis, and increased cardiovascular disease. In normal healthy adults, 8–31 % have vitamin K deficiency. Classically, deficiency results in the prolongation of prothrombin time with impaired clotting or bleeding [1].

Toxicity: Vitamin K1 and vitamin K2 are not associated with toxicity. Rare anaphylactoid reactions with bronchospasm and cardiac arrest after IV vitamin K1 (phytonadione) administration

26.1. When and what to measure

Recommendation 26.1: The vitamin K status may be measured in at risk patients, including pathologies causing steatorrhea, prolonged use of broad-spectrum antibiotics, and chronic kidney disease.

Grade of recommendation GPP – Consensus 89 % (No. 43, No. 170)

Recommendation 26.2: Vitamin K status shall be determined by a combination of biomarkers in combination with dietary intake, as there is no agreed standard.

Grade of recommendation A – Strong consensus 95 % (No. 17)
Grade A awarded based on biochemistry, not clinical trials.

Comment: The quantification of circulating phylloquinone (vitamin K1) in blood plasma or serum remains the most used marker of vitamin K status, although being mainly a biomarker of short term phylloquinone intake.

26.2. How much to provide in typical enteral and parenteral nutrition regimen

Recommendation 26.3: Enteral nutrition in adults should provide at least 120 µg vitamin K per day with 1500 kcal.

Grade of recommendation B – Strong consensus 97 % (No. 83)
Grade B awarded based on DRI/RDA, not clinical trials

Recommendation 26.4: Parenteral nutrition may provide 150 µg of vitamin K1 per day.

Grade of recommendation 0 – Strong consensus 95 % (No. 84)
References [274–276]

27. A. Non-DRI qualified: L-carnitine, choline, and CoQ10

These three micronutrients do not qualify as essential vitamins, despite insufficient or deficiency status having been shown under special clinical situations. There are no DRI for these nutrients, and they will not appear in the flowcharts.

28. B. L-carnitine

28.1. When and what to measure

Recommendation 27.1: Carnitine determination is not a routine requirement. In critically ill patients, carnitine status should be explored in presence of an unexpected loss of lean body mass, with the concomitant presence of hypertriglyceridemia and hyperlactatemia, particularly in case of prolonged parenteral nutrition or continuous renal replacement therapy.

Grade of recommendation GPP – Strong consensus 91 %

Recommendation 27.2: The simultaneous concentrations of total carnitine, free carnitine, carnitine esters and the carnitine precursors should be measured, to enable the calculation of the acyl-to-free carnitine ratio. This should only be used to confirm a clinical diagnosis and should not delay commencing supplements.

Grade of recommendation GPP – Strong consensus 91 %

28.2. How much to provide in typical enteral or parenteral nutrition regimens

Recommendation 27.3: Carnitine is not an essential nutrient: currently there is insufficient evidence to support its routine addition in enteral nutrition or parenteral nutrition.

Grade of recommendation 0 – Strong consensus 100 %
Reference [277]

28.3. When and how to provide additional amounts

Recommendation 27.4: In proven deficiency situations, the administration of L-carnitine supplementation of 2 to 5 mg/kg/day has been suggested via the route used for administration of macronutrients, until carnitine and acyl-to-free ratio revert to normal values.

Grade of recommendation GPP – Strong consensus 91 %

Comment: Availability of suitable supplements may be limited.
Recommendation 27.5: In case of antiretroviral drug toxicity, pharmacologic doses (50–100 mg/kg/day) may be administered.

Grade of recommendation 0 – Strong consensus 100 %
References [278,279]

29. C. Choline

29.1. When and what to measure

Recommendation 28.1: Plasma free choline may be determined in patients on home parenteral nutrition who develop unexplained liver steatosis/steatohepatitis or subclinical muscle damage with high creatine kinase levels.

Grade of recommendation GPP – Strong consensus 100 %

Recommendation 28.2: Plasma free choline can be integrated in long-term follow-up of cystic fibrosis patients.

Grade of recommendation GPP – Strong consensus 91 %

Recommendation 28.3: There is no routinely accessible biomarker in blood, although choline and its metabolites can be measured.

Grade of recommendation GPP – Strong consensus 100 %

29.2. How much to provide in typical enteral or parenteral nutrition regimens

Recommendation 28.4: Choline is not an essential nutrient. Although there is limited evidence, a dose of 400–550 mg per day has been suggested to support lipid metabolism.

Grade of recommendation 0 – Strong consensus 100 %
Reference [171]

29.3. When and how to provide additional amounts

Recommendation 28.5: In patients on home parenteral nutrition and patients presenting with unexplained liver steatosis or steatohepatitis with suspected or proven deficiency, the administration of 550 mg to 2 g/day may be considered.

Grade of recommendation 0 – Strong consensus 100 %
Reference [280]

Recommendation 28.6: In the treatment of patients with probable choline deficiency, and tolerating enteral nutrition, choline rich feeds or enteral choline preparations can be safely provided in equivalents of 500 mg–1500 mg per day for adults.

Grade of recommendation GPP – Consensus 90 %

30. D. Coenzyme Q10

30.1. When and what to measure

Recommendation 29.1: There is no clinical indication to measure plasma coenzyme Q10 (CoQ10) levels. Measurements are largely for research studies.

Grade of recommendation GPP – Strong consensus 100 %

Comment: CoQ10 is a vitamin-like compound, which is predominantly synthesized *de novo* in the human body at an estimated rate of 500 mg/day.

Recommendation 29.2: For the assessment of CoQ10 status for research purposes, the plasma CoQ10 concentration may be measured.

Grade of recommendation GPP – Strong consensus 100 %

31. Conclusion

Some MN deficiencies or inadequacies may lead to, or worsen diseases, whereas other status alterations may be the consequence

of disease or their treatment. Clinicians should be aware of these combinations, and suitable consideration given to the assessment, provision, and monitoring of a group of MNs. The practical version of the 2022 guideline, focuses again separately on all essential MNs, emphasizing their individual specificities and potential importance in acute and chronic disease. This should not result in the wrong perception that MNs can be addressed separately. Micronutrients work as a web, each being responsible, often in combination, for various steps of metabolic, antioxidant, endocrine and immune responses. This is particularly well shown for immunity: Gombart et al. [281] managed to detail how the different vitamins and trace elements interact at different levels to ensure barrier, innate, and acquired immunity. The same is true for virtually all functions. Addressing the MNs globally is essential clinically and in research – the investigation of isolated MNs, ignoring the interactions will not provide real life answers.

The clinical MN data remain limited, but with progression of knowledge, their importance becomes more and more obvious. The MN products that are available on the market only allow a “one size fits all” prescription with fixed multi-micronutrient combinations. Providing the complete range of MNs is vital [282,283], but addressing specific depletion or deficiency with isolated products, is equally essential but not yet possible in most countries. The development of isolated single MN products is required which is particularly true for trace elements.

At a time where the WHO and related agencies insist on the concept that “Food is Medicine”, clinical nutrition is on the top of the pyramid of required actions [284]. This guideline should encourage research on MNs in medical nutrition therapy to make it become true.

Conflict of interest

All the authors declares no conflicts of interest.

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