Parenteral provision of Micronutrients to adult patients: An expert consensus paper

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Abstract

Background:
Micronutrients, an umbrella term used to collectively describe vitamins and trace elements (TEs), are essential components of nutrition. Those requiring alternative forms of nutrition support are dependent on the prescribed nutrition regimen for their MN provision. The purpose of this document is to assist clinicians to bridge the gap between the available guidelines' recommendations and their practical application in the provision of micronutrients via the parenteral route to adult patients.
Methods:
Based on the available evidenced-based literature and existing guidelines, a panel of multidisciplinary healthcare professionals with significant experience in the provision of parenteral nutrition and intravenous micronutrients developed this international consensus paper.
Results:
The document addresses 14 pertinent questions regarding the clinical importance and use of in various clinical conditions. Practical guidelines on how micronutrients should be prescribed, administered and monitored are provided.
Conclusion:
Micronutrients are a critical component to nutritional provision and PN provided without them pose a considerable risk to nutritional status. Obstacles to their daily provision - including voluntary omission, partial provision and supply issues - must be overcome to allow safe and responsible nutrition practice.

Introduction and purpose of the paper

Micronutrients – that is, vitamins and trace elements (TEs) - are essential components of nutrition. While they are provided by a varied diet to the general population, those requiring alternative forms of nutrition support are dependent on the prescribed nutrition regimen for their micronutrient provision.

Although the importance of micronutrients has been known for decades, the use of vitamin and TE admixtures with parenteral nutrition (PN) is often not a routine process, because of the misconception that PN providing macronutrients is "total". The conviction prevails that despite obvious malabsorption in short bowel patients, diet and oral micronutrient supplements can meet the requirements of patients who are able to eat, but nevertheless depend on PN. However, this can be partly true only if the proximal small bowel is still functionally active. Additionally, the lack of reliable assessment for the clinical status of several micronutrients, access to these laboratory measurements, and standardization of techniques in quantifying Micronutrients, make it difficult in most settings to monitor micronutrient levels. Costs and difficulties obtaining remuneration for micronutrient provision, as administrators have trouble paying for what they regard as a "supplement" can also be a factor, as well as a lack of awareness about the importance of micronutrients in metabolism and the need to prescribe it along with PN formulations.

These are some of the reasons a number of multidisciplinary nutrition societies have developed guidelines to help clinicians navigate the issues around the prescription, administration and monitoring of micronutrients in both short (< 3-4 weeks) and long term PN ($\geq$ 4 weeks)[1]. However, a discrepancy between the recommendations in these guidelines and current clinical practice is acknowledged. Also, when guidelines formulated for specific locations are attempted to be implemented outside of the intended region, it can result in confusion (e.g. guidelines quoting specific products which are often not available outside of that region or the use of different units of measurement between regions, etc).

The purpose of this international consensus paper is to assist clinicians to bridge the gap between the available guidelines' recommendations and their practical application in the provision of micronutrients via the parenteral route to adult patients. Therefore, the primary intended audience is clinicians prescribing PN to adults, and secondarily the organisations and health services in which PN is being utilised to support safe PN practice. It is hoped that in making clear the practice application of the guidelines this expert consensus paper will assist in guiding international practices in PN provision to the evidence based guidelines available, and to serve as a platform for clinicians, organisations and regions to advocate for access to the resources required to administer PN safely.

This paper is not intended to provide a comprehensive systematic review of all aspects of intravenous (IV) micronutrients, although where clinically relevant, micronutrient provision independent of PN may

be addressed. Where the depth of relevant clinical content is out of scope of this paper, readers will be directed to more comprehensive references to obtain further information.

The views presented here reflect the interpretation of the literature and existing guidelines by clinicians with significant experience in the provision of PN in a range of contexts from different geographic locations around the world. The information presented will be limited to adult patients due to the differences in physiology, metabolism, requirements and nutritional goals in the pediatric population. The following micronutrients have been addressed: fat soluble (vitamins A, D, E, K) and water-soluble (vitamins B and C) vitamins, and trace elements (TEs) copper (Cu), iodine (I), Iron (Fe), selenium (Se), zinc (Zn), chromium (Cr), manganese (Mn) and molybdenum (Mo). Fluoride is available in some markets for addition to PN sformulations where indicated, however the majority of patients meet their requirements through fluoridated beverages (including water). Due to flouride not being a routine addition to PN, it has not been addressed within this review.

Methodology

A panel of multidisciplinary healthcare professionals recognised as experts in the provision of PN and IV micronutrients were invited to participate in the development of an international consensus statement. Initial face to face meetings were held for various regional clusters (North America, Latin America, Europe and Africa, and Asia Pacific), where the scope and planning of the statement were discussed. The individual inputs incorporate literature searches through MEDLINE (accessed via PubMed) and personal databases. Thereafter the panel functioned remotely through the facilitation of a steering committee (RB, KS, EO) which designed and compiled the framework of the document. The final paper was compiled based on input received from all members. It was circulated for comments and consensus within the group prior to finalization under the guidance of the steering committee.

Terminology

Hereafter the word supplementation will be used when the aim is to achieve supra-normal levels, including pharmaconutrition attempts. Complementation will be used to indicate the delivery of micronutrients to cover basal needs in case of low macro-substrate intakes (e.g. to complete enteral feeds or PN). Repletion will be used when deficiency or losses are identified and the administration aims at restoring a normal status, and only restoring gaps **(Figure 1)**.

Dietary recommended intakes (DRI) although intended for enteral use will be used to indicate proportions of micronutrients.

Q1: Why are micronutrients important?

Recommendation:

Micronutrients are essential for the metabolism and utilization of macronutrients and affect virtually every enzyme system in the body. As such, they constitute a crucial component of nutrition therapy and should be consumed in the recommended amounts daily.

Rationale:

Micronutrients play important roles in intermediary metabolism through their function as cofactors in enzymes and as co-enzymes, antioxidant systems and gene transcription. Micronutrients act in concert

with one another. PN provided without proportionate micronutrients over time will result in the development of deficiency, metabolic dysfunction, and in some cases, death.

A full description of the primary role and function of individual micronutrients and the clinical manifestations of deficiency states are outside the scope of this consensus paper. Full micronutrient monographs can be found in a publication by Sriram and Lonchyna[2] .

Q2: What is the history of micronutrients in parenteral nutrition?

The awareness about micronutrients needs in PN goes back to the 1970s. PN was developed in the 1950s and early 1960s[3], as a combination of three distinct components: amino acids, glucose, and finally lipid emulsions in 1961. The initial amino acid solutions were prepared by acid hydrolysis of so called "high quality proteins" such as casein. Later, the preparations were purified by dialysis, until the synthesis in 1964 of crystalline amino acids. Due to the purification process, the amino acid solutions became deficient in TEs and vitamins, which resulted in clinical deficiencies developing in patients depending on prolonged PN.

Trace Elements: Kay et al[4] published a case series of 37 adult patients in 1976, in whom Zn deficiency was diagnosed after 3 weeks of PN. The combination of diarrhea, mental depression, para-nasal, oral and peri-oral dermatitis, and alopecia, was called the Zn deficiency syndrome. These symptoms were reversed by the administration of Zn.[5] A case of reversible Cr deficiency presenting with peripheral neuropathy and severe glucose intolerance after 5 years of PN was published. All symptoms resolved with Cr administration.[5] In 1977, Jacobson et al[6] studied the balances of 20 TEs during PN in 4 male patients who were receiving additional Cu, fluoride (F), Fe, I, Mn, and Zn. The authors observed unintentional administration of several non-prescribed TEs, due to contamination of the solutions. The authors also observed a decline of the serum concentrations of 13 TEs (including Cu, Fe, Mo, Se and Zn), corresponding to the negative balance values. Based on their findings, the authors wrote the first recommendation to administer systematically TEs with PN.[7] In 1979, the American Medical Association published the first guidelines for essential TE provision during PN.[8]

Vitamins: While the FDA had validated an adult formulation for 9 water-soluble and 4 lipid-soluble vitamins in 1979[9], awareness about potential vitamin deficiency during PN came later, with the diagnosis of cardiac failure with lactic acidosis in patients after 4 weeks of PN.[10] Awareness about deficiencies occurred simultaneously in the US and Europe.[11] Cases of Wernicke's encephalopathy were described.[12] Labadarios et al showed that several vitamins exhibited a deficiency pattern after prolonged PN despite the administration of available IV multivitamin (MV) products.[13] Vitamins of the B group, vitamin C, A and D were low in 40 to 80% of patients.

In 2009, an American workshop analyzed the available vitamin and TE solutions.[14] While the product contents were considered sufficient for stable patients, concerns were formulated as to the unavailability of separate vitamin and TE solutions to face increased needs. The reality of TE and vitamin administration in clinical settings was questioned. This led the European Society for Clinical Nutrition and Metabolism (ESPEN) to make a formal statement in 2009 about the

necessity to systematically prescribe one MV and one multiple trace element (MTE) preparation for each single day of PN.[15] This statement was recently reinforced by a meta-analysis.[16] In 2012, an American Society for Parenteral and Enteral Nutrition (ASPEN) statement was published.[17] It again stated that the parenteral MV and MTE preparations, available in the U.S, met the requirements for most PN patients but the development of new products addressing specific needs was required. Recommendations included the reduction of Mn and Cr and the addition of choline to commercial MTE preparations, and the development of a separate injectable vitamin D. The available parenteral MTE preparations were considered to require revision. These recommendations have not been implemented to date. Guidelines developed by AuSPEN for Australia and New Zealand endorsed similar changes to recommendations and MTE preparations in their market.[18 19] Finally, the 2018 ESPEN guidelines restate the absolute necessity to deliver micronutrients daily with PN.[20]

Q3: Other than during parenteral nutrition, do patients need intravenous micronutrient supplementation?

Recommendation:

Yes, there are mainly three additional situations during which micronutrient *administration may be needed in the absence of PN. These include conditions associated with specific losses, oxidative stress and situations where inadequate enteral nutrition is provided.*

Rationale:

In cases where PN is not indicated, or in cases where it is not the sole route of nutritional provision, alternative micronutrient supplementation/replacement options may exist enterally or orally. It is, however, beyond the scope of this paper to discuss enteral micronutrient replacement. For this purpose of this paper the discussion will be focused on IV replacement routes in the context of PN, or in cases where enteral routes are not sufficient or reliable to deliver the intended doses.

1) Specific losses: Some medical interventions, such as dialysis and continuous renal replacement therapy (CRRT), cause significant TE losses. Prolonged CRRT has a particularly negative impact on Cu status, causing severe clinical deficiency.[20–22] Patients with high output intestinal fistula, ostomy effluent, or severe diarrhea can have significant Zn losses - up to 12 mg/L for small bowel effluent and 17 mg/L in stool output. [23] Major burns are also characterized by micronutrients containing exudative losses warranting careful monitoring and supplementation.[22]
2) Oxidative stress: Several acute pathologies are characterized by increased oxidative stress, consuming the available endogenous antioxidants. Several studies have attempted to restore antioxidant defense with very high doses of IV Se (10 to 100 times the DRI). Recently it was shown that such isolated administration of one single TE was not associated with any significant benefit.[24] The case for high dose ascorbic acid (200 mg/kg/24 h) in septic shock during the first 72 hours, however, seems promising[25], and phase III trials are in progress. In major burns resuscitation the administration of high dose ascorbic acid has been associated with reduction of fluids required. These micronutrient interventions, affecting endothelial function and other inflammation related responses, cannot be considered as nutrition and therefore should be categorized as pharmaco-nutrition.[26] (Please refer to Q5 and Q6).
3) Patients on enteral nutrition (EN) may not receive the DRI amounts of micronutrients for several reasons. In the acute care setting, EN is frequently interrupted for various procedures

and tests or slow progressive feeding to target. This results in nutrition targets not being and/or energy needs less than 1500 kcal/day. In these cases patients are likely to receive insufficient daily amounts of micronutrients, as most commercial solutions meet daily micronutrient requirements only when 1-1.5 litre of product (± 1500 kcal) is administered.[22 27] Further, enteral absorption is variable, particularly during critical illness and in other conditions that alter gut function (such as intestinal failure).

These conditions may justify the temporary administration of IV micronutrients at doses sufficient to cover basal metabolic needs during the acute phase of disease, i.e. the first 5-7 days, when EN is not yet at full requirements[28], especially in those patients with prior poor nutritional status or suspected gastrointestinal malabsorption.

Q4: Is there a need to provide intravenous micronutrients to critically ill patients?

Recommendation:
During metabolic stress, reprioritization of micronutrients occurs to support the acute phase response, with a redistribution of micronutrients out of the circulating compartment. It is important to interpret blood concentrations below reference range within the context and the degree of the acute phase response. Therefore, serum C-reactive protein (CRP) levels should always be determined along with micronutrient assessment for interpretation.

As most patients are enterally fed, the provision of additional micronutrient should follow recommendations described in question 3. In those receiving PN support, daily IV MV and MTE provision avoids/delays the development of micronutrient deficiencies. For critically ill patients with specific identified micronutrient deficiency risks, additional supplementation may need to be considered and the use of higher doses of IV micronutrients, either as part of PN provision or as a standalone intervention, may be warranted.

Rationale:
Critical illness represents an extreme form of metabolic stress, which exhibits a phased response (ebb followed by flow phase).[29] Physiologically the metabolic changes associated with metabolic stress are referred to as the acute phase response.

The acute phase response affects micronutrients by increasing requirements (due to increased catabolism, increased losses, decreased intake and increased usage) and by redistributing the micronutrients due to the release of pro-inflammatory cytokines.[2,19,29–32] This results in altered serum concentrations and decreased total body reserve.[2] It is important to determine the cause of decreased circulating levels in order to correctly treat the situation. The plasma concentration of several micronutrients decrease during the systemic inflammatory response syndrome (SIRS) in critical illness; therefore laboratory tests showing decreased plasma values may not necessarily reflect a true deficiency.[32],[33] Provided they have not been administered prior to blood testing, serum levels of vitamins B_1, B_2 and B_{12} provide an accurate reflection of deficiency, since they are not affected by inflammation. [2] Sequestration of TEs in various organs (mainly liver) results in decreased circulating serum levels. This impacts especially Fe, Se, and Zn. [2] The impact of metabolic stress on status is depicted in **Table 1**.

Various micronutrient derangements have been described in critically ill patients. Decreased serum levels do not always indicate actual deficiencies, but rather redistribution and utilisation which could represent a beneficial adaptive response to critical illness.[34] Patients with potential pre-existing vulnerability should be identified and treated early in the admission, and all patients receiving

PN support in the ICU should be provided daily IV MV and MTE preparations to avoid/delay the development of micronutrient deficiency.[18,19,30]

Conditions in the ICU that have been associated with micronutrient depletion include sepsis and SIRS[35], burns[22], losses from surgical or traumatic wounds[23], gastrointestinal (GI) fistulae[23] and CRRT[20 21 22]. Unbalanced and insufficient administration during medical nutrition therapy throughout the critical care journey places patients at greater risk during these situations.[2] Various deleterious consequences have been linked to micronutrient deficiencies, including poor wound healing, muscle weakness, inadequate immune response and organ dysfunction. [2 30] While the critically ill population represents a heterogeneous group of clinical pathologies, commonly reported micronutrients of concern include Zn, Fe and Se.[2] **[Table 2].**

Due to the impact of the inflammatory response on micronutrient status, micronutrient concentrations should always be determined in conjunction with parameters reflecting inflammatory status. [18,19 33 36] CRP is such a parameter and can be used to classify minor (< 10 mg/l), moderate (11-80 mg/l) and major (> 80 mg/l) inflammation.[33]

It is acknowledged that it is very difficult to differentiate between a true micronutrient deficiency and an inflammation-induced deficiency in the presence of infection. This is an area of active research and various researchers have proposed different models which include adjusting micronutrient concentration for albumin status[37], plasma retinol concentration [33 38] and using various regression-correction models to account for inflammation.[39] Currently there is no universal approach to account for inflammation when determining micronutrient status.[40]

To assist with this dilemma, we propose that interpretation of these results and subsequent action, needs to differ for acute or chronic conditions.
Acute care: In the case of an acute illness, any deficiency in micronutrient concentrations needs to be corrected, irrespective of the cause (transient drops in serum levels due to fluxes through utilisation in metabolic pathways and/or pre-existing deficiency states) in attempt to improve clinical outcomes. Correction is necessary due to the harmful effects of the micronutrient deficiencies on antioxidant defense mechanisms, metabolic pathways and general immune pathways.[41 42] CRP in these cases is less relevant because the effect of inflammation is known and expected, and the supplementation is intended to circumvent the effect of the inflammation on the serum levels of these micronutrients.
Longer term HPN: The concept is around monitoring of nutritional status and identifying developing deficiency or toxicity states assumed to be at least in part contributed to (and therefore ameliorated by modifying) the composition of the HPN formulation. In these cases knowledge of CRP with respect to micronutrient interpretation is essential to avoid inadvertently modifying long term provision without due cause, and which may cause unnecessarily patient expose to harm (ie reducing levels or increasing levels that are artificially elevated or lowered by an inflammatory response). Therefore, for chronic illness, correction of a micronutrient deficiency in the presence of infection should be deferred until the inflammation has been resolved. The micronutrient status needs to be repeated and if still deficient, supplementation is recommended to restore concentrations. [19]

With CRP increasing over 50 mg/l, the interpretation of the micronutrient levels should be mitigated and only values <20% below the reference value should be considered indicative of deficiency. In addition such values should be repeated to observe trends. [Mette, do we have a reference for the recommendation of < 20% above.

Q5: Which intravenous micronutrients are necessary in patients with burns?

Recommendation:
Most burn patients do not require PN but may need IV micronutrient repletion depending on the magnitude of the burns injury (see also Questions 1 and 3). If on PN, doses provided through

standard MTE and MV supplementation are sufficient for smaller burns (<20% body surface area [BSA]). However higher micronutrient doses are required for major burns, and IV micronutrient replacement may be warranted independent of PN provision. Antioxidant micronutrients are probably most important in the first 48hrs, with a transition to wound healing and immunity during the next 2-3 weeks, followed later during rehabilitation by prolonged globally increased multi- micronutrient requirements and specific vitamin D needs.

Rationale:

Burn injuries resulting in homeostatic changes that are proportional to the size of the burn injuries.[43] Resulting hypermetabolism and catabolism increase the nutrition needs (energy, protein, and micronutrients), while oxidative stress and large exudate losses from the burn wounds drive major fluid and TE losses. It is therefore vital that burnspatients receive additional micronutrients, even if not on PN provision.[43]

For small burns (defined as those <20% BSA), micronutrient maintenance doses (as defined by DRI or local equivalent indicating daily balanced needs) seem sufficient.[44] For major burns >20% BSA systematic micronutrient repletion is recommended from admission.[43] The requirements typically differ according to the treatment phase: TE losses must be repleted for 2-3 weeks from admission, and decrease with wound healing.[43]

Early resuscitation phase: Vitamin C has been identified as having a potential role in reducing fluid resuscitation requirements through stabilizing the endothelial membrane against increased permeability.[45] Vitamin C can be safely used without an increased risk of renal failure.[46]

Wound healing phase: Micronutrient status is particularly vulnerable during the active healing phases of burns – this is particularly true for micronutrients involved in antioxidant pathways.[47] [48] Large TE losses (particularly of Cu, Se and Zn) in wound exudates have been demonstrated during the first week post injury[49] [41], while active repletion of these TEs have resulted in reduced infectious complications, improved skin graft take, and reduced length of ICU stay.[50] [51] Proposed Se repletion doses of 700 µg/d IV have been shown to be safe for 2-3 weeks (burns >20% and 50% BSA respectively) and do not require specific blood concentration monitoring.
Additional considerations during this phase include the impact of other supportive therapies. CRRT of greater than 2 weeks duration has been shown to increase the risk of Cu depletion, and warrants regular monitoring.[52] (See Table 2 for other micronutrient considerations of CRRT).

In 1986, Boosalis et al were the first to show that the Se status of major burn patients was severely compromised.[47] In 1991, Cunningham et al showed severe Cu deficiency in extensively burned children. [48] Balance studies conducted in Lausanne showed that previous reports on Cu, Se and Zn deficiencies in burns settings[53] were the result of early large exudative losses of TEs during the first week post-injury, particularly for Cu, Zn[53] and Se.[49] [41] Randomized controlled repletion trials with Cu, Se and Zn doses calculated to compensate the measured exudative losses initiated upon admission resulted in clinical benefits, such as reduction of infectious complications, improved skin graft take, and reduction of length of ICU stay.[50] [51] Recently the Lausanne group published a dose finding study conducted in 139 patients with burns injuries on 35% BSA showing that their actual IV repletion protocol was safe and normalized Cu and Zn concentrations.[54] Despite the oxidative stress present in major burns the 845 ug/d Se doses delivered until 2016 resulted in supra-normal Se concentrations, suggesting a reduction to 700 ug/d: this dose proves safe for the described durations, and do not require specific blood concentration monitoring. Nevertheless, in case of CRRT exceeding 2 weeks in major burns, the additional high risk of Cu depletion due to prolonged effluent losses[55] requires weekly Cu blood monitoring in locations where timely laboratory support is possible.[52] Copper deficiency, in the presence of inflammation where increased levels are normally found[29] [56] requires immediate corrective action.[21]

Recovery/rehabilitation phase: Vitamin D deficiency has been demonstrated in major burns and is caused by skin damage and absence of sun exposure.[57] The standard DRI doses are insufficient to cover the needs and maintain circulating Vitamin D within normal ranges.[58] However, a systematic addition of supra-nutritional doses has not been recommended so far.

Q6: When should intravenous micronutrients be provided to surgical patients?

Recommendation:

M icronutrient abnormalities are common following some gastrointestinal tract (GIT) surgeries. A clear understanding of the remaining anatomy is important to anticipate changes to absorption or metabolism of individual micronutrients.
PN is indicated only when the gut is not functioning or if enteral feeding is not safe. This would therefore require micronutrient addition to the PN.

Rationale:

A thorough knowledge of the GIT absorption sites for the various micronutrients is essential to predict potential deficiencies due to malabsorption post GIT surgery. **Figure 2** depicts the most common absorption sites for micronutrients, and **Table 3** summarizes the most common micronutrient deficiencies that can develop post GIT surgery due to the area resected. Complications following surgery could also impact micronutrient losses. Patients developing enterocutaneous fistulae (ECFs) can have excessive losses of Zn and Se[2 18], whereas patients presenting with chyle leaks could become Se deficient due to increased losses.[59]

Zinc requirements are increased in intestinal and biliary losses, including fistulae, severe diarrhoea and chyle leaks, as well as sepsis, hypercatabolic states and burns, where additional supplementation is required.[60] Replacement of about 12 mg of Zn per litre of GIT losses in patients with fistulae, stomas and diarrhea has been recommended.[23] Additional Zn, over and above the daily recommended parenteral doses, may be added to short-term IV infusions in at-risk patients, however, it must also be noted that there is inadequate published information on the compatibility between injectable Zn solutions and other IV admixtures. As Zn is readily absorbed in the duodenum, the enteral route may be used if this part of the intestine is accessible and functional. Monitoring of serum Zn levels is necessary.[23]

Vitamin K deficiency may be unrecognized, as the laboratory test for coagulation (Prothombin time, International Normalized Ratio or INR) may not be sensitive enough to detect subclinical deficiency states, which can become unmasked after surgical procedures or resuscitation. Antibiotics often alter the intestinal flora and potentially decrease the bacterial production of vitamin K. If the patient is also *nil per os* (NPO) the usual oral source of vitamin K is not available. Some MV preparations may contain insufficient amounts of vitamin K or none at all. Small amounts of vitamin K, although highly variable with the product being used, are available from fat emulsions, but cannot be relied upon. The prudent clinician should consider additional parenteral vitamin K (IM or added to PN) whenever the clinical situation demands it, especially prior to elective surgery, irrespective of laboratory tests. A weekly dose of 250 – 400 µg is recommended if the additives does not contain vitamin K. [61 62]

Selenium deficiency may occur with GIT, bile or chyle losses or when Se is not added to PN. Chylous fistulae, for which PN is often required, result in micronutrient losses due to the large volumes of protein-rich fluid being lost. Selenium deficiency secondary to these losses has been reported and it is highly likely that other TEs are also lost.[59] Selenium is not a component of MTE admixtures in some countries. However, it is an important essential TE, with major anti-

oxidant functions. It is recommended that patients with small bowel resection, inflammatory bowel disease or other intestinal disorders should have their Se level checked prior to starting PN and every 3 months if deficiency is found.[63] When Se deficiency is suspected based on clinical presentation or laboratory tests, clinicians should first make sure that the MTE admixture does indeed contain Se. Pharmacologic doses of Se for specific conditions have been studied, and shown to be safe, but is not the standard of practice.[64]

Bariatric surgery, and especially malabsorptive procedures, can result in many micronutrient deficiencies. This includes fat-soluble vitamins (A, D, E, K), water-soluble vitamins (especially vitamins B_1, B_6 and B_{12}), as well TEs (Fe, Cu and Zn).[2] It is recommended that micronutrient status should be determined prior to and after bariatric surgery. [65] . This should begin at least one month before the procedure and continue lifelong thereafter.[65] Pre- and post-bariatric surgery nutrient screening and supplementation recommendations to prevent and treat micronutrient deficiencies are available.[65 66]

It is clear that surgery, inclusive of bariatric surgery, could have direct consequences on micronutrient status and additional micronutrient requirements are needed in cases of wound healing. However, in cases of a functional gut, micronutrient correction can be done via the oral or enteral route. In general an adequate supply of micronutrients is considered essential for any surgical patient on long-term PN. [67] The route of supplementation will be dictated by the adequate functioning of the GIT.

Q7: What are the roles and importance of micronutrients in home parenteral nutrition?

Recommendation:
Micronutrients provided as part of an individually prescribed home parenteral nutrition (HPN) formulation are essential to patients with long term HPN requirements and may represent the only reliable source of micronutrient provision and replacement. Monitoring of micronutrient status should be overseen by a team with expertise in HPN / intestinal failure management.

Rationale*:*
Micronutrient status of HPN patients has traditionally been a focus of concern [68], and levels continue to be demonstrated to be vulnerable.[69] Therefore micronutrients need to be seen as an essential component of HPN provision[18,19,70], and in some cases may be the only reliable source of micronutrient provision in this population. Unless otherwise clinically indicated they should be provided with each bag of HPN.[19]

Due to the long term nature of HPN provision, monitoring of micronutrient status is required at baseline and at 6 to 12 month frequency[18,19,70] to detect deficiency and/or toxicity states. The frequency can vary according to changes in clinical status and micronutrient prescription.[19] Individualised prescriptions and supplementation courses need to be modified according to micronutrient levels and their trends as well as the clinical situation.[18,19,70]

In HPN patients, vitamin D levels should be monitored every 12 months and corrected accordingly (IM, separate IV infusion or higher PN dose).[19] Bone mineral density measurements should also be done annually in long-term HPN patients.[71]

Micronutrient prescription for HPN patients, as all aspects of HPN management, should be overseen by a multidisciplinary nutrition support team (NST) with skills and experience in managing intestinal failure and HPN.[70] Micronutrient prescriptions for HPN patients should be

individually tailored in response to monitoring and clinical changes throughout the duration of a patient's HPN journey.[18,19,70] Factors requiring consideration include:

- Vulnerable M micronutrient status at baseline/HPN commencement,
- Micronutrient losses or malabsorption due to anatomical considerations (e.g. fistulae, altered GIT anatomy, etc.) or increased physiological turnover due to concurrent comorbid conditions (e.g. for wound healing, chronic inflammation etc.),
- Alterations to micronutrient excretion that may require reduced doses or omission of some micronutrient (e.g. such as may occur in cholestasis, chronic kidney injury, etc.), and
- The degree to which oral or enteral intake may contribute to the partial provision of some micronutrients, and the changes that may occur in this over time in the setting of natural or pharmacologically facilitated intestinal adaptation.

Q8: How should micronutrients be provided intravenously?

Recommendation:
Various PN admixtures are available around the world, however, the composition of these admixtures differ, the majority being without micronutrients. It is essential that micronutrients be administered together with any PN prescription.[2,17,19,30,64,72] *These can be added to the PN formulae, or administered directly to patients via IV fluids.*[30] *Due to chemical stability, vitamins and TEs sometimes need to be added to PN admixtures separately, or be compounded in individual combinations according to robust matrices based on evidence wherever possible.*[18,19]

Rationale:
Issues of compatibility and stability must always be considered when providing micronutrients concurrently with PN formulations. By definition ready-to-use PN formulations contain no micronutrient, except in case of compounding, and the latter implies limited stability of the PN formulation. It is essential that micronutrients be administered daily with PN: failure to do so may affect substrate bioavailability, metabolic function and clinical efficacy.[73–76] Formulations of micronutrient admixtures vary by region, and these differences may impact chemical stability and subsequently mandate specific methods by which individual combinations are added to PN.[18,19] It is therefore essential that clinicians and technicians involved with this process have knowledge about the dose, incompatibilities, stability and skill to administer micronutrients[72] in accordance with the practices appropriate to their location.

In the absence of strong evidence in the literature comparing the efficacy of different methods of micronutrient delivery in conjunction with PN formulations, decisions of how best to administer IV micronutrients are in practice based on organisational policy and/or facility capabilities. Common options for micronutrient provision include:

- Incorporation into PN formulations at the time of initial compounding (commercial facilities, hospital pharmacy);
- Addition to individually compounded or commercially available ready-to-use PN formulations closer to the time of provision under sterile conditions (commercial facilities, hospital pharmacy);
- Micronutrient provision separate to PN formulation, but within the same 24hr period, such as through side lines during PN infusion or prior to the commencement of PN provision. In these cases micronutrients should ideally be delivered over the maximum time period recommended and in accordance

with the administration recommendations provided by the manufacturer (hospital pharmacy, ward level).

- Micronutrients can be given via central or peripheral veins. Concentrated multiple TE admixtures must be diluted appropriately and administered slowly and never given as bolus administration. The manufacturer's directions for dilution and administration and compatibility with other components must be followed.

Various situations of micronutrient losses associated with PN delivery have been reported. Inadequate micronutrient provision may occur through the incomplete infusion of the full bag of PN to which the micronutrients have been added. A further means of micronutrient activity loss of photosensitive micronutrients (vitamins A, C and E) may come through photo-degradation through contact of UV light.[77] If sunlight exposure is a consideration, e.g. ambulatory patients receiving PN as inpatients or home PN patients, there is the potential for detectable loss of vitamins A and C from the infusion[77 78] and light protective coverings can be used during infusions to avoid nutrient losses.[19] This is however not a routine practice in the hospital environment.

When micronutrients are added to the PN formulation prior to infusion, in-bag losses of vitamin activity due to oxidation and interactions must be considered. Varying recommendations exist as to how to manage this, which range from addition of IV micronutrients to PN formulations soon before infusion, to infusing TE and vitamin components separately to minimise losses.[68] However further research is required to provide clear evidence based guidance regarding this.

Inadvertent TE contamination from individual PN components has historically been considered as an additional source of TEs in PN formulations above MTE provision. However it is unclear to what degree TE contamination patterns have changed with the evolution of storage and handling practices of PN and micronutrient components in recent decades.[19] Manufacturers of individual PN components should carefully monitor and describe TE contamination in their products. Maximum levels of TE contaminants should be included on all PN product labeling.[76,79–81]

Irrespective of the methods utilized, the establishment of regulations and handling standards for pharmacy and healthcare services involved with PN provision are essential to safeguard sterility of introducing micronutrient to PN formulations, as well as stability and compatibility considerations due to the high-risk nature of PN as a nutritional intervention.[72] These standards should be guided by Good Pharmaceutical Manufacturing Practice[82] and include specifications regarding the characteristics of the physical areas, equipment and the knowledge and skills of the personnel who make the mixtures for PN. The standards should also be updated periodically.[83]

For patients with longer term PN requirements, such as those requiring HPN who may have some residual gut function, oral or enteral supplementation may be feasible depending on their remaining anatomy and other clinical factors. The risk of not meeting requirements is therefore greater via the EN route[30], and IV options should be favoured unless evidence of integration of oral/enteral supplementation can be demonstrated.

Q9: What are the challenges in administering Intravenous micronutrients?

Recommendation:
Equity of consistent access to IV micronutrient preparations must become an international priority to support clinicians to provide safe PN and to be able to respond with clinically appropriate replacement therapies for patients with non-functioning guts.

Rationale:
Individual IV forms of various micronutrients are not freely available in all countries and provide challenges in correcting abnormal values.[2] For instance, Zn, I and Se are not available in parenteral form in many countries. Under these situations, clinicians have no alternative than to provide micronutrient enterally or orally in an attempt to meet patient requirements. This approach is fraught with risk as alteration of oral preparations (i.e. crushing tablets, piercing gelcaps and allowing contents to dissolve sublingually) is often required to allow administration, and when PN is indicated, case reports have demonstrated the lack of effectiveness of oral/enteral routes to adequately provide micronutrient requirements.[84] Equitable access to IV micronutrient preparations and individual micronutrients are required for safe clinical practice and must be an international priority to allow the safe and appropriate provision of PN.

Another issue is the intermittent shortages of micronutrients which are significant challenges for clinicians trying to provide safe and effective PN. North America has periodically experienced shortages of IV micronutrients over the last 30 years.[85] The reasons for this include regulatory issues, natural disasters, voluntary recalls, issues with raw materials, increase in demand, discontinuation, loss of manufacturing sites, and quality issues.[85] Mortality and morbidity associated with these shortages are acknowledged, with the most well described being complications of thiamine deficiency (fatal episodes of lactic acidosis, Wernicke's encephalopathy and beri beri).[84 86] However a variety of other clinical manifestations have also been reported including Cu deficient anaemia and hyposelenemia.[87] ASPEN has provided guidance on how to minimise clinical risk to patients in cases of periodic micronutrient shortage[88 89], and the FDA and other agencies are taking steps to improve the continuity of access of injectable drug products.[85 90] While these steps are helpful, rectification of the underlying causes for the shortages are critical to safe provision of PN. Further discussion of the topic and resources to assist clinicians in navigating shortages of PN components have been reviewed elsewhere.[85]

Q10: Who is responsible for prescribing intravenous micronutrients?

Recommendation:
The clinician responsible for prescribing and/or charting the PN macronutrient formulation(s) is ultimately responsible for prescribing the IV micronutrients to ensure complete nutrition is provided. This, as for all aspects of PN, should occur as part of a multidisciplinary Nutrition Support Team (NST) governance of PN. Where NSTs do not exist, the advocacy for the establishment of an NST should become an organisational focus.

Rationale:
The value of a multidisciplinary team-based approach to the provision of nutrition support including PN is well established, with demonstrated benefits including improved adherence to evidence based practice, improved clinical outcomes and financial savings.[91 92] The clinician who initially enters a PN order, irrespective of the discipline (physician, nurse, dietitian or pharmacist) is ultimately responsible for including orders for micronutrient additives, both MV and MTEs. Although regulations vary in geographic areas, in most countries a physician's order is required for PN. However, the physician may not have specific nutrition support training and may depend on the recommendations from members of a NST who have. When PN is compounded by pharmacists, yet another opportunity is available to assure addition of micronutrients.[93 94]

It is crucial that all NST members have adequate knowledge about the functions and requirements of micronutrients in patients receiving PN to avoid deficiencies and excess.[17 72]. In facilities where PN is compounded on site, the pharmacist is responsible for the PN admixtures preparation and should participate in the development and adherence to policies and procedures related to the compounding and delivery of safe and effective PN formulations. [72,73,95] Similarly, sound knowledge about Good Pharmaceutical Manufacturing Practice[82] in terms of standards, maintenance and training is essential.

Q11: How and when should micronutrient status be assessed /monitored*?*

Recommendation:
Micronutrient status assessment is recommended for vulnerable populations of patients with high index of suspicion for micronutrient deficiencies or toxicities. This patient group include those with conditions associated with increased utilization or excessive losses of micronutrients.

The following should be considered in the assessment of micronutrient status:
(a) clinical manifestations of symptoms that may suggest micronutrient abnormalities,
(b) appropriate laboratory examinations coupled with other tests such as CRP that may render results invalid or unreliable.

Monitoring of micronutrient status is recommended when active correction has taken place and when a patient is on long-term PN. Frequency of monitoring and the parameters or tests to be used will be based on clinical judgement.

***Rationale*:**
As the concurrent provision of MV and MTE supplementation with PN should provide micronutrient requirements serum levels of MN do not require routine monitoring in patients receiving short term PN. [2 19]

When monitoring is required, laboratory testing to guide micronutrient provision include serum, plasma or whole blood levels, or enzyme function.[96] There is, however, a lack of universal consensus as

to the optimal measures to use to assess status of specific micronutrients.[96] The availability and methods of testing vary widely between micronutrients and between regions, and clinicians are advised to liaise with their local laboratories and clinical experts for advice on what is available. In addition, micronutrient testing is often expensive[18 19] and, therefore, judicious assessment and targeted monitoring is advised.

The decision to assess micronutrient status with biochemical measures may be considered in a number of clinical situations.[18 19] These include where a high degree of clinical suspicion exists due to:

- Pre-existing lifestyle factors (self-neglect, alcohol and substance abuse, etc.)
- Clinical conditions that may increase micronutrient losses or requirements (malnutrition, altered GIT anatomy, critical illness, trauma, burns) use of medications (anticonvulsant and anti-retroviral therapies), baseline levels in long term PN, etc.
- Clinical conditions that may predispose to retention of micronutrients or their metabolites (renal or liver failure[2 30], cholestasis, etc.)
- Known regional or cultural predisposing factors (regional endemic vulnerability such as Iodine in Australia and New Zealand; Vitamin D deficiency in long term hospitalised patients, factors that limit skin exposure to UV light (skin pigmentation, cultural or religious clothing customs), regions with less sunlight during winter months; Fe deficiency in the Philippines, Se deficiency in China and Europe, etc.)

The decision to monitor micronutrient status biochemically may be considered in clinical situations that represent

- Follow up after micronutrient replacement therapies are provided[19]
- Routine surveillance of patients receiving long term/home PN[18,19,70]
- In cases of organ failure (liver or kidney), danger of toxicity necessitates monitoring.[2 30] Renal function should be considered when vitamins and TEs are supplemented.[64]
- In case of prolonged (>2 weeks) CRRT[21,22] a monthly monitoring of hydrosoluble micronutrients may be considered. [97 98]

If micronutrients are included with macronutrient provision (i.e., each day PN is provided) and have been prescribed in consideration of the individual clinical requirements, the risk of developing micronutrient complications is low, and isolated micronutrient monitoring may be of limited value in otherwise stable patients in the acute setting.[18,19] Therefore, careful consideration of the clinical significance of micronutrient testing needs to be considered in the acutely unwell patient, and routine measurement of serum vitamin levels is not usually recommended in critical care.[2] If micronutrient testing is considered to be appropriate, it should always be done in conjunction with a concurrent CRP level to allow interpretation.[18 19] (Refer to question 4 and Table 1). Similarly, the time elapsed from the last provision of IV micronutrient infusion to the timing of the sample collection should be considered in the interpretation of results. It is unfortunately not possible to provide a definite time period, since the infusion of micronutrients are sometimes done simultaneous to PN (in which case there is no time lapse) or the infusion can be separate from PN and given over 6 houts. In the latter case, a time lapse of 2 hours can be implemented before blood sampling.

Ideally samples should be obtained after the longest possible break from PN/IV micronutrient infusion

The Australian PEN society (AuSPEN) Trace element Guidelines (2014) and Vitamin Guidelines (2016) provide an outline of clinical considerations for when and how to biochemically assess individual micronutrient in the setting of PN.[18 19]

Q12: What are the consensus recommendations for micronutrient administration to parenteral nutrition?

Recommendation:
*ASPEN[17], AuSPEN[18 19] and ESPEN[67] have produced evidence-based documents that provide recommendations regarding micronutrient practice in the context of PN. Guidelines addressing PN micronutrient provision highlight the need to provide micronutrients daily together with PN and individualisation of micronutrient requirements and monitoring in long term PN. Consensus recommendations for routine micronutrient administration via PN formulations from our group are provided in **Table 4** and are largely consistent with previous recommendations.*

Rationale:
Due to the essential role of micronutrients in metabolism, micronutrients should be provided daily in conjunction with PN to prevent the development of deficiency. Contemporary commercial MV and MTE preparations currently available meet the recommendations for most patient groups and should be used as a first line provision. Consideration of additional replacement requirements may also be indicated in some clinical situations.

While there are some minor differences between these international guidelines owing to variation in methodology in the development process, clinical focus of guidelines, and/or regional vulnerability with regard to specific micronutrient deficiency, they all agree in principle on key overarching factors:

1. Micronutrients are essential components of PN, without which the nutrition provided is metabolically incomplete. As such they should be provided from day one of PN commencement until PN cessation.
2. Micronutrient prescription should be individualised to the clinical requirement of the patient.
3. Micronutrient status should be monitored in long term PN patients at baseline and 6 to 12-month intervals thereafter.[19 67] At risk patients may be monitored at the discretion of the overseeing clinicians.

Toxicity due to increased administration of fat-soluble vitamins can occur. A safe intake level is 10 times DRI. Up to 100 times DRI intake can be safely handled for water-soluble vitamins such as thiamine and vitamin C with toxicity development highly unlikely especially with short term administrations. For TEs caution should be given not to exceed 10-15 times the DRI for periods exceeding a few weeks.[2] Additional vitamin E is added to PN formulations containing high quantities of PUFA's to combat lipid peroxidation rendering systematic addition unnecessary. [19] Clinicians, therefore, need to be familiar as to whether the routine addition of vitamin E to PN formulations occurs during compounding in their local setting, as higher maintenance doses may need to be prescribed for patients receiving second and third generation lipids without vitamin E added during compounding to compensate for in-bag losses.

Additional considerations around individual micronutrient such as supplementation dosages, conditions requiring additional levels, dangers of toxicity and monitoring guidelines are discussed in Osland et al.[18,19]

Q13: Are there any risks associated with intravenous micronutrient provision at routine parenteral nutrition dosages?

Recommendation:
The highest risk regarding routine doses is not delivering them with PN. There are few instances in long term PN where the choice of parental micronutrient products administered should be carefully considered. In certain conditions, e.g. Mn encephalopathy and hemochromatosis (Fe) individual trace elements may need to be omitted and not routinely administered.

***Rationale*:**
Routine doses of Fe belong to standard practice amongst patients with intestinal failure or with very limited oral Fe absorption capacity (e.g., due to extensive resection of the upper GIT), as this element is essential. However, the optimal IV maintenance Fe regimen in the absence of anemia associated with chronic kidney disease (e.g., short bowel syndrome, bariatric surgery) warrants further investigations. It must be noted that IV Fe administration bypasses the normal regulatory mechanism of Fe bioavailability and homeostasis in the GIT. Since the daily turnover of Fe is low in most patients without anemia or chronic bleeding, oversupply of IV Fe risks causing Fe overload, increased oxidative stress, and infectious complications. Determining additional requirements in critically ill patients is difficult as inflammation alters Fe regulation and affects the accuracy of its laboratory assessments (e.g. ferritin). The prevalence of real Fe deficiency on ICU discharge, distinct from the inflammation sequestration issue, is elevated and contributes significantly to fatigue observed after discharge.[99] Recently a better understanding of Fe metabolism has shown that blood hepcidin may assist in diagnosing Fe deficiency in the presence of inflammation[100] and is currently under investigation.[101] The benefits of short-term IV supplementation (0.5-1 g for a few days) in reducing transfusion requirement have not yet been proven[102], but the trials have shown no increase in infectious complications[102 103], which were previously considered a prohibitive risk. It is therefore prudent to provide Fe to critically ill patients only in cases of proven Fe deficiency (which is best defined by hepcidin levels)[100] and not routinely.[103]

Cu and Mn are excreted in the bile. In patients on long term PN with hepatic failure, it is prudent to limit these TEs prior to obtaining serum levels. In addition, there are cases of Mn toxicities reported in long-term PN patients with magnetic resonance imaging of the brain showing Mn deposition in the basal ganglia (Mn encephalopathy).[104] This can be associated with neuropsychiatric symptoms and parkinsonism[105] which can be reversed upon removing Mn from PN .[106] The newer commercial MTE available in some parts of the world have lower amounts of Mn compared to previous solutions, and this needs to be considered.

Patients with renal failure are at potential risk of vitamin A toxicity due to reduced excretion. [68] In case of prolonged PN, both excessive and insufficient levels may be observed, which may justify dosing vitamin A in plasma on a annual or bi-annual frequency.

Q14: Are there specific micronutrient risks upon initiation of parenteral nutrition?

Recommendation:

The rapid reintroduction of glucose (such as commencing on full dose PN or high dose glucose infusion) to a patient experiencing starvation may precipitate refeeding syndrome. Thiamine is the main micronutrient implicated in refeeding syndrome complications.

Though rare, there have been reports of hypersensitivity reactions developing to vitamins and/or their components provided intravenously.

Rationale:

For a detailed review of refeeding syndrome see Boateng et al 2010.[107] Thiamine administration should be provided as a loading dose (300mg/d IV) prior to nutrition commencement, followed by a maintenance dose of 100 mg/d during nutrition to avoid deficiency complications developing. Broader MV and MTE supplementation should also be considered due to the risk of broad micronutrient vulnerability in patients at risk of refeeding, and concurrent micronutrient supplementation is essential in those receiving PN.

Hypersensitivity reactions to PN are uncommon. However, case reports have identified the component, thiamine, vitamin B complex, vitamin K and magnesium sulfate as likely causes of hypersensitivity reaction. Polyoxyethylated fatty acid derivatives, similar to Cremophor EL, can also be found as a vehicle for fat soluble vitamins leading to C activation-related pseudoallergy (CARPA). In addition, the inactive component, polysorbate, is believed to be a primary cause of hypersensitivity. Other case reports have identified the lipid emulsion component as the causative agent.[108] The option in these cases with regard to vitamins (not TE), might be to resort to modular assembly of a panel of vitamins which conforms to patient's requirements if using single-entity products in lieu of commercial bundled micronutrient products. But there are currently no studies available. When vitamins or trace elements cannot be added to PN for hypersensitivity reasons, it can be given enterally in situations where the GI tract is accessible and at least partly functional.[109]

Conclusion and call to action

This expert consensus paper has sought to highlight the importance of micronutrient provision as an integral, daily part of safe and responsible PN provision. It has also attempted to translate the intent of the existing guidelines available as they pertain to micronutrient provision in a range of PN patient populations into practical terms. It is our hope that this will assist with the adoption of evidence based recommendations irrespective of the level of experience of the clinician providing the PN intervention.

In terms of advocacy, there are a number of calls to action we wish to draw attention to. These affect the international nutrition community, the organisations they exist in, and the industries that support them.

1) The recognition that micronutrient must be provided daily from the commencement of PN macronutrients to provide safe and complete nutrition, and that failure to do so will pose nutritional risk. Delays to micronutrient commencement, their voluntary omission or partial provision is unacceptable practice that must be abandoned, and any additional cost considerations must be considered as inclusive of the PN provision.
2) The acceptance that PN is not the only indication to prescribe IV micronutrients. There are other high-risk groups (e.g. inadequate enteral intake, excessive losses) that also necessitate additional micronutrients.
3) The imperative of having required IV micronutrient preparations – in individual or MV/MTE preparations – available within all markets in which PN is provided, and in consistent supply, cannot be understated as an essential element to the safe provision of PN. Steps must be taken to resolve the current discrepancies of regional access and inconsistency in supply.
4) Coupled to adequate supply of IV micronutrient preparations, the importance of ensuring that the available products comply to the evidence-based recommendations in terms of composition.
5) More research should be conducted on the following:
    a. Method of administration of PN micronutrients
    b. Current situation with TE contamination in current compounding methods
    c. Compatibility and stability of micronutrients, especially TE solutions
    d. Multiple MN requirements in patients with special needs such as in the ICU
    e. Development of affordable assays to determine multiple micronutrient levels
6) Commitment to provide advanced nutrition support training for clinicians to promote and deliver safe PN practice

Ultimately micronutrients need to be understood as a critical component to nutritional provision and PN provided without them pose a considerable risk to nutritional status.

Conflict of interest:

The authors declare that they have no conflict of interest.

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Table 1: Impact of metabolic stress on micronutrient status

Micronutrient	Effect of acute phase response
Copper	• Increased Copper serum levels.[18,29,31] Pro-inflammatory cytokines stimulate the acute phase response. More copper is needed for increased ceruloplasmin synthesis, which is required for iron transport. • Serum copper levels should be interpreted in the context of inflammatory markers (e.g. CRP).[18]
Iron	• Decreased serum iron levels to ensure that less circulatory iron is available for bacteria to thrive on and to decreased oxidative damage to cells [2,18,29–31 40 33] • Increased ferritin (store) levels [18,29,31,66 40 33] • Serum iron levels should be interpreted in the context of inflammatory markers (e.g. CRP).[18]
Selenium	• Decreased serum levels [2,18,29–31,64 33 36] in proportion to the magnitude of the inflammatory response and also due to increased urinary losses • Serum Selenium levels should be interpreted in the context of inflammatory markers (e.g. CRP).[18] • Selenium concentrations can only be interpreted if CRP levels are <10 mg/L. [32 31] In presence of inflammation, and in absence of glutathione peroxidase determination, only very low values of Selenium (< 50% of reference value) should be considered as reflecting deficiency. [Colleagues, do we have a reference for this?]
Zinc	• Initial serum increase due to tissue damage that results in excessive zinc release [29] • Followed by decreased serum levels due to increased losses (skin, urine and stool) and decreased serum albumin levels. Albumin is a negative acute phase protein and since zinc is bound to albumin for transport, decreased albumin levels will result in less available zinc.[2,18,29–32,64 33 36] • Redistribution of zinc also results in an increased accumulation of zinc in the liver where it acts as co-factor for acute phase protein (APP) synthesis. • Serum zinc levels should be interpreted in the context of inflammatory markers (e.g. CRP). [18 32] • A reliable Zinc deficiency interpretation can only be made if serum CRP levels are < 20mg/L. [31,32] Very low levels <50% below reference values should always be considered as suspect of deficiency [Colleagues, do we have a reference for this?] • Excessive Zinc supplementation can induce copper deficiency.
Vitamins - general	• Decreased serum levels due to increased requirements (which could be due to increased metabolic rate and also because vitamins are used for biochemical functions during the acute phase response e.g. protein metabolism), increased catabolism, malabsorption, increased urinary losses and potential drug interactions.[29] • May return to normal serum levels after infection resolves without any treatment. For instance, vitamin A is bound to retinol-binding protein (RBP) for transport. Albumin (a negative APP) status will normalize after infection clears and hence vitamin A levels will improve.[29]
Vitamin A	• Vitamin A decreases during the acute phase because retinol binding protein acts as a negative acute phase protein.[29,31 36]
Vitamin B_1 – Thiamine	• Increased requirements for Vitamin B_1 may be needed during periods of increased metabolic stress and increased dietary carbohydrate provision.[19] • Serum levels not affected by periods of inflammation.[2]
Vitamin B_2	• Serum levels not affected by periods of inflammation.[2]
Vitamin B_6	• A decrease in serum vitamin B_6 is seen with only a slight increase in CRP (5-10 mg/L)[32 36]; therefore caution should be taken when

	interpreting true deficiency
Vitamin B_{12}	• Serum levels not affected by periods of inflammation.[2]
Vitamin C	• A decrease in serum Ascorbic acid [31 33 36] is seen with only a slight increase in CRP (5-10 mg/L)[32] • Therefore caution should be taken when interpreting true deficiency • Decreased plasma concentrations are seen within 24 hours post acute injury [110]
Vitamin D	• A decrease in serum 25(OH)-vitamin D is seen with only a slight increase in CRP (5-10mg/L)[32 33 36], therefore caution should be taken when interpreting true deficiency
Vitamin E	• Circulating Vitamin E declines modestly during inflammation [19,31 33 36], without reflecting deficiency[32]

Table 2: Micronutrient considerations for critical illness beyond provision of daily maintenance MTE provision.

Copper	• Negative copper balances have been demonstrated in CRRT[20 22 55 111] with copper losses of up to 6.5 µmol/24hrs on CRRT reported [55]
Iron	• Despite iron deficient anaemia being commonly observed during critical illness, this is multifactorial and may represent a beneficial adaptive change during critical illness. • There are presently no recommendations to manage iron deficiency with iron as a monotherapy.[103,112]
Selenium	• Selenium supplementation has been studied in sepsis and septic shock with mixed findings, and high dose, supra-physiological supplementation is not presently recommended in critically ill patients. [20 113] • Negative selenium balances have been demonstrated in CRRT[55 111], with losses of up to 1 µmol/24hrs of CRRT reported.[55]
Zinc	• Zinc is recognised to be a vulnerable trace element in the critically ill that should be monitored and replaced if underlying deficiency or high risk of developing a deficiency is suspected[114] • However no recommendations currently exist to guide optimal zinc dosing in the critically ill (IV or otherwise)[115] • For acute renal failure requiring CRRT, 50 mg per day of zinc is recommended.[116]
Mixed antioxidant vitamins (A,C,E)	• Supplemental vitamin and trace element combinations (Zn, Se, Vits A, C, E, N-acetylcysteine, provided via EN or IV or combination) are not recommended in critically ill patients.[113] • In major burns, combination of Cu, Se, Zn, Vitamin C in doses 5-10 times DRI combined with standard multimicronutrient are provided IV during the first 2-3 weeks and result in normalisation of antioxidant function.[43]
Vitamin B_1 - Thiamine	• Thiamine is emerging as an increasingly important vitamin in the management of sepsis. Normalising thiamine levels during septic shock may reduce mortality and reduce progression to renal replacement therapies although these results require validation.[117] • High thiamine losses have been demonstrated with CRRT and thiamine supplementation should be considered in this patient group to avoid the development of deficiency.[22 55 111] • Refeeding syndrome may be seen in ICU, particularly with the high rates of malnutrition observed in the critically ill. Depending on refeeding risk, IV thiamine replacement prior to or together with commencement of feeding is recommended in refeeding prevention and treatment.[118] • MV admixtures contain the DRI for thiamine, but this amount may be insufficient with a high dextrose load, leading to iatrogenic deficiency states. Considering its low risks, a liberal amount of thiamine should be

	administered in critical care practice at daily dosages of 300 mg IV for at-risk patients, and 100 mg in all other patients, during the first 48 hours of ICU admission.[117]
Vitamin B_6	• Patients with acute renal failure requiring CRRT should receive 100mg vitamin B_6 daily for 3-5 days.[116] • Monitor serum levels.
Vitamin C	• Vitamin C may be beneficial in times of oxidative stress[119] and requirements are acknowledged to increase during critical illness[117] • Pharmacological doses may be of benefit in the early stages of critical illness[117], however these results require validation.[113] • Vitamin C replacement may be of benefit to reverse depletion demonstrated during cardiopulmonary bypass[120] • Monitoring of plasma concentrations is recommended in patients requiring PN for more 6 months or more [42] • The risk of nephrolithiasis should be monitored in long-term HPN patients[68]
Vitamin D	• Vitamin D levels is recognised to be commonly low in critically ill populations and a predictor of outcome. [113,121 117] • Vitamin D is ineffective in the acute setting. The 1,25 hydroxy form is needed when liver and renal functions are suboptimal.[122] Until the results on on-going trials are available and accepted (VIOLET study, NCT 03096314 and VITDALIZE study, NCT 031188796), the routine administration of additional Vitamin D (by oral or intra-muscular route) for patients on short-term PN cannot be justified.[123] • It should be noted, however, that some papers describing lack of benefit of vitamin D in critically ill patients may be flawed in design as the levels were obtained after resuscitation. [124]

Table 3: Potential micronutrient deficiencies following surgical resections of different segments of the intestine

GIT Area resected	Potential micronutrient deficiency
Gastric resection	• Vitamin D [17] • Vitamin K [17] • Iron [2 19] • Vitamin B_{12} [2 19]
Gastric bypass surgery	• Vitamin K deficiency [17] • Copper [18]
Gallbladder resection	• Vitamins A, D, E and K [2]
Jejuno-ileal bypass surgery	• Vitamins A, D, E, K [17,125] Calcium[125]
Whipple (pancreatico-duodenectomy)	• Vitamins A, D, E, K, vitamin B_{12} and iron[126]
Proximal jejunum	• Duodenum and proximal jejunum – zinc [66], copper [127]
Terminal ileum resection	• Vitamin B_{12} [2,17,19,125]
Short bowel syndrome	• Vitamin B_2 [17], A, E, K (if colon is resected) [17,19], folic acid, chromium [17], zinc and iron due to losses [18]

Table 4: Comparison of consensus recommendations for daily micronutrient administration

	2012 ASPEN consensus statement [17] North America	2016 AuSPEN Vitamin Guidelines[19] 2014 AuSPEN Trace Element Guidelines[18] Australia and New Zealand	2016 ESPEN CIF guidelines [70] Europe	Consensus recommendation
Vitamin A / Retinol	3300 IU (990 µg RE)	3500 IU (1050 µg RE)	No recommendation	3300-3500 IU (990-1050 µg RE)
Vitamin D / Cholecalciferol	200 IU (5µg)	200 IU (5 µg)	No recommendation	200 IU (5µg)
Vitamin E / Alpha tocopherol	10 mg	10 mg	No recommendation	10 mg
Vitamin K / phytomenadione	150 µg	No recommendation made: Individual assessment recommended.	No recommendation	Individual assessment
Vitamin B_1 / Thiamine	6 mg	3 mg	No recommendation	3-6 mg
Vitamin B_2 / Riboflavin	3.6 mg	4-5 mg	No recommendation	3.6-5 mg
Vitamin B_3 / Niacin	40 mg	40-47 mg	No recommendation	40-47 mg
Vitamin B_5 / Pantothenic Acid	15 mg	16-17 mg	No recommendation	15-17 mg
Vitamin B_6 / Pyridoxine	6 mg	3 mg	No recommendation	3-6 mg
Vitamin B_{12} Cobalamin	5 µg	5-6 µg	No recommendation	5-6 µg

Vitamin B_9 / Folic acid	600 µg	400 µg	No recommendation	400-600 µg
Ascorbic Acid / Vitamin C	200 mg	110-150 mg	No recommendation	110-200 mg
Biotin	60 µg	60 µg	No recommendation	60 µg
Zinc (Zn)	39-76 µmol (2.5-5 mg)	50-100 µmol (3.2-6.5mg)	38-61 µmol (2.5-4mg)	39-100 µmol (2.5-6.5 mg)
Copper (Cu)	4.7-7.8 µmol (300-500 µg)	5-8 µmol (317-508 µg)	4.7-9.6 µmol (0.3-0.5mg)	4.7-9.6 µmol (300-610µg)
Selenium (Se)	0.75-1.25 µmol (60-100 µg)	0.75-1.25 µmol (60-100 µg)	0.2-0.8 µmol (16-63 µg)	0.25-1.25 µmol (20-100 µg)
Manganese (Mn)	1 µmol (55 µg)	1 µmol (55 µg)	1.1-1.8 µmol (60-100 µg)	1-1.8 µmol (55-100 µg)
Iron (Fe)	No routine recommendation in US	20 µmol (1.1 mg) may not be necessary	17.9 mmol (1 mg)	1-1.2mg in those recommending Fe
Chromium (Cr)	0.2-0.3 µmol (10-15 µg)	0.2-0.3µmol (10-15 µg) may not be necessary	No recommendation	0.2-0.3µmol (10-15 µg)
Molybdenum (Mo)	No routine recommendation in US	0.2 µmol (19 µg) probably not necessary	No recommendation	No recommendation
Iodine (I)	No routine recommendation in US	1 µmol (126 µg)	0.5-1.2 µmol (70-150 µg)	0.5-1.2 µmol (70-150 µg) in those recommending it

CIF: Chronic intestinal failure

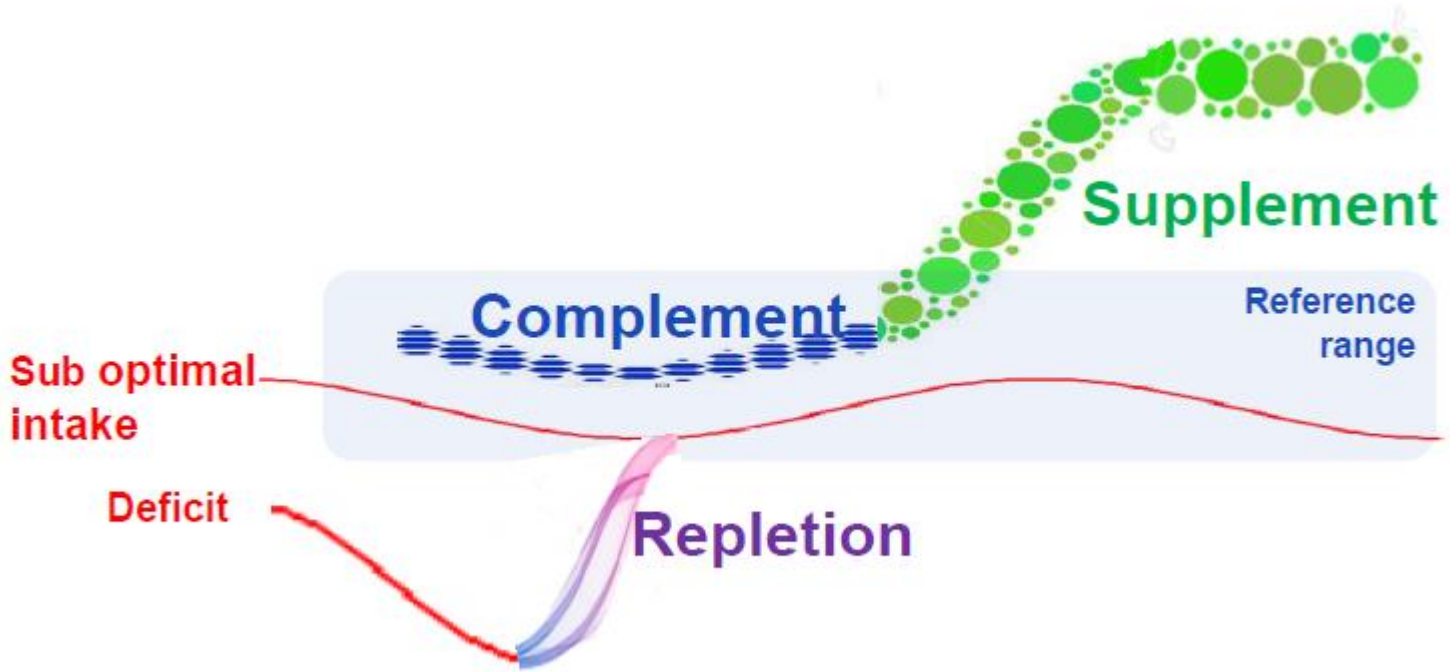

Figure 1: Trace element correction options

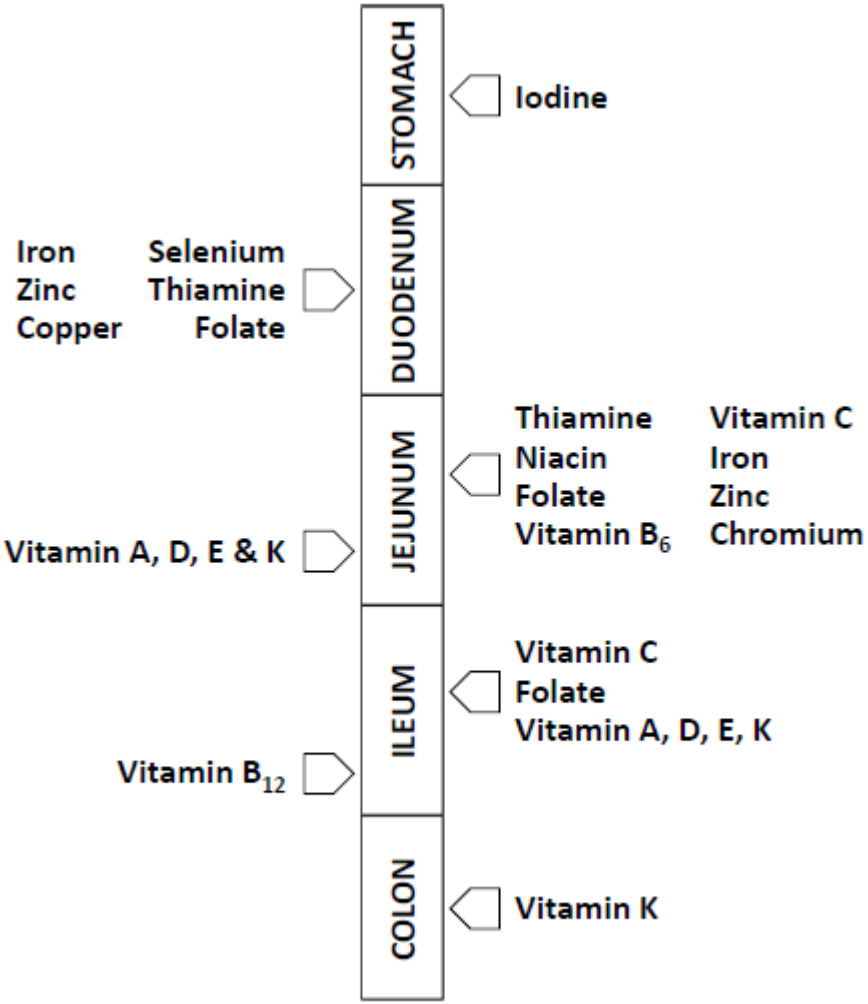

Figure 2: Micronutrient absorption sites