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Parenteral Provision of Micronutrients to Pediatric Patients: An International Expert Consensus Paper

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Abstract

Introduction: Micronutrients (vitamins and trace elements) are essential to all nutrition. For children and neonates who are dependent upon nutrition support therapies for growth and development, the prescribed regimen must supply all essential components. This paper aims to facilitate interpretation of existing clinical guidelines into practical approaches for the provision of micronutrients in pediatric parenteral nutrition. *Methods:* An international, interdisciplinary expert panel was convened to review recent evidence-based guidelines and published literature to develop consensus-based recommendations on practical micronutrient provision in pediatric parenteral nutrition. *Results:* The guidelines and evidence have been interpreted as answers to 10 commonly asked questions around the practical principles for provision and monitoring of micronutrients in pediatric patients. *Conclusion:* Micronutrients are an essential part of all parenteral nutrition and should be included in the pediatric nutrition therapy care plan. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S2):S5–S23)

Keywords

minerals/trace elements; neonates; parenteral nutrition; pediatrics; public policy; vitamins

Introduction

Micronutrients refers to all vitamins and trace elements (TEs) known to be essential constituents of the diet that are required to maintain fundamental metabolic functions. A lack of any of these essential components results in nutrient-specific deficiencies that can be symptomatic and interfere with growth and development. Routine provision of micronutrients from commencement of pediatric nutrition therapy is widely recommended but is far from universal practice. The underlying condition of the patient may result in specific requirements for individual micronutrients.[1,2]

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Providing micronutrients to patients in a parenteral nutrition (PN) regimen requires all nutrients to be in a form suitable for administration via the parenteral route.[3,4] Mixing everything into a single PN admixture simplifies administration at the bedside but presents the challenge of physical and chemical compatibility and stability.

Incorporating >50 different chemical species, some in an emulsified form, in the same container means that the majority of admixtures have limited shelf-life, usually not more than 1–7 days' stability.[3-5] PN products marketed by different manufacturers may differ markedly in their composition.[6,7] Mixing products from different manufacturers and suppliers without supporting stability data is not advisable.[8]

Monitoring micronutrient status is complex; whereas an absence of water-soluble vitamins may produce visible symptoms such as Wernicke's encephalopathy within 2–3 days, for many other micronutrients the deficiency picture is more complex and slower to develop. For many patients receiving PN, there will be concurrent enteral nutrient intake, moderating the need for parenteral micronutrient supplementation, although the extent of absorption may vary. For TEs, monitoring is complex but nevertheless important to avoid potential toxicity, notably in, for example, patients with liver disease and patients receiving long-term parenteral support.[2,7] Furthermore, it is known that significant but irregular amounts of TEs are present as contaminants of the other PN products that could influence daily dosage.[9]

National and international nutrition societies have produced guidelines to assist those responsible for prescribing PN to children and neonates and reduce variations in practice.[10-13] However, these guidelines are large and complex documents, often covering oral, enteral, and parenteral requirements. The availability of products and the skill mix and experience of local staff and the facilities at their disposal vary widely, often making it difficult to precisely follow the official guidelines. The aim of this paper is to bridge the gap between evidence-based guidelines and practical application of PN at the bedside by providing recommendations based upon our expert consensus interpretation of published guidelines together with links back to the evidence. It aims to provide advice on what a PN regimen should provide and assist users to recognize when to seek region-specific advice from national and regional centers of excellence. The provision of micronutrients in adults was similarly interpreted recently.[14]

The micronutrients addressed are fat-soluble vitamins (A, D, E, K), water-soluble vitamins (B and C), and TEs copper (Cu), iodine (I), iron (Fe), selenium (Se), zinc (Zn), chromium (Cr), manganese (Mn), and molybdenum (Mo).

Methodology

An interdisciplinary panel was convened representing clinical, pharmaceutical, laboratory, and academic input with a focus on practical experience in provision of nutrition therapy in neonatal and pediatric patients. Working from existing published guidelines and evidence-based publications, supplemented by searching databases such as Medline and Science Direct and personal resources, the group has attempted to answer 10 common questions to guide clinical practice in a range of settings. The sections were allocated to individual members of the team to prepare a working draft to be circulated for discussion among the group.

Terminology and Metrology

The term "supplementation" is used for the delivery of micronutrients to cover basal needs when PN administration aims at restoring deficiencies and ongoing losses, or when the aim is to achieve supranormal levels, including pharmaconutrition. Dietary recommended intakes (DRIs), will be used to indicate recommended dosages. With no international agreement on micronutrient Units, posology will be expressed in both microgram and micromol.[15] Ten common questions for practical consideration regarding the use of micronutrients in pediatric PN are:

1. Which are the essential micronutrients for neonatal and pediatric patients?
2. When and under what conditions are parenteral micronutrients indicated?
3. Which micronutrients are important and when are they required for neonatal and pediatric critically ill patients?
4. Which micronutrients are important and when are they required for neonatal and pediatric burns patents?
5. Which micronutrients are important and when are they required for neonatal and pediatric surgical patients?
6. Which micronutrients are important and when are they required for pediatric home PN (HPN) patients?
7. What are the practical considerations when providing micronutrients parenterally?
8. How and when should micronutrient status in neonatal and pediatric patients be assessed/monitored?
9. What are the clinical risks of providing micronutrients to neonatal and pediatric patients?
10. What are the recommendations for providing micronutrients to neonatal and pediatric patients when suitable products are unavailable?

Table 1. Recommended Doses for Parenteral Supply of Fat-Soluble and Water-Soluble Vitamins for Preterm Infants, Infants, and Children.

Vitamins	Preterm infant <37 weeks' gestation	Infant >12 months old	Children/adolescents 1–16 years old
Vitamin A	700–1500 IU/kg/d	500–1000 IU/kg/d	500 IU/d
Thiamin B_1	0.35–0.5 mg/kg/d	0.35–0.5 mg/kg/d	1.2 mg/d
Riboflavin	0.15–0.2 mg/kg/d	0.15–0.2 mg/kg/d	1.4 mg/d
Pyridoxine	0.15–0.2 mg/kg/d	0.15–0.2 mg/kg/d	1.0 mg/kg/d
Niacin	4–6.8 mg/kg/d	4–6.8 mg/kg/d	17 mg/d
Vitamin B_{12}	0.3 µg/kg/d	0.3 µg/kg/d	1 µg/d
Pantothenic acid	2.5 mg/kg/d	2.5 mg/kg/d	5 mg/d
Biotin	5–8 µg/kg/d	5–8 µg/kg/d	20 µg/d
Folic acid	56 µg/kg/d	56 µg/kg/d	140 µg/d
Vitamin C	15–25 mg/kg/d	15–25 mg/kg/d	80 mg/d
Vitamin D	200–1000 IU/d or 80–400 IU/kg/d	400 IU/d or 40–150 IU/kg/d	400–600 IU/d
Vitamin E	2.8–3.5 mg/kg/d	2.8–3.5 mg/kg/d	11 mg/d
Vitamin K	10 µg/kg/d	10 µg/kg/d	200 µg/d

Modified with permission from ESPGHAN 2018 recommendations by Bronsky et al.[1]

Table 2. Suggested Parenteral Trace Element Recommendations.

	Maintenance daily PN dose, µg/kg (µmol/kg)		
Trace element	Preterm infants	Infants and children	Maximum per day
Chromium	–	0.2 (0.004)	0.5 (0.1)
Copper	40 (0.6)	20 (0.3)	500 (10)
Iodine	1–10 (0.01–0.1)	1.0 (0.01)	
Iron	200–250 (3.6–4.5)	50–100 (0.9–1.8)	5000 (89)
Manganese	1.0 (0.02)	1.0 (0.02)	50 (1.0)
Molybdenum	1.0 (0.012)	0.25 (0.003)	5.0 (0.06)
Selenium	7.0 (0.09)	2–3 (0.03–0.04)	100 (1.3)
Zinc	400–500 (6.2–7.8)	50–250 (0.78–3.8)	5000 (78)

Modified with permission from ESPGHAN 2018 recommendations by Domellöf.[2]

Summary of Recommendations

Q1. Which Are the Essential Micronutrients for Neonatal and Pediatric Patients?

1. As micronutrients are essential for optimal human growth and development, daily provision should be an integral part of any PN therapy.
2. The appropriate route of micronutrient administration should be determined in an initial comprehensive patient assessment and included within an interdisciplinary nutrition care plan.
3. Recommended daily vitamin and TE requirements for PN are shown in Tables 1 and 2.
4. The underlying condition of the patient may result in specific requirements for individual micronutrients.

Q2. When and Under What Conditions Are Parenteral Micronutrients Indicated?

1. Micronutrients are indicated in all pediatric PN regimens and should be administered as early as possible and certainly not withheld for more than a few days.

Q3. Which Micronutrients Are Important and When Are They Required for Neonatal and Pediatric Critically Ill Patients?

1. Micronutrients should be an integral part of nutrition therapy in the critically ill pediatric patient to reduce oxidative stress and support immune functions, wound healing, and organ recovery.

2. If clinically indicated, micronutrient status during an ongoing inflammatory state should be assessed and interpreted based on physical examination, dietary history, and biomarkers unaffected by the acute inflammatory response.
3. Clinicians should prescribe according to the individual patient requirements to address deficiencies while avoiding toxicity.
4. The pediatric critically ill cardiac patient may require higher micronutrient supplementation, especially during long-term therapy with diuretics.
5. Significant micronutrient losses due to prolonged continuous renal replacement therapy (CRRT) in the critically ill should be replaced daily.
6. Special consideration regarding micronutrient supplementation should be given to both obese and undernourished critically ill children, particularly taking account of dietary history, ideal body weight, inflammation, and possible organ dysfunction.

Q4. Which Micronutrients Are Important and When Are They Required for Neonatal and Pediatric Burn Patients?

1. Burned neonatal and pediatric patients must be assessed as early as possible for their micronutrient needs.
2. If PN is deemed necessary, then the full range of micronutrient supplementation should be part of their ongoing nutrition management, both during hospitalization and for up to 24 months after the burn incident.
3. Vitamins A, C, and D and TEs Fe, Cu, Se, and Zn may be significantly depleted in patients with burns, necessitating supplementation with these specific micronutrients at doses greater than those provided in standard products.

Q5. Which Micronutrients Are Important and When Are They Required for Neonatal and Pediatric Surgical Patients?

1. Clinicians must be familiar with the extent of tissue resection and the remaining anatomy to help predict and manage postoperative micronutrient deficiencies.
2. Assessment of the patient's surgical history, including the length of the remaining bowel, is essential to determine whether fat-soluble vitamins are being absorbed enterally.
3. Zn, Fe, Cu, Se, and Mn status must be assessed in postoperative intestinal failure (IF).
4. The implementation of a standard nutrition therapy protocol, including micronutrients, can improve outcomes of necrotizing enterocolitis (NEC) in very low-birth-weight (VLBW) infants.

Q6. Which Micronutrients Are Important and When Are They Required for Pediatric HPN Patients?

1. Micronutrients should be provided routinely to all pediatric patients receiving HPN.
2. Daily micronutrient requirements for HPN are listed under Q1 and Tables 1 and 2, but higher doses may be necessary when there are abnormal intestinal losses, such as post surgery.
3. Patients receiving long-term HPN need their micronutrient status monitored periodically to avoid deficiencies and/or toxicities.
4. HPN represents an extremely diverse group of patients, for whom advice from national or regional specialist centers will often be helpful, particularly with practical funding and supply issues in specific countries and regions.

Q7. What Are the Practical Considerations When Providing Micronutrients Parenterally?

1. Clinicians should be aware of the potential stability issues with nonroutine pediatric PN regimens containing higher concentrations of specific nutrients/micronutrients.
2. Fe may lead to destabilization of intravenous lipid emulsion (ILE), so all-in-one (AIO) admixtures containing Fe should be avoided unless stability information is available for the specific PN formulation.
3. Addition of multivitamins to the PN bag on the day of administration reduces the risk of degradation.
4. Protection of the PN bag from oxygen and light minimizes light-catalyzed oxidation of micronutrients and has been shown to reduce mortality in preterm infants.
5. Reliance on variable amounts of micronutrient contaminants in some PN components to provide the daily PN requirement would require monitoring to ensure adequate provision.

Q8. How and When Should Micronutrient Status Be Assessed/Monitored?

1. Assessment of blood measurements of micronutrients should be best performed in the absence of systemic inflammation and should be interpreted in the context of the clinical condition and history. Water-soluble vitamins should be assessed more frequently than fat-soluble vitamins.

2. Patients suspected to have a previous micronutrient deficiency should be initially monitored at least monthly.
3. Patients receiving stable micronutrient supplementations can have a reduced 3-monthly frequency of monitoring.
4. Measuring serum/plasma levels alone might not reflect true micronutrient status.

Q9. What Are the Clinical Risks of Providing Micronutrients to Neonatal and Pediatric Patients?

1. To avoid the risk of deficiencies, micronutrients should be included routinely in all neonatal and pediatric PN regimens
2. The risk of refeeding syndrome (RFS) can be minimized with a nutrition care plan incorporating a protocol for administering an immediate dose of thiamin, restricting energy provision, and closely monitoring electrolytes, especially serum phosphate.
3. Fe, Cu, and Mn levels should be regularly monitored, especially in patients with liver disease who are receiving long-term (or home) PN, to avoid potential toxicity.
4. In centers using PN products and other pharmaceuticals packaged in glass, aluminum levels in blood should be checked monthly.
5. Potential hypersensitivity reactions, largely due to excipients in certain vitamin preparations, should be heeded.
6. In some situations, such as in premature neonates, individual micronutrients may need to be prescribed separately, as there is a risk that standard commercial micronutrient products may provide too much or too little of the other micronutrients.

Q10. What Are the Recommendations for Providing Micronutrients When Suitable Pediatric Products Are Unavailable

1. Maintain regular access to national society and/or regulatory agency websites for updates on the supply/availability situation.
2. Evaluate the use of adult multivitamin/multi-TE products at reduced doses for pediatric PN regimens.
3. If adult multivitamins are used in neonates, products containing polysorbate 80 or 20 or propylene glycol should be avoided.
4. Administer individual micronutrient parenteral additives, especially the key vitamins—thiamin, folic acid, and pyridoxine—that are required daily.
5. Consider using oral/enteral micronutrient alternative products when clinically possible.
6. Increase monitoring and awareness of micronutrient deficiencies.
7. Document all adverse reactions related to shortages or unavailability of pediatric products.

Q1. Why Are Micronutrients Important for PN and When Should They Be Provided?

Answer 1: Micronutrients are essential for optimal human growth, health, and development, necessitating daily supplementation in PN regimens. Depletion can affect immune status, lead to organ dysfunction and muscle weakness, or impair wound healing.

Recommendations

1. As micronutrients are essential for optimal human growth and development, daily provision should be an integral part of any PN therapy.
2. The appropriate route of micronutrient administration should be determined in an initial comprehensive patient assessment and included within an interdisciplinary nutrition care plan.
3. Recommended daily vitamin and trace element requirements for PN are shown in Tables 1 and 2.
4. The underlying condition of the patient may result in specific requirements for individual micronutrients.

Rationale

Micronutrients are essential to life. They function as important coenzymes and cofactors for the metabolism of macronutrients and are usually obtained through the diet.[14] Provision must be appropriate to the life stage and clinical requirement of the patient and should be part of any nutrition intervention from commencement of therapy. Patients with insufficient gastrointestinal (GI) function, who are unable to maintain adequate nutrition by GI absorption, will also have micronutrient depletion. In cases of insufficient dietary intake, signs and clinical symptoms of micronutrient deficiency may manifest as functional or structural abnormalities that may be reversed by supplementation of the micronutrient.[16,17]

Many patients will have higher demands caused by excessive losses, redistribution from circulation to tissues, abnormalities in metabolism, or inadequate GI absorption. In children, malabsorption conditions include short-bowel syndrome, autoimmune enteropathies, and congenital diarrhea, among others. Micronutrient deficiencies can deleteriously affect enzyme functions and other biochemical processes, leading to organ dysfunction, muscle weakness, poor wound healing, and altered immune status. Deficiency or excess of a single micronutrient may impact the availability and function of another.[18] Since it is known that reserves of most water-soluble vitamins are minimal[1] and

little is known about tissue reserves of TEs,[2,19] early supplementation of micronutrients seems reasonable to support their essential roles in metabolic processes. The appropriate route of administration should be determined in the initial assessment and if there is a change in the clinical state of the patient.

Micronutrient deficiency, when unrecognized, may lead to developmental delay or organ damage,[20] but there is insufficient research to clarify which micronutrients are critical for regular monitoring. Mild to moderate Zn deficiency, but only severe vitamin A and Fe deficiencies, appears to affect growth,[21] whereas properly planned and delivered nutrition therapy may improve growth and weight gain.[22,23] Screening for vitamin D deficiency is currently recommended only for individuals who present with risk factors for hypovitaminosis.[24]

Micronutrient-enriched enteral nutrition (EN) or oral nutritional supplements are the preferred first option for the provision of micronutrients in hospital. However, when the enteral route is unavailable or inefficient, micronutrients must be administered in PN. DRIs have been developed in healthy populations, and as such, their application to acutely or chronically ill patients requiring parenteral supplementation are only estimates and should always be considered together with a comprehensive initial assessment aimed at identifying deficiencies so that preexisting malnutrition or specific requirements can be addressed.[25] Whatever the administration route, individual micronutrients undergo the same metabolic and elimination pathways. Nevertheless, when provided orally, they are regulated by normal physiological mechanisms, whereas the parenteral route may lead to deposition of nonphysiological levels and chemical forms in tissues.[26]

The pan-European guidelines endorsed by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/European Society for Clinical Nutrition and Metabolism (ESPEN)/European Society for Pediatric Research (ESPR)/Chinese Society for Parenteral and Enteral Nutrition (CSPEN)[27] have published evidence-based recommendations concerning provision of micronutrients in PN for children. These emphasize the importance of an interdisciplinary team developing an overall "nutrition care plan" when administering PN. This should include defined goals and an estimate of the expected duration of PN, based upon assessment of vital signs, physical state, anthropometry, laboratory indices, and dietary intake.[11,12,19] A thorough initial assessment is required to determine special needs. The consensus view is that micronutrients should be an integral part of PN from the first day of therapy.

Q2. When and Under What Conditions are Parenteral Micronutrients Indicated?

Answer 2: Regular administration of micronutrients is essential for all hospitalized pediatric patients, and when the oral/enteral route is not available or is insufficient, then PN is indicated.

Recommendation

1. Micronutrients are indicated in all pediatric PN regimens and should be administered as early as possible and certainly not withheld for more than a few days.

Rationale

Micronutrients are generally provided by a balanced diet in neonates and infants by the normal progression from breastfeeding to mixed feeding to "normal" diet; but in patients requiring EN support and/or PN, they must be prescribed and provided by these alternative routes.[23,28] All PN regimens should include micronutrients. Regular parenteral administration of vitamins and TEs ensures the provision of essential substrates and cofactors involved in many metabolic processes.

The assessment and prescription of micronutrients, as part of a PN regimen, should ideally be performed by an experienced interdisciplinary nutrition support team (NST),[12] including a pediatrician or neonatologist, specialist pharmacist, dietitian, nutrition nurse, and a medical laboratory scientist. The NST should also be responsible for children with IF in need of long-term PN or HPN. In some countries, care of long-term patients is further supported by one or more national "center(s) of excellence."

In pediatrics, and especially neonatology, the nutrition needs for growth and development require a higher nutrient density in the PN admixture. Ideally, regimens should include the "conditionally essential" amino acids: cysteine and taurine[29] contain sufficient calcium and phosphate for skeletal development and the full range of micronutrients.[27] Pediatric patients require differing amounts of the TEs Cr, Cu, I, Mn, Mo, Se, and Zn, according to age and weight (see Table 2, Q1), and may be particularly susceptible to Fe deficiency, especially neonates requiring multiple frequent blood sampling or patients requiring long-term PN with minimal enteral intake. When Fe is required, it should be administered separately as an intermittent infusion or as an oral supplement.[2]

Q3. Which Micronutrients Are Important and When Are They Required for Pediatric Critically Ill Patients?

Answer 3: Micronutrients play important roles as free radical scavengers and in supporting immune functions and tissue repair during critical illness.

Recommendation

1. Micronutrients should be an integral part of nutrition therapy in the critically ill pediatric patient to reduce oxidative stress and support immune functions, wound healing, and organ recovery.
2. If clinically indicated, micronutrient status during an ongoing inflammatory state should be assessed and interpreted based on physical examination, dietary history, and biomarkers unaffected by the acute inflammatory response.
3. Clinicians should prescribe according to the individual patient requirements to address deficiencies while avoiding toxicity.
4. The pediatric critically ill cardiac patient may require higher micronutrient supplementation, especially during long-term therapy with diuretics.
5. Significant micronutrient losses due to prolonged CRRT in the critically ill should be replaced daily.
6. Special consideration regarding micronutrient supplementation should be given to both obese and undernourished critically ill children, particularly taking account of dietary history, ideal body weight, inflammation, and possible organ dysfunction.

Rationale

During critical illness, micronutrients play important roles as free radical scavengers and in supporting immune functions and tissue repair.[30] Deficiencies may increase the critically ill child's susceptibility to sepsis and ventilator support.[31]

The redistribution of micronutrients between tissues and body fluids and the reduced synthesis of carrier proteins induced by the inflammatory response syndrome result in a significant depletion of many plasma micronutrient concentrations regardless of actual body stores (Se, Zn, vitamin A, vitamin B_6, vitamin D, and vitamin C).[32,33] This has important implications for the interpretation of individual plasma concentrations. For instance, low vitamin D concentration is associated with worse clinical outcomes in pediatric intensive care patients, but it is difficult to determine whether a low concentration reflects a true deficiency or if it is an epiphenomenon.[30] Thiamin and folic acid have also been reported to be reduced in congestive heart failure, sepsis, and inflammation and during oxidative stress, whereas the concentrations of the positive acute phase reactants serum ferritin and ceruloplasmin increase during critical illness, likely underestimating Fe and Cu deficiencies.[33] The interpretation of micronutrients status may further be complicated by anti-inflammatory treatment counteracting the effects of the inflammatory response syndrome. Postnatal dexamethasone administration has been shown to increase vitamin A concentrations (retinol and retinol-binding protein) in preterm infants.[33-35] Long-term use of the diuretic furosemide may also cause acute depletion of thiamin, leading to exacerbation of congestive heart failure.[37]

Sepsis, trauma, or multiple organ failure may induce acute renal failure (ARF).[40] The principal aim of nutrition therapy in ARF is to enhance immunocompetence and improve wound healing and organ dysfunction. Individual ARF patients' nutrition requirements can vary considerably,[41] but those with underlying malnutrition will be at increased risk of micronutrient deficiencies due to decreased intake, malabsorption, increased utilization, and greater losses from CRRT because of the high fluid turnover. Prolonged CRRT can contribute to Cu deficiency, and plasma levels of Se, Zn, and most vitamins, except vitamin K, are also decreased, such that requirements will generally exceed healthy recommended dietary allowance (not daily) (RDA). Thiamin removal during CRRT may potentiate the deleterious effects of decreased thiamin levels,[42] and a loading dose has been advocated upon intensive care unit (ICU) admission,[43] followed by regular intermittent infusions during CRRT while monitoring whole-blood levels. Recent evidence suggests pyridoxine and folate losses with CRRT may be greater than earlier reported, requiring higher daily supplementation and routine monitoring of serum levels in accordance with ESPEN guidelines.[44] Supplementation of vitamin C has also been proposed,[41] but caution is advised because of the potential for excess ascorbate to be converted to the toxic oxalate salt.

Childhood obesity can increase the risk of mortality in the critically ill child,[45] necessitating special considerations for nutrition therapy in the pediatric ICU (PICU). Obesity is an inflammatory syndrome that results in increased blood volume, increased cardiac output, and decreased renal and/or hepatic function, which can all affect the metabolism of parenteral micronutrients. Previous dietary intake of foods with low nutrient density and bariatric surgery increase the risk of micronutrient deficiencies in the PICU, particularly vitamin D, thiamin, folate, B_{12}, and Fe.[46] PN dosing should be based on ideal body weight, but because of the complex factors that affect safe and effective administration and dosing of nutrients and other medications, consultation with a pediatric pharmacist is important.[47]

Clinicians and NSTs should address micronutrient deficiencies according to the individual ICU patients' requirements and prescribe accordingly. Of note, Dao reported that supplementation of micronutrients during times of severe illness has not demonstrated clear benefit in either survival advantage or reduction of adverse outcomes.[30] Conversely, Berger asserted that there is evidence that a combined PN supplement of Cu, Zn, and Se can decrease the risk of nosocomial infections in the ICU.[48] Any supplementation of TEs at greater than RDA posology must be accompanied by serial monitoring of renal function and blood levels.

Table 3. Vitamin and Trace Element Requirements in Children With Burns.

Age, y	Vit A, IU	Vit D, IU	Vit E, IU	Vit C, IU	Vit K, μg	Folate, μg	Cu, mg	Fe, mg	Se, μg	Zn, mg
0–13										
Nonburned	1300–2000	600	6–16	15–50	2–60	65–300	0.2–0.7	0.3–8	15–40	2–8
Burned	2500–5000			250–500		1000[a]	0.8–2.8		60–140	12.5–25
≥13										
Nonburned	200–3000	600	23	75–90	75–120	300–400	0.9	8–18	40–60	8–11
Burned	10,000			1000		1000[a]	4		300–500	25–40

Vit, vitamin.
Reproduced under creative commons license (http://creativecommons.org/licenses/by/4.0/) from Clark et al.[50]
[a]Administered 3 times weekly.

However, standard commercial fixed-formulation products have limitations.[49]

Q4. Which Micronutrients Are Important and When Are They Required for Pediatric Burns Patents?

Answer 4: Micronutrients are essential to improve immune status and wound healing after burns.

Recommendation

1. Burned neonatal and pediatric patients must be assessed as early as possible for their micronutrient needs.
2. If PN is deemed necessary, then the full range of micronutrient supplementation should be part of ongoing nutrition management, both during hospitalization and for up to 24 months after the burn incident.
3. Vitamins A, C, and D and TEs Fe, Cu, Se, and Zn may be significantly depleted in burns, and nutrition management could benefit from supplementation with these specific micronutrients at doses greater than those provided in standard products.

Rationale

The metabolic response of the human body to severe burn (>40% of total body surface area [TBSA]) increases >2-fold, leading to a hypermetabolic and hyperdynamic state. In children, a significant increase in resting energy expenditure has been found to persist for up to 24 months.[50,51] Protein loss, with concurrent loss of micronutrients and insulin resistance and an increase in liver size by up to 200%, is also reported.[51]

Children with burns have unique clinical and nutrition challenges—fluid and electrolytes, energy requirements, differing body proportions, TBSA to body mass ratio, rate of fluid loss, risk of hypothermia, nonshivering thermogenesis (increased metabolic rate, oxygen consumption, and lactate production), and thin skin—resulting in difficulties assessing the depth of the burn.[52] If nutrition therapy is commenced early, these challenges may be addressed, preventing impairment of wound healing, weight loss, and immune compromise.[51] Fluid retention in children may mask loss of body mass.

Vitamins and TEs are essential from the initiation of therapy because of their importance for the immune system and wound healing process.[50] The greatly increased inflammatory response and consequent oxidative stress may exceptionally deplete a number of micronutrients, including vitamins A, C, and D (See Table 3). Vitamin A is known to improve epithelial growth, and vitamin C is known to enhance collagen production and cross-linking.[50] Burned skin is not able to manufacture vitamin D, and both calcium and vitamin D homeostasis are altered because of an increase in osteoblast apoptosis, bone resorption, and urinary calcium loss. Additionally, the TEs Fe, Cu, Se, and Zn are lost in burn wound cellular exudates.[50]

Q5. Which Micronutrients Are Important and When Are They Required for Neonatal and Pediatric Surgical Patients?

Answer 5: Important micronutrient deficiencies arising from surgery may need specific supplementation.

Recommendation

1. Clinicians must be familiar with the extent of tissue resection and the remaining anatomy to help predict and manage postoperative micronutrient deficiencies.
2. Assessment of the patient's surgical history, including the length of the remaining bowel, is essential to determine whether fat-soluble vitamins are being absorbed enterally.
3. Zn, Fe, Cu, Se, and Mn status must be assessed in postoperative IF.
4. A standard nutrition therapy protocol including micronutrients can improve NEC outcome in VLBW infants.

Table 4. Association of Micronutrient Deficiencies With Intestinal Surgery.

Zone of GIT resection	Potential micronutrient deficiency
Gastric	Vitamin D[53,56] Vitamin K[56] Iron[19,53] Vitamin B_{12}[19,53]
Gastric bypass	Vitamin K deficiency[56] Copper[23]
Cholecystectomy	Vitamins A, D, E, and K[53]
Jejuno-ileal bypass	Vitamins A, D, E, and K[56,57] Calcium[57]
Pancreatico-duodenectomy	Vitamins A, D, E, K, and B_{12} and iron[58]
Proximal jejunum	Zinc[59] and copper[60]
Terminal ileum	Vitamin B_{12}[19,53,56,57]
Extensive short bowel	Vitamins $B_{2,}$[56] A, E, and K and, if colon resected, folic acid, chromium,[56] zinc, and iron[19,23]

GIT, gastrointestinal tract.

Rationale

Pediatric surgical patients often respond differently than adults to the stresses of surgery. Although many of the basic principles of nutrition therapy still apply, the nature of the surgical procedures and any specific diagnoses warrant individual consideration. Postoperative complications can also impact micronutrient loss, and previously asymptomatic deficiency states may become symptomatic following surgery. Thus, as documented in adult patients, Zn and Se depletion has been associated with enterocutaneous fistulae,[23,53] and Se deficiency with leakage of chyle.[54]

Following GI surgery, an accurate clinical assessment of the patient's surgical history, including the length of the remaining bowel, is essential. The presence or absence of the ileum will determine whether long-chain fatty acids and fat-soluble vitamins A, D, E, K, and B_{12} are being absorbed enterally. Table 4 associates the zone of GI tract resected with potential micronutrient deficiencies. Vitamin K deficiency may not be well recognized, as the international normalized ratio for prothrombin time lacks sensitivity and treatment with broad-spectrum antibiotics changes the intestinal flora, a major source of vitamin K. Irrespective of laboratory tests, the prudent clinician should consider additional parenteral vitamin K either by intramuscular injection or by addition to the PN, especially prior to elective surgery.[55] Small and highly variable amounts of vitamin K may be available from the ILE, and some of the standard multivitamin preparations provide insufficient vitamin K.

TE deficiencies are relatively common, so assessment should include status of Zn, Fe, Cu, and Se.[60] Symptoms that may be oberved are shown in Table 5. All outputs from stoma, stool, and urine must be assessed in IF, as large stool losses are associated with acidosis and micronutrient deficiencies. Ileostomy effluent particularly contains high levels of Zn.[61] Serum Zn levels therefore need to be monitored and appropriate supplementation prescribed. Since evidence shows that Cu and Mn can accumulate in the liver, the PN dose of standard TE supplements is commonly halved in the presence of IF-associated liver disease, and regular monitoring is instituted to avoid excessive Cu/Mn toxicity while aiming to avoid deficiencies of the other elements.

Nutrition management of pediatric IF in multidisciplinary centers has been instrumental in improving patient outcomes, whereas treatment of NEC remains controversial, with many different practices being employed. Using a standard plan for feeding VLBW (<1500 g) infants with a regimen that included micronutrients contributed to improvements in NEC rates and infant mortality but the authors did not separately investigate any contribution from micronutrients.[63] Some children with NEC or gastroschisis can tolerate EN, but anorexia, feeding intolerance, and perioperative ileus can limit the effectiveness of EN and present unique nutrition challenges. Small amounts of trophic EN can be hepatoprotective for PN patients. Oral intake should therefore be encouraged as early as possible, and whenever feasible, the EN should contain contributory micronutrients for ambulatory surgical PN patients, but parenteral supply should continue until enteral feeding is well established and PN weaned. Cyclic PN can prevent hyperinsulinemia and may decrease the risk of hepatic steatosis and cholestasis in older children but is not recommended for neonates and young children.[64]

Q6. Which Micronutrients Are Important and When Are They Required for Pediatric HPN Patients?

Answer 6: Micronutrient deficiencies can be high in long-term HPN. Pediatric HPN patients need daily supplementation and their status monitored regularly.

Recommendation

1. Micronutrients should be provided routinely to all pediatric patients receiving HPN.
2. Daily micronutrient requirements for HPN are listed under Q1 and Tables 1 and 2, but higher doses may be necessary when there are abnormal intestinal losses, such as post surgery.
3. Patients receiving long-term HPN need their micronutrient status monitored periodically to avoid deficiencies and/or toxicities.

4. HPN represents an extremely diverse group of patients, for whom advice from national or regional specialist centers will often be helpful, particularly with practical funding and supply issues in specific countries and regions.

Rationale

Physiological reasons for the need for micronutrients include maintenance of GI epithelial integrity and development, but micronutrients are also important for intestinal adaptation. Individual requirements may depend upon gestational age, presence of a high-output stoma, hepatic or renal dysfunction, and any enteral absorption. Abnormal losses such as from fistulae and chronic inflammation should also be considered in the individual patient requirements.

Without supplementation, micronutrient deficiencies are common among pediatric patients receiving HPN. Vitamin D, Fe, vitamin A, Zn, and Cu are among the most common deficiencies[60,65,66] and can be as high as 90% of HPN patients.[65] Rat models showed vitamin A deficiency is associated with reduced mucosal protein and DNA content as well as alkaline phosphatase activity.[60] A nonexhaustive list of symptoms of deficiency include cardiomyopathy (Se), growth retardation and poor wound healing (Zn), leukopenia (Cu), contribution to type 2 diabetes development (Cr), anemia (Fe), goiter (I),[20] loss of vision (vitamin A), weak muscles (vitamin B_1), bleeding gums (vitamin C), osteopenia (vitamin D), and macrocytic anemia (vitamin B_{12}).[49]

The reason for the extent of deficiencies seen can be due to a lack of appropriate provision with standard micronutrient parenteral supplements, limitations of solubility in PN, and premature weaning from micronutrient-containing PN. Commercially available standard supplements might not deliver, for example, sufficient Zn for premature infants.[2] Equally, when there is cholestasis or renal impairment, micronutrients such as Cu should be reduced or removed.[67]

Q7. What Are the Practical Considerations When Administering Micronutrients Parenterally?

Answer 7: Practitioners should be cognizant of micronutrient contamination and consider stability/compatibility issues when devising a PN formulation containing micronutrients.

Recommendations

1. Clinicians should be aware of the potential stability issues with nonroutine pediatric PN regimens containing higher concentrations of specific nutrients/micronutrients.
2. Fe may lead to destabilization of ILEs, so AIO admixtures containing Fe should be avoided unless stability information is available for the particular PN formulation.
3. Addition of multivitamins to the PN bag on the day of administration reduces the risk of degradation.
4. Protection of the PN bag from oxygen and light minimizes light-catalyzed oxidation of micronutrients and has been shown to reduce mortality in preterm infants.
5. Reliance on variable amounts of micronutrient contaminants in some PN components to provide the daily PN requirement would require monitoring to ensure adequate provision.

Rationale

Regular daily administration of vitamins and TEs allows for the provision of essential substrates and cofactors involved in many metabolic processes. Micronutrients are usually administered as part of a PN regimen or separately, if PN is not required. Patient/caregiver convenience is usually increased when micronutrients are incorporated in the PN, thereby decreasing the number of infusions that must be managed on a daily basis. Nevertheless, it is vital that parents or caregivers are trained in aseptic techniques if tasked with making additions of multivitamins to the PN bag.

Stability issues related to vitamins and TEs guide how micronutrients should be administered. When "off the shelf" standard multitrace and/or multivitamin products are used within approved stability matrices, PN admixtures are generally safe. Institutions should employ processes to ensure the integrity of the additives during PN compounding and/or administration.

Ascorbic acid (vitamin C) exhibits significant chemical lability through oxidation within PN.[68] Light and PN packaging composition influences the rate of oxidation.[69] Various B vitamins are susceptible to breakdown, such as the chemical reduction of thiamin and photodegradation of vitamin B_2 or riboflavin (RF). RF is extremely light sensitive and an efficient photosensitizer inducing oxidative damage to light-exposed tissues, foods, and nutrients.[70] It absorbs both visible and UV light, is an efficient oxygen radical sensitizer, and is a strong oxidant in its triplet state. Consequently, UV therapy in the neonatal ICU for hyperbilirubinemia can degrade the vitamin and lead to RF deficiency.[71] RF photosensitization is also responsible for oxidative degradation of protein, polyunsaturated lipids, and other vitamins such as folate, thiamin, and ascorbate. For example, *in vitro* studies have demonstrated that free radical–mediated reactions contributed to the rapid photodegradation of up to 69.0% of methionine.[72] The S–amino acid methionine protects against hepatotoxic

agents by providing intracellular cysteine for biosynthesis of the hepatoprotective antioxidant glutathione (GSH). Thus, by degrading this important GSH substrate, RF photo-oxidation can have an inhibitory effect on amino acid uptake and may contribute to the cytotoxicity of hepatocytes. Partial protection against RF photosensitization is offered by specific nutrients such as chromanols, like vitamin E, but the most simple and effective practice is to exclude oxygen and light from the PN system. Ribeiro et al have reported that oxidation of an unprotected pediatric PN admixture decreases RF content by around 40% within 6 hours and 63% in 24 hours. With photoprotection of the PN container, residual RF remained at 99% after 72 hours at 4 °C and 95% at 25 °C.[73]

Thus, destruction time of vitamins (and other nutrients) appears dependent on the PN formula, storage, transportation, and administration conditions such as light exposure. To maximize the integrity of the micronutrients, one approach utilizes adding vitamins to PN admixtures on the day of administration, rather than at the time of compounding, when the admixture is going to be stored at home or within an institution, for multiple days before use. The suggestion that administering micronutrients in ILE or AIO PN[1] protects the light-sensitive vitamins appears to miss the point that such practice leads inevitably to light-induced peroxidation of the lipid component. Simple light protection of the PN system is the obvious solution and is now a regulatory requirement in some countries.[77]

Administration of Fe in PN has been particularly problematic because of the trivalent cation's destabilizing effect on ILE. Of all PN components, iron dextran disrupted ILE stability to the greatest extent,[78] but the more recent reformulated dextran products and alternative compounds, such as iron sucrose/saccharate, may be more stable. However, even in AIO admixtures protected by light, Fe supplementation in the presence of vitamin C causes reduction of ferric iron to ferrous iron, leading to an increase in lipid peroxidation, and is not recommended.[79] The stability of Fe in lipid-free 2-in-1 PN varies by formulation, with low-protein admixtures being least stable.[79] Based on rather old data, the American Society for Parenteral and Enteral Nutrition (ASPEN) suggests options for supplementation of adult PN with iron dextran or iron sucrose, but the guideline emphasizes the lack of stability evidence for supplementing pediatric PN, pointing out that many hospitalized children also receive blood transfusions, which may provide adequate Fe. Compounding iron salts in AIO PN should therefore be avoided. Administering orally or as an intermittent Fe infusion, combined with regular monitoring of Fe status, is preferred by the ESPGHAN guidelines.[2]

The necessity of additional provision of certain TEs, such as Cr and Mn, has been questioned because of the ubiquitous contamination of these elements within other PN components.[80] Reliance on unknown and variable amounts of contaminants to provide these micronutrients is still being recommended but is not a defensible policy.[2] Since neonates may be particularly vulnerable to excessive doses of these contaminants, more research is needed to further inform the maximum allowable levels of these contaminants and their relative safety.

Q8. How and When Should Micronutrient Status Be Assessed/Monitored?

Answer 8: Preexisting deficiencies/toxicities will influence the frequency and method of monitoring.

Recommendations

1. Assessment of blood measurements of micronutrients should be best performed in the absence of systemic inflammation and should be interpreted in the context of the clinical condition and history. Water-soluble vitamins should be assessed initially, more frequently than fat-soluble vitamins.
2. Patients suspected to have a previous micronutrient deficiency should be initially monitored at least monthly.
3. Patients receiving stable micronutrient supplementations can have a reduced 3-monthly frequency of monitoring.
4. Measuring serum/plasma levels alone might not reflect true micronutrient status.

Rationale

Assessment of preexisting micronutrient issues. Assessment and interpretation of micronutrient status in critically ill children is difficult and should ideally be delayed until the inflammatory state is resolved and the patient's condition has stabilized.[33]

An ESPGHAN position paper on the assessment and interpretation of vitamin and TE status in sick children was published in 2020.[81] It particularly emphasized that the use of a multimodal approach, including clinical examination, dietary assessment, and biomarkers, is the optimal way to ascertain the vitamin and TE status of individual patients. It is recommended that blood measurements of vitamins and TEs should be best performed in the absence of an acute inflammatory response and should be interpreted in the context of the clinical condition and history. As a consequence, it is suggested that C-reactive protein and serum albumin level should be measured alongside plasma vitamin and TE concentrations, particularly where the disease state may result in a systemic inflammatory response.

The likelihood of pre-existing micronutrient deficiency needs to be ascertained by a detailed history (to include dietary, medical, and surgical). Seeing patients from geographical areas where certain micronutrients are scarce,

from socially disadvantaged backgrounds, or with certain medical conditions should alert prescribers to potential deficiencies. For example, Se deficiency in Heilongjiang province in China, folate deficiency in patients with neural tube defects, mixed or generalized low micronutrient accretion in premature infants and refugees, deficiency in fat-soluble vitamins in patients with chronic liver disease, and changes in growth pattern might also warrant investigation.[33]

Below is an indicative list of scenarios where screening infants and children for vitamins and trace elements may be required, based upon Gerasimidis et al (2020).[81] This is not an exhaustive list but considered typical of examples of patients at risk.

- Clinical symptoms of malabsorption or protracted vomiting
- Established malnutrition/growth failure
- Presence of multiple food allergies
- Long-term exclusion of major food groups; inherited disorders of metabolism, exclusion diets
- Presence of >15% unintentional weight loss
- Medications interacting with vitamins/trace elements, eg, folate antagonists
- Use of artificial nutrition lacking vitamins and trace elements for >2 weeks
- Pancreatic insufficiency, eg, cystic fibrosis with poor compliance on replacement therapy
- Long-term use of postpyloric feeding
- Presence of refeeding syndrome
- Major burns
- Major resection of small intestine or high-output stoma
- Severe insensible losses such as severe skin disease, eg, epidermolysis bullosa
- Severe liver disease or cholestasis

The decision to perform vitamin and trace element assessments remains at the discretion of the health professionals within the context of the clinical case.

Frequency of monitoring. Water-soluble vitamins rapidly deplete when intake is insufficient, as they are not stored in the body in significant amounts (apart from vitamin B_{12}). Deficiency can arise within 2–3 weeks of a micronutrient-deficient diet. If a deficiency is suspected, then biochemical monitoring should initially be no less than monthly. Appropriate investigations are listed in Table 6.

Table 5. Typical Symptoms Observed in Deficiency States of Micronutrients.

Fat-soluble vitamins	Symptoms
Vitamin A	Ocular manifestations: night blindness, dry eyes, poor growth, papillary hyperkeratosis, and impaired resistance to infections
Vitamin D	Rickets (enlargement of costochondral junctions, cranial bossing, persistently open anterior fontanelle, bowed legs, and epiphyseal enlargement)
Vitamin E	Hemolytic anemia in the newborn, hyporeflexia, and spinocerebellar and retinal degeneration
Vitamin K	Prolonged bleeding and hemorrhagic manifestations
Water-soluble vitamins	
Thiamin (vitamin B_1)[a]	Peripheral neuropathy, cardiac failure, lactic acidosis
Riboflavin (vitamin B_2)	Cheilosis, glossitis, corneal vascularization, and photophobia
Niacin	Pellagra: diarrhea, dermatitis, dementia
Pyridoxine (vitamin B_6)	Microcytic anemia, seizures
Vitamin B_{12}	Megaloblastic anemia, neurological changes
Folate	Megaloblastic anemia
Vitamin C[a]	Scurvy, petechial hemorrhages, bleeding gums
Trace elements	
Iron	Microcytic anemia, irritability
Zinc[a]	Hypogonadism, growth failure, diarrhea, decreased taste acuity, hair loss, and skin rash
Chromium	Glucose intolerance
Copper[a]	Neutropenia, anemia, neurological manifestations
Selenium[a]	Myalgia, cardiomyopathy

Adapted from Wong and Hardy.[18]
[a] Deficiencies that may be more commonly apparent in the intensive care unit are shown in bold.

Table 6. Tests for Assessing/Monitoring Micronutrients in Pediatric PN Patients.[106,107]

Micronutrient[a]	Test[b]	Comment	Reference
Vitamin A (retinol)	RBP and serum retinol levels	Plasma RBP and the serum retinol response to parenteral vitamin A is a better assessment of functional vitamin A status compared with random serum vitamin A levels alone, as its level only decreases when liver vitamin A storage is severely depleted	78, 80, 86, 94
Vitamin E (tocopherol)	Serum tocopherol level (common) Tocopherol: total lipid ratio (preferred)	Although tissue vitamin E level is the most informative for vitamin E status, serum or plasma tocopherol level is more commonly used. Because vitamin E level depends on plasma lipid concentrations the vitamin E, total lipid ratio is preferred	85
Vitamin D	25-OHD	25-OHD is considered the best biomarker in blood	85
Vitamin K (phytomenadione)	APTT and PTT	Adequacy of vitamin K–dependent clotting factors is normally used to determine status using APTT and PTT	85
Vitamin B_1 (thiamin)	Whole-blood concentration of thiamin (excess), erythrocyte transketolase assay (deficiency), urine thiamin	As thiamin is integral to carbohydrate metabolism, those infants with lactic acidosis receiving high quantities of glucose would be suspected of having thiamin deficiency	85
Vitamin B_2 (riboflavin)	Vitamin B_2 activation coefficient	Erythrocyte glutathione reductase activity with flavin adenine dinucleotide treatment before and after is the method of choice in assessing riboflavin deficiency. Activation coefficient >1.2 is suggestive of deficiency	85
Vitamin B_6 (pyridoxine)	No single agreed best test	Methods include using microbiological assays, plasma pyridoxal-5-phosphate, erythrocyte aspartate, and alanine aminotransferase activity as well as a tryptophan load test	85
Vitamin B_{12}	Serum vitamin B_{12}	Serum vitamin B_{12} is most commonly used, although for functional studies, measurement of methylmalonic acid excretion is used	85
Vitamin C	Plasma and leukocyte vitamin C		85
Niacin	Urine *N*-methylnicotinamide and *N*-methyl-6-pyridone-3-carboxamide	Urinary measurement of niacin metabolites (*N*-methylnicotinamide and *N*-methyl-6-pyridone-3-carboxamide) is considered the best measure of niacin deficiency	85
Folate	Red blood cells and serum folate level	Red blood cells and serum folate level are used to assess long-term intake	85
Zinc	Serum alkaline phosphatase level, serum zinc level	There are no sensitive markers of zinc status, but serum alkaline phosphatase (marker for zinc stores) is commonly used. Results can be affected by infection and stress as well as by exercise	85
Copper	Serum copper and ceruloplasmin levels	Marginal deficiency might be normal when using serum copper and ceruloplasmin levels. These may also be raised in inflammation	77, 85

(*continued*)

Table 6. (continued)

Micronutrient[a]	Test[b]	Comment	Reference
Selenium	Serum selenium (common), glutathione peroxidase levels (preferred)	Serum selenium indicates more recent selenium intakes whereas erythrocyte concentration is a marker for long-term (120-day) intake. For functional status, glutathione peroxidase is now preferred	85
Iodine	Urine iodine (common), serum thyroxine level, or TSH levels (surrogate)	Iodine excretion in urine is the best method for iodine status determination, but this might not be available in most centers. Surrogate measurements of serum thyroxine level or TSH levels can be used	85
Chromium	Serum levels	Chromium is present in small quantities in the body and it is extremely difficult to measure. Serum levels may not reflect body stores. Chromium can be also measured in the hair	77, 85, 87
Manganese	Serum levels (for deficiencies), whole blood, or urine (for suspected toxicity)	Serum levels should be monitored on long-term PN, but contamination of samples is problematic and levels might not reflect nutrition status. If Mn toxicity is suspected, then an MRI scan is recommended	2, 85
Iron	As part of iron study test	Ferritin and hemoglobin status should be monitored regularly in long-term PN	2, 85

25-OHD, 25-hydroxyvitamin D; APTT, activated partial thromboplastin time; MRI, magnetic resonance imaging; PN, parenteral nutrition; PTT, prothrombin time; RBP, retinol-binding protein; TSH, thyroid stimulating hormone.
[a] Red flags for possible deficiencies: malnutrition/malabsorption, complex drug therapy, complex comorbidities, high physiological demands due to infection, surgical procedures, blood loss, or severe burns.
[b] Frequencies of testing: normal pediatric patient if deficiency or toxicity symptoms clinically manifested; pediatric patient with nutrition support—every clinical nutrition review; sick or very sick pediatric patient if deficiency or toxicity symptoms clinically manifested.

Fat-soluble vitamins, on the other hand, can be measured on a 6- to 12-weekly basis[80,83] in patients receiving long-term PN.

All patients receiving long-term PN should have their TE status monitored regularly.[1,84]

In centers using PN products packaged in glass, aluminum blood levels of pediatric PN patients should be checked monthly (see Q9 and Answer 9)

Limitations of biochemical assessment. Clinicians need to be aware that plasma/serum measurements might not be appropriate for all micronutrients (see below). Note also that inflammation might change micronutrient levels, and pairing with C-reactive protein is recommended. Not all micronutrients are routinely measured, and only those that are commonly measured are listed.

Q9. What Are the Clinical Risks of Providing Micronutrients to Neonatal and Pediatric Patients

Answer 9: The greatest risk is not providing micronutrients in a PN regimen.

Recommendations

1. To avoid the risk of deficiencies, micronutrients should be included routinely in all neonatal and pediatric PN regimens.
2. The risk of RFS can be minimized with a nutrition care plan incorporating a protocol for administering an immediate dose of thiamin, restricting energy provision, and closely monitoring electrolytes, especially serum phosphate.
3. Fe, Cu, and Mn levels should be regularly monitored, especially in patients with liver disease receiving long-term PN or HPN, to avoid potential toxicity.
4. In centers using PN products and other pharmaceuticals packaged in glass, aluminum levels in blood should be checked monthly and maintained at <5 μg/kg/d.
5. Potential hypersensitivity reactions, largely due to excipients in certain vitamin preparations, should be heeded.
6. In some situations, such as premature neonates, individual micronutrients may need to be prescribed

separately, as there is a risk that standard commercial micronutrient products may provide too much or too little of the other micronutrients.

Rationale

Deficiency of water-soluble vitamins can occur within days of commencing nonsupplemented PN, and stores of other micronutrients in pediatric patients are negligible. The greatest risk in PN therefore appears to be not providing micronutrients routinely.

RFS, caused by overenthusiastic use of nutrition support after a period of starvation, is potentially life-threatening, especially in the critically ill, but unfortunately there is no standard definition for assessment. Nevertheless, routine laboratory markers for hypophosphatemia, hypokalemia, and hypomagnesemia, plus clinical symptoms, indicate a risk of cardiac, pulmonary, or GI complications and/or organ failure. RFS and its management was reviewed by Boateng,[88] and a pediatric focus was provided by Dunn and Fuentebella.[89,90]

A full assessment as part of a multidisciplinary nutrition care plan prior to commencement of nutrition support, with a protocol for regular monitoring of patients who develop RFS, can potentially decrease complications and overall mortality. Therapeutically, an immediate dose of 100 mg thiamin[13,91] and thereafter maintenance doses, together with close monitoring of calcium, magnesium, potassium, and especially serum phosphate, minimizes the risk. However, recent trials among critically ill patients suggest supplementation of electrolytes and vitamins alone is insufficient. Energy restriction for several days and subsequent gradual increase of energy intake is now recommended.[92]

Fe is an essential micronutrient but is not currently included in most pediatric TE products. However, the symptoms of "anemia of inflammation" such as lethargy and tachycardia, due to the inflammatory response and/or Fe deficiency, are relatively common in the critically ill child, leading to loss of appetite and susceptibility to infection.[93] Consequently, monitoring of Fe status and evaluating the need for separate oral or parenteral Fe supplements need to be included in the nutrition therapy care plan. The destabilizing effects of Fe on lipid stability limit the amount that can be safely incorporated into AIO admixtures. Nevertheless, supplementation at 50–100 μg/kg/d (0.9–1.8 μmol/kg/d), to a maximum of 5 mg/d (88 mmol/d), is recommended.[2] Most allergic reactions have been associated with earlier iron dextran products. More recently, reformulated product and the use of iron sucrose/saccharate appears to minimize this risk. Nevertheless, the products are not recommended for administration to children younger than 4 months, and there may still be stability issues when either product is combined with AIO admixtures.[80]

The most recent ESPGHAN/ESPEN/ESPR/CSPEN guidelines provide a summary of the special requirements and toxicity risks of excessive micronutrient supplementation.[1,2] Cu and Mn require additional monitoring in patients with hepatic failure and/or cholestasis, as they are known to be excreted in bile, and levels higher than normal are potentially toxic.[67] Previous recommendations to remove Cu from PN in cholestasis, however, have been rescinded.[94-97] Current guidelines recommend 20–40 μg/kg/d (0.3–0.6 μmol/kg/d) with a maximum of 500 μg/d (7.5 μmol/d).[2] In long-term PN, there have been reports of Mn accumulation and toxicity, from deposition in the basal ganglia of the brain[98] and neuropsychiatric symptoms.[99] These occurrences are reported to be reversible over time, upon removing Mn from the PN, but this is difficult when using a fixed-formula multi-TE product. With only very few published case reports of PN-related Mn deficiency, the need to routinely supplement PN has been questioned.[100] Nevertheless, the lower Mn content in some of the recently reformulated commercial products[96] has partially addressed these risk concerns at a recommended dose of no greater than 1 μg/kg/d (0.018 μmol/kg/d), to a maximum of 50 μg/d (0.9 μmol/d).[2]

The TE aluminum has no significant therapeutic benefits but is present as a contaminant in some PN additives and can accumulate to toxic levels when the GI tract is bypassed, as in the case of neonates and patients with renal impairment.[101] Aluminum accumulation has been associated with neurotoxicity, metabolic bone disease, and Alzheimer disease in patients receiving long-term PN/HPN. PN products and other potential drug additives packaged in glass containers are more susceptible to aluminum contamination, notably, calcium gluconate, inorganic phosphates and cysteine hydrochloride, albumin, and sucralfate.[102]

The US Food and Drug Administration (FDA) mandate in 1986 restricting the aluminum content of large-volume PN products to 25 μg/L was modified in 2000 to require small-volume PN additives to be labeled with their maximum aluminum concentration and that PN patient levels should not exceed 5 μg/L (0.2 μmol/kg/d).[103] The new British Pharmacopoeia monograph for parenteral solutions (volumes unspecified) is proposing a similar limit of 25 μg/L. Until all manufacturers have significantly reduced the aluminum content of their products, it is recommended that in centers using PN products packaged in glass, blood levels of pediatric patients receiving long-term PN should be checked monthly.

Although rare, there have been case reports of hypersensitivity reactions believed to be due to surfactant excipients in certain, but not all, fat-soluble vitamin products. Acute adverse reactions have also been reported from rapid administration of large doses of some vitamins.[104]

Even though currently available commercial TEs and vitamin products are convenient PN additives, beware that they might not meet the nutrition requirements of some

pediatric populations (for example, Zn requirements for premature neonates).[2]

When only one micronutrient is deficient, it may not be appropriate to increase the total volume of admixture to achieve requirement, as this will increase the provision of all other micronutrient components in the admixture. The opposite is true when one micronutrient is in the toxic range. Micronutrient components might need to be added individually rather than as premixed products.

Q10. What Are the Recommendations for Providing Micronutrients to Neonatal and Pediatric Patients When Suitable Products Are Unavailable?

Answer 10: Resources to assist healthcare professionals identify and manage shortages are available on the ASPEN, American Society of Health-System Pharmacists (ASHP), and FDA websites and from local regulatory authorities.

Recommendations

1. Maintain regular access to national society and/or regulatory agency websites for updates on the products' supply/availability.
2. Evaluate the use of adult multivitamin/multi-TE products at reduced doses for pediatric PN regimens.
3. If adult multivitamins are used in neonates, products containing polysorbate 80 or 20 or propylene glycol should be avoided.
4. Administer individual micronutrient parenteral additives, especially the key vitamins—thiamin, folic acid, and pyridoxine—that are required daily.
5. Consider using oral/enteral micronutrient alternative products where clinically possible.
6. Increase monitoring and awareness of micronutrient deficiencies.
7. Document all adverse reactions related to shortages or unavailability of pediatric products.

Rationale

Nonavailability of appropriate pediatric micronutrient products or persistent shortages can lead to inadequate dosing and consequently nutrient deficiencies. If specific pediatric micronutrient products are unlicensed in a particular country or are unavailable because of prolonged shortages, regulatory agencies may approve the temporary importation of alternative products.

ASPEN and other national PN and EN societies continuously monitor shortages of PN components through regular communications with the FDA, other regulatory agencies, pharmaceutical manufacturers, professional healthcare organizations, and clinicians.

Since 2016, ASPEN's Clinical Practice Nutrition Product Shortage Subcommittee has developed product-shortage recommendations to help clinicians manage PN therapy during times of product shortages. These recommendations, which are continuously updated, can be accessed via the ASPEN website (www.nutritioncare.org). In essence, it is recommended to reserve parenteral micronutrients for PN-dependent patients and reserve pediatric products for children. If no pediatric micronutrient products are available, then adult products can be considered at a pro rata reduced daily dose based on the weight of the patient. However, it is important to be aware that some adult products may contain levels of certain excipients and of aluminum, which may be toxic to neonates; some adult multivitamins contain propylene glycol and polysorbate 80 and 20 as excipients, which could be toxic in infants born at <36 weeks' gestation or under 1500 g. Other organic excipients such as glycine are not believed to be toxic. However, their use will marginally increase the total glycine content of the PN regimen. Clinical judgment must therefore balance the potential risks of micronutrient deficiencies from prescribing micronutrient-free PN against the potential toxicity from incorporating these adult components into the PN regimen.

If neither pediatric nor adult multivitamin or multi-TE products are available, then individual parenteral micronutrient products should be considered at dosages appropriate for the patient's age and weight. In particular, thiamin, ascorbic acid, pyridoxine, and folic acid should be given daily.[104] Switching to oral or enteral multivitamin/multi-TE supplements should also be considered if appropriate, with certain provisos.

Whichever strategy is adopted, it is important to notify patients receiving long-term PN/HPN when and how their PN formulation has been modified by incorporating alternative PN components. It is also advisable to increase the frequency of monitoring of serum or other appropriate biochemical markers for micronutrient status and to increase awareness of signs and symptoms of deficiencies. All adverse events or medication hazards related to shortages or unavailability of micronutrients should be documented.

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It is asserted that all listed authors contributed to conception/design of the project; contributed to acquisition, analysis, and interpretation of the data; and contributed sections from which P. A. Ball, G. Hardy, T. Wong, and S. J. Moltu drafted the article. All authors critically revised the article; and all authors

agreed to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final article.

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