Clinical Nutrition Guidelines

Australasian society for parenteral and enteral nutrition (AuSPEN) adult vitamin guidelines for parenteral nutrition

Emma J Osland AdvAPD MPhil[1,2], Azmat Ali AdvAPD[3], Truc Nguyen MPharm[4], Melvyn Davis PhC FSHP[5], Lyn Gillanders NZRD[6,7]

[1]*Department of Nutrition and Dietetics, Royal Brisbane and Women's Hospital, Butterfield Street, Brisbane, Australia*
[2]*Faculty of Health and Behavioural Sciences, School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Australia*
[3]*Department of Nutrition and Dietetics, Princess Alexandra Hospital, Brisbane, Queensland, Australia*
[4]*Department of Pharmacy, Middlemore Hospital, Auckland, New Zealand*
[5]*Mel Davis and Associates, Sydney, Australia*
[6]*Nutrition Support Team, Auckland City Hospital, Auckland, New Zealand*
[7]*Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand*

Background and Objectives: This work represents the second part of a progressive review of AuSPEN's 1999 Guidelines for Provision of Micronutrient Supplementation in adult patients receiving parenteral nutrition. **Methods and Study Design:** A systematic literature review was undertaken and recommendations made based on the available evidence and with consideration to specific elements of the Australian and New Zealand (NZ) practice environment. The strength of evidence underpinning each recommendation was assessed. A multidisciplinary steering committee and external reviewers provided feedback on the guidelines. **Results:** On review of the available literature it appears that the parenteral multivitamin preparations presently available in Australia and NZ are to sufficient avoid deficiency without causing toxicity in most clinical situations for adults receiving PN when provided regularly as part of the PN prescription. Vitamin D is the most vulnerable vitamin for the Australian and NZ PN population. **Conclusions:** Vitamins are an essential component of PN and should be provided from commencement for all patients receiving PN. With the exception of vitamin D, which is recommended to be monitored annually, routine monitoring of vitamin levels is unlikely to be necessary in patients receiving regular parenteral multivitamin preparations. Clinical judgement is an important element when assessing, prescribing and monitoring patients receiving PN. Areas requiring further research have been identified.

Key Words: vitamins, guidelines, parenteral nutrition, vitamin D, micronutrients

INTRODUCTION

A vitamin is "an organic compound, essential in very small amounts in supporting normal physiologic function, that cannot be biosynthesized at rates equivalent to the body's requirements".[1] Vitamins function to stabilize membranes, as coenzymes, as hydrogen and electron donors and acceptors, or have hormonal function.[1] They may exist in one or more active forms, may be fat or water-soluble in nature, and these properties largely govern storage and cellular distribution.[1]

Fourteen vitamins have Estimated Average Intakes (EARs) and Recommended Daily Intakes (RDIs) or Adequate Intakes (AIs) assigned by the National Health and Medical Research Council (NHMRC) as Nutrient Reference Values (NRVs) for oral or enteral provision: these include vitamins A, D, E, K, thiamin, riboflavin, niacin, vitamin B-6, vitamin B-12, folate, pantothenic acid, biotin, choline and vitamin C.[2] Other compounds, such as carnitine and inositol, have also been considered to possess vitamin-like qualities though are not considered to be essential.[1]

The provision of vitamins during parenteral nutrition (PN) is often limited by chemical stability, necessitating that they be added to PN admixtures separately, closer to the time of administration using commercially available parenteral multivitamin preparations or through compounding individual vitamin combinations, to meet individual clinical requirements.

Corresponding Author: Emma J Osland, Department of Nutrition and Dietetics, Level 2 Dr James Maybe Building, Royal Brisbane and Women's Hospital, Herston, Qld, 4029 Australia.
Tel: 61 7 3646 7597; Fax: 61 7 3646 1874
Email: Emma.Osland@health.qld.gov.au
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In 1999 AuSPEN published "Guidelines for Intravenous Trace Elements and Vitamins",[3] following the Micronutrient workshop held during the 1996 Annual Scientific Meeting. This document aimed to provide guidance to Australian and New Zealand (NZ) clinicians for the provision of micronutrients. The current review represents the second stage of the review of the 1999 guidelines. The initial stage covered trace element recommendations and was published in Asia Pacific Journal of Clinical Nutrition in 2014.[4]

Scope and purpose of the vitamin PN guidelines

The guidelines are designed to support Australian and NZ clinicians prescribing and monitoring PN to those over >15 years old, and are intended to be used in conjunction with the previously published Trace Element Guidelines (TEGs). They are intended to provide guidance on maintenance doses for vitamin provision, based on the currently available evidence. They are not intended to replace clinical judgement or to comprehensively cover the requirements of all clinical conditions and comorbidities that may require further individualisation of PN micronutrient prescriptions.

These guidelines are also intended to guide industry in the development of appropriate parenteral multivitamin preparations, as well as research within PN populations within the Australian and NZ populations to better inform future practice in this area.

Definitions outlined in the TEGs have been adopted for the vitamin guidelines.[4]

METHODS

The systematic review process undertaken for the development of the vitamin guidelines has followed the process previously outlined in the TEGs.[4]

An additional layer of feedback was incorporated through the introduction of a multidisciplinary steering committee to ensure the perspectives of all disciplines involved in PN provision were considered prior to being sent for external expert reviewer consultation.

RECOMMENDATIONS

While the 2012 ASPEN Position Paper: "*Recommendations of changes in commercially available parenteral multivitamin and multi-trace element products*"[5] was used as starting point for the AuSPEN guideline review process, considerable differences may be seen the between AuSPEN and ASPEN recommendations made for vitamins C, B-6, K, folate and thiamin. These may be explained by the differing approaches used to formulate recommendations in the absence of dosing studies. ASPEN has adopted and endorsed the revised Food and Drug Administration (FDA) recommendations for "effective adult parenteral vitamin products",[6] which are based on expert opinion following a 1985 workshop.[6] AuSPEN on the other hand has accepted the safety and efficacy of the doses currently routinely provided. This decision has been made in acknowledgement of the lack of widespread deficiency or toxicity in patients receiving the available parenteral multivitamin products for over two decades. However it is also acknowledged that the absence of deficiency signs or symptoms should not be taken to imply optimal nutritional status as the presence of subclinical deficiency is well recognised, and biochemical or clinical effects may be seen before classical deficiency. It may be that a higher dose of certain vitamins are beneficial in particular patients or disease states and further research on this area is required.

The review of each vitamin was approached using the following clinical question: *"For adult patients receiving short and long-term PN, what level of vitamin supplementation, compared to no supplementation, is required to avoid deficiency and toxicity (including during pregnancy), and what are the appropriate methods of assessing levels?"*. A summary of recommendations is provided in Table 1.

Vitamin A

Vitamin A deficiency is uncommon in the wider Australian and NZ population, however those with short bowel syndrome (SBS) may be at risk due to interruption to fat absorption and decreased bile salt reabsorption.[7,8] Vitamin A deficiency or toxicity has not been described in patients receiving either short- or long-term PN to date. Vitamin A (retinol) has been demonstrated to be subject to photodegradation when infused in full light without protection, and therefore light protective covering should be used during infusions to avoid unintentional underdosing.[9,10]

While high doses of vitamin A are cautioned against during pregnancy due to teratogenic effects, adequate doses throughout pregnancy are important for embryonic development.[11] Doses of above 10,000 IU (3,000 μg RE) retinol have been recommended to be avoided during pregnancy and pre-conception.[11] While synthetic retinoids used in the management of severe acne are recognised to be teratogenic,[11] there is little guidance on the impact of vitamin A (retinol) during pregnancy when provided as part of parenteral multivitamin preparations.

AuSPEN recommends a routine maintenance dose of 3,500 IU (1,155 μg RE) in both short and long-term PN patients (including HPN). While no specific recommendations can be made for Vitamin A as part of PN provision during pregnancy or lactation due to lack of safety data in this population group via the parenteral route, the provision of 3,500 IU (1,155 μg RE) dose seems appropriate throughout the last trimester of pregnancy, if not during the entire pregnancy. Routine surveillance of serum retinol levels is unlikely to be necessary in most clinical situations. Should assessment be required, serum retinol levels with concurrent retinol binding protein levels may be performed, however there are significant limitations of these markers during acute illness.

Vitamin D

A significant sector within the general Australian and NZ population have vitamin D levels that are considered insufficient (25-hydroxy vitamin D (25OHD) levels <50 nmol/L) for at least part of the year.[12-14] There have been a number of studies suggesting that Vitamin D deficiency and insufficiency is common in patients receiving long-term or HPN.[15-19] These findings appear to occur despite the provision of regular vitamin D as part of the parenteral multivitamin preparation (200 IU [5 μg]),[16] ongo-

Table 1. Summary table of vitamin recommendations for PN in adults[†]

	What is the safe and adequate daily supplementation for short-term PN?	What is the safe routine and adequate supplementation for long-term PN?	Are there any conditions in which higher supplementation should be considered?	Are there any conditions in which reduced supplementation should be considered?	What should be monitored and how frequently.	Standard assay
Vitamin A	3,500 IU (1,155 μg RE)	3,500 IU (1,155 μg RE)	Fat malabsorption, SBS, chronic alcohol.	Caution in pregnancy above maintenance supplementation doses	Routine monitoring not required if receiving routine parenteral multivitamin.	Serum retinol levels Retinol binding protein
Vitamin D	200 IU (5.5 μg)	200 IU (5.5 μg)	Those living in NZ and southern regions of Australia, pregnancy. Long-term PN patients may require additional Vitamin D.	Nil	Serum 25OHD should be measured annually, in conjunction with serum concentrations of calcium, magnesium and phosphate; serum parathyroid hormone in long-term PN and HPN patients.	Serum 25OHD
Vitamin E	10 mg	10 mg	SBS, critically ill including those with multi-organ failure and SIRS.	Nil	Routine monitoring not required if receiving routine parenteral multivitamin.	Plasma α-tocopherol Plasma α-tocopherol: plasma lipids ratio
Vitamin K	Not required in patient receiving lipid-containing PN	Dependent on individual clinical situation	SBS in the absence of a colon, primary biliary sclerosis, during pregnancy, those with reduced BMD.	Caution for those receiving oral anticoagulation	Routine monitoring not required unless on anti-coagulation therapy - close monitoring provided during commencement, cessation or any changes to PN formulation/ supplementation is recommended in this population.	INR, PT, APTT serum phylloquinone and PIVKA-II
Vitamin B-1	3 mg	3 mg	Alcohol dependence, dialysis, HIV/AIDS, (other auto immune) malnutrition, malabsorption, hypermetabolism.	Nil	Routine monitoring not required if receiving routine parenteral multivitamin.	erythrocyte transketolase activity/ whole blood or RBC thiamin pyrophosphate
Vitamin B-2	4-5 mg	4-5 mg	Nil	Nil	Routine monitoring not required if receiving routine parenteral multivitamin.	RBC glutathione reductase before and after addition of flavin adenine dinucleotide/riboflavin in RBC or plasma
Vitamin B-3	40-47 mg	40-47 mg	Malabsorption, large effluent losses via dialysis, alcohol.	Nil	Routine monitoring not required if receiving routine parenteral multivitamin.	Plasma niacin Urinary excretion NI-methyl nicotinamide and its derivatives (NI- methyl-2-pyridoxin-5-carboxamide)

CKD: chronic kidney disease; CRRT: continuous renal replacement therapy; ECF: enterocutanous fistula; IBD: inflammatory bowel disease; IFALD: intestinal failure associated liver disease; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency virus; PNALD: parenteral nutrition associated liver disease; SBS: short bowel syndrome; SIRS: systemic inflammatory response syndrome; TB: tuberculosis, NZ: New Zealand.

[†]Adults >15 years old. These recommendations represent *maintenance* doses for otherwise stable patients receiving PN. Individual clinical situations should be considered when prescribing vitamin doses and determining the appropriateness of monitoring.

Table 1. Summary table of vitamin recommendations for PN in adults[†] (cont)

	What is the safe and adequate daily supplementation for short-term PN?	What is the safe routine and adequate supplementation for long-term PN?	Are there any conditions in which higher supplementation should be considered?	Are there any conditions in which reduced supplementation should be considered?	What should be monitored and how frequently	Standard assay
Vitamin B-5	16-17 mg	16-17 mg	Nil	Nil	Nil available	Nil available
Vitamin B-6	3 mg	3 mg	Pregnancy, autoimmune disorders, coeliac disease, IBD, malabsorption, alcohol, renal impairment.	Nil	Routine monitoring not required if receiving routine parenteral multivitamin.	Pyridoxal 5 phosphate in RBC or plasma
Vitamin B-12	5-6 µg	5-6 µg	Gastric resection (including bariatric surgery), older age, atrophic gastritis or pernicious anaemia, chronic pancreatitis, Cystic Fibrosis, bacterial overgrowth, ileal resection.	Nil	Routine monitoring not required if receiving routine parenteral multivitamin.	Serum or plasma B-12
Folate	400 µg	400 µg	Pregnancy, malabsorption, alcohol.	Nil	The presence of macrocytic megoloblastic anaemia on routine FBC screening in long-term and HPN patients indicates the need for further investigation of folate status. Otherwise routine monitoring not required if receiving routine parenteral multivitamin.	FBC Serum folate
Vitamin C	110-150 mg	110-150 mg	Oxidative stress, 3rd trimester of pregnancy, malabsorption, haemodialysis, burns, trauma, critically ill.	Nil	Routine monitoring not required if receiving routine parenteral multivitamin.	Serum ascorbate
Biotin	60 µg	60 µg	Nil	Nil	Nil available	Nil available
Carnitine	Nil parenteral supplementation presently available in Australia or NZ	Nil parenteral supplementation presently available in Australia or NZ	liver disease +/- SBS or ECF, CKD, malnutrition, cancer cachexia, pregnancy, dialysis, CRRT, surgery, burns, TB.	Nil	Regular monitoring not required/ available.	Urine or blood Carnitine levels
Choline	Nil parenteral supplementation presently available in Australia or NZ	Nil parenteral supplementation presently available in Australia or NZ	Pregnancy, possibly in PNALD/IFALD	Nil	Regular monitoring not required/ available.	Plasma free choline

CKD: chronic kidney disease; CRRT: continuous renal replacement therapy; ECF: enterocutanous fistula; IBD: inflammatory bowel disease; IFALD: intestinal failure associated liver disease; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency virus; PNALD: parenteral nutrition associated liver disease; SBS: short bowel syndrome; SIRS: systemic inflammatory response syndrome; TB: tuberculosis, NZ: New Zealand.

[†]Adults >15 years old. These recommendations represent *maintenance* doses for otherwise stable patients receiving PN. Individual clinical situations should be considered when prescribing vitamin doses and determining the appropriateness of monitoring.

ing oral intake,[16,17] and/or large dose oral supplementation of vitamin D.[17,20] Vitamin D status in the Australian or NZ PN population has not been studied, and as such it is unclear if it is appropriate to generalise these results to our local conditions where baseline vulnerable vitamin D status is assumed.

Metabolic bone disease (MBD) is the most frequent metabolic complication in long-term HPN for chronic intestinal failure, occurring in 80% of 165 HPN patients who had dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and femoral neck in a multi-centre cross sectional survey.[21] It is unclear if vitamin D status in long-term HPN is associated with worsening bone structure.

It has been suggested that vitamin D toxicity may occur through impairment of PTH. In early studies in HPN patients vitamin D withdrawal resulted in an increase in bone mineral density together with normalisation of PTH and vitamin D.[22] No reports in the last decade have confirmed these findings.

AuSPEN recommends that all short and long-term patients receiving PN have a routine dose of 200 IU (5.5 μg) vitamin D. Patients receiving longer term and HPN may benefit from additional vitamin D on a case-by-case basis. Women on long-term PN with low vitamin D levels should have vitamin D supplemented. Additional oral vitamin D supplements should be considered. In stable long-term and HPN patients serum 25OHD should be measured annually. 25OHD has been reported as the metabolite that best reflects overall vitamin D status.

Recent recommendations for MBD monitoring include use of bone mineral density assessment and (a) measurement of serum concentrations of calcium, magnesium and phosphate, (b) serum concentrations of 25OHD and parathyroid hormone and (c) biochemical markers of bone turnover.[23] Prevention and treatment are based on lifestyle and dietary recommendations, treatment of the underlying disease-related factors and optimizing vitamin D status and inclusion of vitamin D in the PN admixture.[23]

Vitamin E

Though a rare occurrence, there are several case reports of patients with additional risk factors developing vitamin E deficiency while receiving long-term or intermittent PN.[24,25] These incidences occurred in conjunction with the provision of high poly-unsaturated fatty acids (PUFA) lipids (100% soy) with inadequate vitamin E provision to overcome lipid peroxidation, and are not likely to an issue with contemporary PN practices (the use of second and third generation lipids). There are no reports of vitamin E toxicity with PN provision.[26]

Lipid emulsions used in PN vary greatly in their naturally occurring vitamin E levels (reported from 58-384 μg/L).[27] This variation may be attributed to the type of lipid emulsion,[27] 100% soy lipid having the lowest concentrations and 100% fish oil having the highest.[27] PN solutions with high PUFA lipid emulsions may need additional vitamin E to combat lipid peroxidation without compromising the amount available for physiological requirements.[26]

Significant light degradation has been reported in vitamin E and for this reason light protection during PN administration and/or vitamin infusion is recommended.[9,10] Vitamin E (α and γ tocopherol) demonstrates increased stability in mixtures containing medium chain triglycerides than soy and olive oil.[28]

There is insufficient data for recommendation of adequate intake of vitamin E in PN as the available studies recommending high dose of vitamin E are based on 100% soy lipid emulsions, and as such are not transferable to contemporary practice in Australia and NZ. With new second and third generation lipid emulsions now most commonly used, AuSPEN recommends that a dose of 9-10 mg/day of vitamin E be provided for patients receiving short and long-term PN, to meet physiological needs with an additional allowance for the peroxidation of lipids.

Routine assessment of vitamin E for those on PN is not necessary while parenteral multivitamin preparations are regularly provided. Should assessment be clinically indicated, plasma α tocopherol level is the most accessible measurement available,[29] though the ratio of plasma α tocopherol to plasma lipids has been suggested as being the most accurate measure for deficiency in adults.[26]

Vitamin K

In patients receiving PN, vitamin K has been assumed to be provided by the soy lipid component traditionally provided as the primary lipid source. Moderate amounts of naturally occurring vitamin K are also provided by fish oil containing lipid, and an average of 50 μg vitamin K per 100 g fat is present in the emulsions commonly used in Australia and NZ.[30] As a naturally occurring product, quantities within the commercially available lipid solutions will be subject to seasonal variation.[31] Vitamin K is not routinely supplemented in patients receiving PN in NZ, and practice varies between centres in Australia.

While there are no cases in the literature of overt vitamin K deficiency in adults receiving PN, mild coagulation abnormalities have been reported in a small study in which vitamin K-free PN was provided.[32] A further case of an adolescent developing vitamin K deficiency after commencement of PN in the setting of bone marrow transplant, recent antibiotic use and minimal oral intake has been reported.[33] Toxicity for vitamin K has not been reported and is not considered a concern in those receiving PN.[31]

A weekly 10 mg vitamin K dose in Canadian HPN patients suggested a trend toward improved bone mineral density compared with patients who did not receive additional parenteral vitamin K supplementation.[34] However further research is required to confirm benefit of vitamin K supplementation on bone health of HPN patients.

Provision of supplemental vitamin K should be a therapeutic decision based on individual requirements. AuSPEN recommends patients receive individual assessment for consideration of routine vitamin K supplementation during short-, long-term and HPN provision. Consideration should be based on the source of lipid prescribed, the frequency of PN provision and any underlying conditions requiring alterations to standard recommendations. These may include the provision of lipid free PN, those receiving oral anti-coagulation therapy, disrupttion to bile acid circulation, during pregnancy or in long-term HPN patients with metabolic bone disease.

Routine monitoring of vitamin K levels are not necessary for inpatients receiving PN unless patients have concurrent conditions that require regular oral anticoagulation medication. In these patients, closer monitoring during changes to PN regimen, including commencement and cessation may be warranted. Should monitoring be indicated, coagulation tests (INR, prothrombin time) are often utilised, however these are not specific to vitamin K status and may be may be affected by other clinical conditions (i.e. liver failure). Global coagulation assays will not detect subclinical deficiency of vitamin K[35].

Thiamin (vitamin B-1)

The essentiality of regular thiamin provision as part of PN provision may be best demonstrated by the adverse outcomes reported in the United States in the 1980s and 1990s during periods of parenteral vitamin shortages.[6] During these times the death of at least three PN-dependent patients were attributed to the consequences of thiamin deficiency.[6] Thiamin intakes of 0.6 mg/day or less result in the development of deficiency.[36,37]

Malnourished individuals can be affected by refeeding syndrome - a cluster of signs and symptoms, which may include the development or unmasking of thiamin deficiency[38], which may impact at the commencement of PN in some patients. Metabolic stress as a result of severe illness acutely increases the need for thiamin, as a result of increased oxidative metabolism and increased carbohydrate provision in the diet. It should be noted that those who develop a thiamin deficiency are likely to have concomitant deficiencies in other water soluble vitamins.[39]

There have been numerous studies highlighting various doses of thiamin successfully used to treat deficiency states, ranging from 50 mg once daily to 500 mg IV three times a day for three days, with no reports of toxicity.[40-42] No universally accepted guideline for optimal dose, frequency or duration of use of thiamin presently exist.[43]

A study of long-term PN patients that had parenteral thiamin supplementation of 3 mg/day showed that all had adequate levels.[44] Additional supplemental doses of thiamin may be given in populations at risk of deficiency or if symptomatic.

AuSPEN recommends a routine maintenance dose of at least 3 mg thiamin/day in all patients receiving PN. Routine surveillance of thiamin levels are not required, and in the case of suspicion of thiamin deficiency, rapid intervention is indicated and will always take precedence over obtaining serum levels and providing clinical intervention on these. Should assessment be required erythrocyte transketolase activity represents a functional measure of thiamin status, while concentrations of thiamin pyrophosphate in RBC or whole blood may be an alternative quantitative measure available in some labs.[45]

Riboflavin (vitamin B-2)

Clinical signs of riboflavin deficiency have been described in parts of the world with inadequate dietary intakes of riboflavin, however only biochemical abnormalities have been described in riboflavin deficient PN.[46,47] Riboflavin toxicity has not been described as excess is readily excreted as with other water soluble vitamins.[48]

Small older studies on short-term PN patients have shown adequate biochemical levels of riboflavin when given at 1.8-10 mg/day,[49,50] however it should be noted that the higher requirement was in a population of critically ill patients, where increased energy metabolism may be expected. In six HPN patients daily infusions of 3.6 mg of riboflavin maintained biochemical stability but infusions thrice weekly showed a biochemical decline in only one patient.[47] No published literature was located that described riboflavin levels or requirements in pregnancy or lactation during the provision of PN. In the absence of larger well controlled studies to evaluate a precise need for riboflavin the current data indicate that the current additives given routinely will meet the requirements of most patients receiving short and long-term PN.

AuSPEN recommends that adult patients receiving short and long-term PN receive between 4-5 mg riboflavin each day. Assessment of riboflavin status should be restricted to those who have overt clinical signs or symptoms of riboflavin deficiency and should not form part of regular surveillance of short or long-term patients receiving PN. Should assessment be indicated, whole blood to measure erythrocyte riboflavin levels is the most commonly available method in Australia and NZ, though urinary excretion, activation of erythrocyte glutathione reductase activity may also be measured.[5]

Niacin (vitamin B-3)

No cases of niacin deficiency or toxicity in either short or long-term PN patient have been reported with the currently provided doses (40-46 mg/day). No studies in pregnant or lactating patients receiving PN have been conducted.

AuSPEN recommends the routine provision of 40-46 mg niacin as part of a complete parenteral nutrition provision in both short and long-term PN patients, including during pregnancy. Routine measurement of niacin is not recommended in short or long-term PN patients and should only be considered in the context of clinical suspicion of niacin deficiency or toxicity. In these occasions, the most reliable measure of niacin status is urinary excretion of NI-methyl nicotinamide and its derivatives (NI-methyl-2-pyridoxin-5-carboxamide).[2]

Pantothenic acid (vitamin B-5)

Pantothenic acid deficiency state has only been observed in experimental settings when volunteers have been fed deficient synthetic diets or fed an antagonist.[51] Deficiency has never been described in a patient receiving PN. No adverse effects have been associated with high intakes of pantothenic acid,[52] and there is limited data about any additional requirement for pantothenic acid in pregnancy.

Given the essential nature of pantothenic acid in intermediary metabolism and lack of evidence of any toxic effects AuSPEN recommends that 16-17 mg/day of pantothenic acid be provided to patients receiving PN. Biochemical assessment of pantothenic acid status is not routinely available and remains largely experimental.[53,54]

Pyridoxine (vitamin B-6)

Vitamin B-6 deficiency is uncommon and is usually associated with low concentrations of other B group vitamins such as vitamin B-12 and folic acid.[55] Serious illness leads to increased protein and amino acid turnover and

will lead to an increased requirement for pyridoxine. Clinical deficiency is rare but has been seen in experimental doses of 0.16 mg/day, but never with intakes of over 0.5 mg/day.[2,56] Cases of toxicity in PN administration have not been reported.[57] Intentional self-poisoning can occur with chronic administration of oral doses of 100 mg daily.[58]

Sunlight may lead to pyridoxine degradation hence protection from light is recommended.[59]

In the absence of evidence for the development of deficiency or toxicity with both short and long-term provision of currently provided doses of pyridoxine in parenteral multivitamin preparations, AuSPEN recommends pyridoxine maintenance dose of 2.9 mg/day. Routine monitoring of pyridoxine levels are not required, however should assessment be clinically indicated, blood pyridoxal 5 phosphate levels should be measured.[60]

Vitamin B-12

A healthy person with replete body stores has sufficient vitamin B-12 to last between 3 to 6 years without supplementation.[2,61] Absorption of vitamin B-12 is a complex process, and any condition affecting the stomach or terminal ileum may reduce oral/enteral absorption.[5,62]

No cases of vitamin B-12 deficiency have been reported in those receiving PN since vitamin B-12 has been included in regular parenteral multivitamin preparations. Bariatric surgery patients with unplanned outcomes, which may include HPN, are an emerging population who may be more vulnerable to development of vitamin B-12 deficiency however no reported data is available to date.

Serum vitamin B-12 tends to be elevated in patients on long-term PN receiving daily vitamin B-12, however no adverse outcomes of this have been described.[63] Possible explanations for these elevated levels include the delivery of vitamin B-12 directly into systemic circulation or that this reflects parenteral B-12 infusion rather than (likely normal) tissues stores.[5]

AuSPEN recommends that all adult patients receiving short and long-term PN receive 5-6 μg cyanocobalamin each day. Vitamin B-12 levels in serum or plasma do not need regular assessment in short or long-term PN patients unless the patient is not receiving the routine supplementation of the currently available parenteral multivitamin preparations. If haematological abnormalities are present the underlying cause must be investigated. Evaluation of vitamin B-12 status includes red blood cell parameters, and folate levels.[64] Patients who are receiving a routine dose of vitamin B-12 in the PN prescription are unlikely to be deficient.

Folate

Folate requirements can be affected by bioavailability, nutrient interactions, smoking, certain drugs and genetic variations. Folate deficiency states may manifest in those with inadequate intakes and increased requirements, particularly with malabsorption diseases. The clinical picture of folate deficiency is identical to the haematologic effects of vitamin B-12 deficiency. Folate deficiency or toxicity has not been described in patients receiving routine folate supplemented PN.

AuSPEN recommends that all short and long-term patients receiving PN have a routine dose of 400 μg of folate. Additional folate may be required in the short-term in some clinical settings, for increased requirements such as haematopoiesis. AuSPEN makes no recommendation for additional folate in pregnancy in which case individual clinical judgement is needed. Routine screening for folate is not warranted during PN provision if maintenance doses are routinely provided. If routine screening of long-term PN patients with a full blood count reveals a macrocytic megaloblastic anaemia, this should then trigger a serum folate measurement. Serum folate measurements provide equivalent information to red cell folate measurements when attempting to determine whether folate deficiency is present.[65] There seems to be no basis for the routine testing of all samples for serum/plasma folate and a red cell folate.

Ascorbic acid (vitamin C)

Ascorbic acid deficiency is rare, and is usually limited to individuals or populations who have inadequate dietary intake or absorption.[57,66] It is thought that steady state plasma concentration achieved by 60 mg/day would prevent development of scurvy for approximately one month if ascorbic acid intake was ceased.[67] Hospitalised patients with acute stressors such as those with major burns or trauma, multiple injuries and critically ill patients may display reduced ascorbic acid levels.[68] Supplementation beyond the routine supplementation in this population should be considered and given as necessary.[68] Ascorbic acid deficiency has not been described in PN patients, nor has toxicity. Ascorbic acid is thought to have low toxicity with high intakes.

AuSPEN recommends the continuation of routine ascorbic acid provision around 110-150 mg/day for patients receiving short and long-term PN (including during pregnancy/lactation). Routine blood testing is unnecessary and potentially inaccurate due the various factors mentioned above, and observation of clinical signs would be more appropriate measure of vitamin C status. If assessment is clinically indicated, serum or plasma ascorbate concentrations may be obtained, however as ascorbate is unstable, falsely low levels may be seen if samples do not reach the laboratory on ice, within two hours of sampling.[66,69]

Biotin

Biotin deficiency has been described in people receiving biotin free long-term PN.[71] Symptoms included hair loss, angular cheilosis and dry eyes, which resolved with intravenous biotin. Biotin deficiency was also described in a series of patients with alopecia, rash, depression and low plasma biotin levels. These patients had PN with no biotin supplementation for more than one month.[72] Biotin was administered at 138 μg/day, which resolved symptoms, but CoA carboxylase activity remained subnormal in two of five patients.[72]

Although biotin deficiency has not been demonstrated with biotin supplemented PN some authors have speculated that marginal biotin status may exist more than is thought. [5,73] Biotin toxicity has never been described.

AuSPEN recommends that all short and long-term patients receiving PN receive a routine dose of 60 μg biotin to avoid biotin deficiency. Biotin deficiency may be confirmed by the detection of elevated urinary 3-hydroxyisovaleric acid,[74] however detection generally relies on the identification of related deficiency symptoms.

Carnitine

Though not strictly a vitamin as it is synthesized in the liver and kidney from lysine and methionine, biotin may become conditionally essential in some clinical situations.[5,75,76]

Symptomatic carnitine deficiency has been described in patients receiving long-term PN with significant small bowel resection and enterocutanous fistulae in the presence of impaired liver function.[77-79] Low plasma levels have been described in HPN patients in the absence of symptomatic deficiency but in the setting of other pathologies making it difficult to implicate carnitine alone.[80,81] L- carnitine toxicity has not been reported.

Carnitine is not routinely supplemented in adults receiving short or long-term PN in Australia, NZ or internationally, and at this time there is insufficient evidence to support its routine addition. Should replacement during PN be clinically indicated, supplementation with L-carnitine supplementation of 2 to 5 mg/kg/d has been suggested though higher levels may be required if multiple reasons for carnitine deficiency exist.[76,82] However supplementation options in Australia and NZ are limited with limited access to parenteral carnitine identified at the time of this review. Depending on the individual situation, oral supplementation may be sufficient.[77]

AuSPEN makes no clinical recommendations for carnitine but highlights the need for further research into the possible conditional essentiality of carnitine in PN populations. Carnitine is not routinely assessed in either short or long-term PN patients in Australia and NZ. Should assessment be required blood and urine carnitine levels may be measured.[76,83,84]

Choline

Although choline can be synthesised endogenously, choline has been recognised an essential nutrient since the late 1990s and was included in the NRVs for Australia and NZ for the first time in 2006.[2,85] Pregnancy and the post-partum period are recognised to be times of increased maternal choline requirements.[86,87]

Choline deficiency presents with liver abnormalities, including the development of hepatic steatosis and derangements in aminotransferases.[88-90] This is of particular interest when considered in terms of the similar manifestations in PN or intestinal failure associated liver disease (PNALD or IFALD). Of further significance to those requiring PN, choline deficiency may also be associated with increased risk of venous catheter thrombosis.[91]

Dietary choline deficiency has not been described outside of experimental settings, however malabsorption of dietary sources are anticipated to occur in those with intestinal failure even after substantial bowel adaptation.[92,93] PN products internationally are not currently supplemented with choline. While phosphatidylcholine will be present to varying degrees in parenteral lipid emulsions, these do not appear to provide significant levels of available choline.[92,94,95] Consequently lower than normal concentrations of plasma-free choline have been demonstrated in those reliant on HPN, although plasma phospholipid-bound choline levels remained normal in the majority of patients.[93,94] Small studies in HPN patients have suggested that choline supplementation (2 g/day for 24 weeks) may reverse steatosis in those with PNALD/IFALD as well as improvements in verbal and visual memory.[89,96]

Toxicity has not been reported outside of experimental settings and is not considered a concern for those receiving PN.[92]

While AuSPEN recognises the essentiality of choline and the potential clinical importance of supplementation for adults receiving PN (particularly during pregnancy or in those with IFALD/PNALD), it makes no recommendation for maintenance doses in either short- or long-term PN recipients (including those receiving PN during pregnancy, or in the presence of IFALD/PNALD) at the present time. AuSPEN highlights this is a need for further clinical research in this area. Laboratory assessment of choline status is not currently routinely available, nor is it recommended while no means of correcting abnormalities exists. Should it be required, plasma free-choline concentrations appear to be the most reliable measure of choline status.[92,97]

PRACTICAL CONSIDERATIONS WITH PN VITAMIN ADMINISTRATION

Frequency of administration

Vitamins are an essential component of nutrition support and should be administered any time PN is provided (i.e. daily vitamin provision if daily PN provision; PN three times per week, vitamin provision three times per week). Many established HPN patients do not require daily PN and in these cases parenteral vitamin provision incorporated into the intermittent HPN provision may be adequate to compensate for the deficit in enteral/oral absorption. In other situations, patients may require daily parenteral multivitamin supplementation provided as a single infusion on the days HPN is not administered. Decisions relating to the provision of additional parenteral vitamin preparations on days in which HPN is not provided should be based on the underlying clinical condition of the patient, known deficiency risks and ultimately on the clinical judgement of the PN prescriber/s.

Method of administration

Vitamins may be administered in one of two ways: aseptically added into PN solution and infused as a component of the PN solution, or provided as an intermittent infusion either via a Y-site or as a stand-alone infusion separate to the PN administration. Often the decision as to which method is used is based on the capabilities and policies of individual facilities, rather than clinical recommendations.

If PN micronutrients are added to the PN solution and provided over the duration of the PN administration, clinicians should remain cognisant that on occasions where the full PN bag is not infused, a reduced provision of micronutrients will also be administered.

While there are a number of studies that have investi-

gated the impact of infusion duration on the retention of trace elements in acutely unwell patients,[98,99] no such studies about the impact on the retention of vitamins from PN provision or on the impact of infusion methods for micronutrients on stable or long-term or HPN recipients have been identified. Expert opinion based on the extrapolation of the studies on trace element excretion is that micronutrients including vitamins should be administered over the longest time feasible to optimise the cellular uptake and reduce urinary excretion.[100]

Furthermore providing vitamins concurrently with trace elements may lead to loss of vitamin activity through oxidation and interactions. Vitamin C is particularly vulnerable to loss through interaction with trace elements.[99,101] For this reason expert opinion has suggested these be provided separately, potentially over long-term "piggy back" methods of alternating 12 hrs infusions, or with both vitamins and trace elements included in the PN solution, where vitamins are added immediately prior the commencement of the administration to minimise interaction and loss of vitamin activity.[100]

Effects of light exposure on parenteral vitamins

Numerous studies have demonstrated significant losses of certain vitamins from PN solutions through direct light exposure: vitamins A, C and E appear to be particularly vulnerable to this form of degradation[9,102] and this may occur through both bags and giving sets.[103,104]

Little is known regarding the potential impacts of different types of light sources, such as sunlight versus fluorescent or LED lighting as would be common in hospital facilities and homes. Research suggests that protection of PN solutions from strong light should be accorded greater priority for both hospitalised and ambulant patients than is currently practiced.[105] Amber light-protective infusion sets may also provide additional benefit, particularly in slow infusions. The impact of light and light protective mechanism is an area that warrants further research in contemporary PN administration.

PRACTICAL CONSIDERATIONS FOR THE MONITORING OF PARENTERAL VITAMINS

There are a number of limitations associated with monitoring vitamin levels that should be considered before requests are placed. First, vitamin assays are not highly developed nor are they reliable or widely accessible. While specific issues around testing for individual vitamins have been outlined in the relevant sections of this guideline, broader limitations common to all biochemical tests may also impact on monitoring for vitamin status. These include though are not limited to: factors around transport, handling and storage, analysis of samples and within sample variation.[106-108]

Second, the presence of an acute phase response mediated by acute clinical issues will confound the interpretation of many vitamin tests. This is due to many transport carrier proteins for vitamins and trace elements being either negative or positive acute phase responders.[109] For this reason a CRP level should always be taken concurrently with any micronutrient requests to allow for contextual interpretation. In the case of a known elevated CRP level/acute illness, testing should be deferred until these issues have fully resolved.

Third, reference ranges for many vitamins are not well defined. A reference range is by definition the range that would be observed in an otherwise healthy population.[106] It may be argued that those receiving PN are not representative of the general population and that comparison against a population-based range may confound interpretation in the setting of parenteral vitamin provision. Furthermore, unlike the development of reference ranges around commonly obtained samples, vitamin tests are with few exceptions infrequently ordered and as such the number of analyses on which to base a reference range is likely to be less robust than more common measures.[106]

Fourth, there are significant health care associated costs with micronutrient testing. For example, at the time of writing the cost for a full vitamin panel analysis in Australia may cost in excess of $A170, the price of which more than doubles when trace elements are also tested.[110] The relative benefit and clinical application of the vitamin monitoring must be weighed against the expense of the tests. In the increasingly scarce resourcing in healthcare environments vitamin and other micronutrient testing may represent an unnecessary cost in the care of many PN patients.

For these reasons AuSPEN recommends judicious consideration as to whether vitamin testing is necessary and/or likely to be valid prior to requesting it in each individual clinical situation. With the exception of vitamin D, routine surveillance of vitamin levels in patients receiving regular parenteral multivitamin supplementation is unlikely to be necessary and should be minimised in short-term, long-term or HPN patients. Examples of times when testing and/or a short period of surveillance may be indicated include suspicion of vitamin deficiency/toxicity, follow up post recent vitamin replacement, those at risk of deficiencies due to increased losses or metabolic turnover, or post major changes to frequency of parenteral multivitamin preparation administration (i.e. significant reduction in HPN days on PN). Decisions relating to the frequency of vitamin monitoring should be based on the underlying clinical condition of the patient, known deficiency risks and ultimately on the clinical judgement of the PN prescriber/s.

STRENGTHS AND LIMITATIONS OF THE AUSPEN VITAMIN PN GUIDELINES FOR ADULTS

The strength of the current guideline review is that they represent a thorough and systematic review of the currently available literature for this patient group. Furthermore they have been developed specifically with unique issues relevant to the Australian and NZ population and how this may impact on those receiving PN (including both baseline micronutrient vulnerabilities and locally available parenteral multivitamin preparations).

There are a number of limitations associated with this guideline. First, the majority of studies conducted on micronutrient supplementation or status in PN recipients are limited by small study size and often are in the context of PN practices that are not reflective of contemporary practice.

Second, few studies have been conducted within Australia and NZ. The generalizability of international studies to the local population remains unclear due to different parenteral multivitamin preparations and PN solutions (particularly lipid emulsions) used, and baseline nutritional status influenced by the geographical location.

Finally, each recommendation for the maintenance doses and monitoring of each vitamin has been assessed against the NHRMC matrix to provide an assessment of the strength of evidence supporting the recommendation: these range from a grade of A (highest) to D (lowest) based on the strength of evidence provided on each contributing study and the applicability of the findings to the Australian and NZ context. Based on the limitations of the available research as outlined above the recommendations contained in this document are NHMRC Grade C or D recommendations. However this should be understood in the context of the realities of nutritional research in which the elements of well-designed randomised controlled trials, notably blinding and randomisation, are not always possible due to ethical or logistical reasons. As such, lower grades of evidence often represent the best level of evidence available and this does not necessarily invalidate the recommendations based on them. For this reason, the recommendations for research form an important part of the conclusions of these guideline recommendations.

RECOMMENDATIONS FOR CLINICIANS

1. A parenteral multivitamin preparation should be provided from the day of PN commencement and as regularly as PN is provided.
2. All patients receiving PN should be individually assessed to ensure the vitamin doses provided by standard parenteral multivitamin provision is adequate for their individual clinical circumstances.
3. Due to the vulnerability of the Australian and NZ populations to vitamin D insufficiency and/or deficiency, vitamin D should be monitored annually in patients receiving long-term PN.
4. Routine surveillance and monitoring of vitamin levels other than vitamin D are not required unless there is a clinical suspicion of deficiency or toxicity. Periodic assessment may be indicated in cases where significant clinical or PN prescription changes are occurring.
5. Appropriate light protection should be provided for parenteral vitamin administration.
6. Clinicians should be aware of the local practices that may impact on a reduced dose of parenteral vitamins being delivered to the patient.

RECOMMENDATIONS FOR INDUSTRY AND ADMINISTRATORS

Based on the present review, there is no evidence on which to base recommendations for changes to the parenteral multivitamin preparations currently available in Australian and NZ. Evidence supports the need for effective light protection to prevent photo degradation of vitamins in the PN admixture. Devices which are light protective should be made available within the Australian and NZ.

RECOMMENDATIONS FOR RESEARCH IN PARENTERAL NUTRITION SUPPORT

The literature underpinning the present vitamin guidelines review have identified a number of gaps that require further research to inform further PN provision and optimal nutritional care for this patient population. These include but are not limited to: determination of vitamin D status of those receiving long-term PN in Australian and NZ; investigation of the relationship between vitamin D status/provision and the development of MBD in long-term PN recipients; role of vitamin K in the bone health in long-term PN through prospective studies; the role of choline and/or carnitine in the prevention and treatment of PNALD/IFALD; and clarification of the most effective method/s to administer parenteral vitamin preparations, including investigation into administration methods and methods of reducing vitamin degradation.

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Clinical Nutrition Guidelines

Australasian society for parenteral and enteral nutrition (AuSPEN) adult vitamin guidelines for parenteral nutrition

Emma J Osland AdvAPD MPhil[1,2], Azmat Ali AdvAPD[3], Truc Nguyen BPharm[4], Melvyn Davis PhC FSHP[5], Lyn Gillanders NZRD[6,7]

[1]*Department of Nutrition and Dietetics, Royal Brisbane and Women's Hospital, Butterfield Street, Brisbane, Australia*
[2]*Faculty of Health and Behavioural Sciences, School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Australia*
[3]*Department of Nutrition and Dietetics, Princess Alexandra Hospital, Brisbane, Queensland, Australia*
[4]*Department of Pharmacy, Middlemore Hospital, Auckland, New Zealand*
[5]*Mel Davis and Associates, Sydney, Australia*
[6]*Nutrition Support Team, Auckland City Hospital, Auckland, New Zealand*
[7]*Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand*

澳大利亚肠外与肠内营养学会（AuSPEN）肠外营养成人维生素指南

背景与目的：该项工作是对AuSPEN 1999年指南针对接受肠外营养（PN）的成人患者补充微量元素进行逐步审查的第二部分。**方法与研究设计：**进行系统文献综述，基于现有证据，同时考虑澳大利亚和新西兰（NZ）实践环境的特殊因素提出了推荐。对每一项证据支撑的推荐的强度进行了评估。一个多学科指导委员会和外部评审员对指南提供了反馈意见。**结果：**通过现有文献综述，发现在澳大利亚和新西兰，现有的肠外复合维生素制剂，对常规接受PN且复合维生素作为PN处方一部分的成年人，足以避免不足，且不会造成毒性。维生素D是澳大利亚和新西兰人群最容易缺乏的维生素。**结论：**维生素是肠外营养的重要组成部分，应为所有接受PN的患者提供维生素。除了推荐的每年监测维生素D外，常规监测维生素含量，对接受常规复合维生素制剂的患者未必是必须的。当评估、开处方以及监测接受PN的患者时，临床评估是个重要的因素。有待进一步研究的领域也已经确定。

关键词：维生素、指南、肠外营养、维生素D、复合维生素