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PARENTERAL NUTRITION IN CRITICAL CARE PATIENTS

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ABSTRACT

The nutritional delivery to critical care patients is challenging and may require justified evaluation of its composition. Parenteral nutrition (PN) is still inevitable in several situations. The nutritional support includes provision of calories, proteins, carbohydrates, lipids, micronutrients, electrolytes and fluids in appropriate amounts according to individual needs. We have reviewed the existing guidelines, meta-analysis studies, randomized controlled trials, and review articles for various components of PN and studied their impact on the clinical outcomes.We systematically searched PubMed, Medline and Embase for trials (published from 2017 to 2020) investigating various components of parenteral nutrition and their impact on clinical outcomes. In conclusion, there is still lack of proper large scale trials to justify the optimal combinations with the dosage required of each component of PN.

Keywords: Parenteral nutrition, critical care, guidelines, ICU

INTRODUCTION

Critical care patients are often found malnourished along with impaired immune function and muscle weakness. This finally leads to increased ventilator-dependent days and increased length of stay in ICU (Intensive care unit). The prognosis of such patients is closely associated with the nutritional status (Lee and Heyland, 2019). Cautiously, supplementing these patients for necessary caloric and protein intake would help prevent under or overfeeding and attenuate increased energy deficit and catabolism (Singer, 2019). However several debates are on-going related to the timing, quality of macronutrients, safety, incidence of complications, and route of delivery (Cotogni, 2017). Most of the guidance documents states that nutritional support should be given as soon as possible and within first few weeks of intensive care. Several guidelines have been put forth to streamline the parenteral nutrition given to critically ill patients. This article has taken into consideration mainly the European Society for Clinical Nutrition and Metabolism (ESPEN) and American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines along with some of the other guidelines.

Three principal routes can feed nutrition: oral, enteral and parenteral. Oral route is generally not feasible in critically care patients. Enteral route is the most preferred route for providing nutrition in ICU patients (Macdonald et al, 2013). Several trials have been conducted to assess superiority of enteral nutrition (EN) over parenteral nutrition (PN). Most of them suggest EN to be first line strategy in critical illness and PN to be preferred only if EN is not sufficient or feasible. Further several studies have proved that supplemental PN with EN increases energy delivery when compared to usual EN alone (Ridley et al, 2018a; Wischmeyer et al, 2017). However, the CALORIES (Trial of the Route of Early Nutritional Support in Critically Ill Adults) and NUTRIREA-2 (Enteral versus parenteral early nutrition in ventilated adults with shock: a

randomised, controlled, multicentre, open-label, parallel-group study) trials have suggested PN to be a safe alternative to EN and may be less risky if administered and monitored correctly (Harvey et al, 2014; Reignier et al, 2018). This review focuses on the various studies associated with the design of composition of parenteral nutrition. We systematically searched PubMed, Medline and Embase for trials (published from 2017 to 2020) investigating various components of parenteral nutrition and their impact on clinical outcomes. Total 48 articles were selected and included in the review from 2504 articles obtained by using various keywords. Also several guidelines for the provision and assessment of parenteral nutrition were reviewed and 5 guidelines were referred for the article.

COMPOSITION OF PARENTERAL NUTRITION

Parenteral nutrition can be divided into total parenteral nutrition (TPN) or supplementary parenteral nutrition. The composition of PN depends on medical condition of the patient, patients' needs and metabolic capabilities. TPN is devised to provide complete nutrition and thus is composed of all necessary nutrients like water, carbohydrates (sugar) for energy, proteins (amino acids), lipids (fats) as well as electrolytes (potassium, sodium, calcium, magnesium, chloride, and phosphate), vitamins and trace elements in required proportions. There are several recipes or formulations available commercially, however, all of them must have a certain proportion of nutrients. There must be a balance of calories provided from protein and non-protein sources. Further, the ratio between carbohydrate and lipid calories must also be balanced.

ENERGY REQUIREMENTS

Energy expenditure and requirements are calculated based on nutritional status of the patient prior to admission, number of hospitalization days, endogenous nutrient production, and energy balance etc (Singer et al, 2019). It may be calculated through simplistic formulas, published predictive equations, or more preferably by indirect calorimetry which is considered as gold standard (McClaveet al, 2016; Singer et al, 2019). The recommendations by ESPEN and ASPEN are given in Table 1 for adult critical ill patients without other complications. It is believed that providing energy and protein in prescribed amounts to ICU patients improves morbidity and mortality. However, large prospective randomized controlled trials (RCT) to determine optimal amount of energy intake are lacking. A systematic review and meta-analysis including 10 trials concluded that near target energy delivery in adult critical ill patients did not affect mortality or other relevant clinical outcomes as compared to standard care energy delivery (Ridley et al, 2018b). Amulticentre, pilot RCT enrolling 125 patients indicated that providing supplemental PN with EN to underweight and obese ICU patients significantly increased the calorie/protein delivery during the first week of ICU admission as compared to only EN (Wischmeyer et al, 2017). While post hoc analysis of INTACT trial data comprising of 98 patients found that high calorie exposure between day one to seven in ICU resulted in higher hazard of mortality while same high calorie exposure after eighth day decreased death probability in acute respiratory distress syndrome patients (Peterson et al, 2018). There are several studies determining the benefits of hypocaloric feeding over normocaloric feeding in critical care but the results are still controversial (Patkova et al, 2017; Oshima and Pichard, 2015).

PROTEINS

During critical illness, protein is one of the major macronutrient of importance as it is involved with lean body mass, immune function as well as healing. Critical illness is associated with marked catabolism leading to muscle loss and fatigue. Thus protein requirements are usually higher in ICU patients (McClaveet al, 2016; Singer et al, 2019). However, energy and protein requirements do not go hand in hand and should be considered separately. The recommendations for the protein amounts in PN are dependent upon the clinical status of the patient. General recommendations of ESPEN states 1.3 g/kg/day of protein equivalents in critical illness without

other complications to be given progressively while ASPEN recommends the same to be 1.2-2.5 g/kg/day of protein equivalents (Table 1). Several clinical studies has been conducted to evaluate the beneficial effects of amino acid supplementation in PN during critical illness and a brief summary of the studies carried in the last three years (2017-2020) is given in Table 2. A systematic review underlined the lack of high quality evidence based studies to establish the association between energy and/or protein delivery and skeletal muscle mass changes in acute critical illness and suggested for further studies to be conducted (Lambell et al, 2018). Different trial conclusions and according to the recommendations by ESPEN and ASPEN, higher protein intake near to the target protein is associated with improved outcomes and better prognosis.

The proteins are usually provided as balanced mixtures of amino acid solutions which match with the normal requirements of essential amino acids in healthy subjects. However, there are certain amino acids which may be insufficient in critical illness due to increased demand. These include arginine, cysteine, glutamine, tyrosine, glycine, orthinine, proline and serine. It is questionable whether they should be replaced or not. There are no evidences for supplementing individual amino acids during critical illness while glutamine supplementation may be harmful (Gunst et al, 2018).Certain studies have evaluated effects of glutamine given in Table 2. Both ESPEN and ASPEN recommends that parenteral glutamine should not be used in unstable critical care patients or patients with hepatic or renal failure (McClaveet al, 2016; Singer et al, 2019).

CARBOHYDRATES

Glucose forms the mainstay for providing energy in PN. Carbohydrates form the preferred substrate for energy production but in critical illness, insulin resistance and hyperglycaemia may result due to stress. Thus, guidelines recommend minimal and upper limits for administration (Table 1). The optimal amount of carbohydrate to be administered by PN is yet difficult to determine. Hyperglycaemia may result in glucose based energy provision as compared to lipid based energy provision in critical illness along with increased insulin requirements, increased lipogenesis, increased CO_2 production as well as no advantage in protein sparing leading to poor prognosis (Singer et al, 2019). Also, the ESPEN expert group recommended that insulin resistance and hyperglycaemia in critical illness may have negative impact on clinical outcomes and so should be prevented by either nutritional or pharmacological support (Barazzoni et al, 2017).

A systematic review suggests use of clinical nutrition consisting of ≤15% fat and ≥60% carbohydrate for critically ill burn patients as evidences indicates that low fat and higher carbohydrate levels improve patient outcomes in severely burn patients (Shields et al, 2019). Ma et al (2018) revealed a negative association of total PN associated hyperglycaemia and risk of cardiac complications in a retrospective study comprising of 1517 critically ill elderly patients with no history of diabetes.

LIPIDS

Lipids are an important component of PN providing essential fatty acids which are a source of calories and also serves as building blocks of cell membranes. The nutritional support is usually delivered in the form of medium chain fatty acids, long chain fatty acids (α-linoleic, linoleic, oleic, and palmitic acids) or very long chain fatty acids (eicosapentaenoic acid (EPA) and docasahexaenoic acid (DHA)) (Calder et al, 2018). They need to be provided in emulsions form as they have to be made soluble in aqueous solutions. Based on these, many different lipid emulsions (LE) are available like vegetable soybean oil, medium chain triglycerides (MCT), olive oil (OO), fish oil (FO) etc.

Fat absorption or metabolism is impaired or modified in critical illness. Energy from fat should comprise of about 25-40% of total infused energy as in normal nutrition. The recommendations by guidelines are given in Table 1. ESPEN recommend a blend of fatty acids including medium chain triglycerides, oleic acids and α-linoleic acids (Singer et al, 2019). While ASPEN suggest the use of alternative LE consisting of SMOF (soybean oil, MCT, olive oil and fish oil), MCT, OO and FO (McClaveet al, 2016) if available. Table 2 lists several clinical studies which have been conducted to evaluate different lipid formulations in PN. Soybean oil based emulsions have been shown to be associated with more adverse events than other LE and are being partially replaced by MCT, FO or OO in different combinations. SMOFlipid supplementation in PN of ICU patients has shown to have positive impact through its immunomodulatory and anti-inflammatory effects, safe liver function outcomes, reduction in nosocomial infections and hospital stay. It was also found to be cost effective and suggested to be the gold standard of PN in intensive care patients (Leguina-Ruzzi and Ortiz, 2018). However, even though all studies have shown better clinical outcomes or infection rates in critically ill patients with four-oil mixed LE, they have their own limitations and suggest for more large scale multicentre clinical trials to optimize the strategy for four-oil mixed LE provision.

Intravenous FO containing LE are said to be rich in omega-3 polyunsaturated fatty acids and thus said to possess better anti-inflammatory and immunomodulatory effects. Several clinical studies have been conducted for FO as part of PN as listed in Table 2. Research suggest that FO based LE in PN formulations reduces the risk and progression of PN-associated liver disease in the cases where total PN cannot be avoided (Mitra and Ahn, 2017).Olive and fish oil containing intravenous LE have been shown to improve morbidity in a recent meta-analysis (Singer et al, 2020).Studies have reported reduction in inflammatory response, improvement in gas exchange and reduction in hospital stay in patients receiving FO as part of their PN support (Calder, 2019).

MICRONUTRIENTS

Micronutrients like trace elements and vitamins are required in small quantities as daily requirement. These nutrients play a major role in immunity, metabolism of carbohydrates, proteins and lipids, cell repair and signalling as well as antioxidant activity. Several guidelines recommend provision of trace elements and vitamins with PN for their nutritional and antioxidant aspects. Some of the recommendations are listed in Table 3. However, PN mixtures do not contain trace elements or vitamins due to stability issues. They require separate prescribing and are usually added under controlled aseptic pharmaceutical condition (Chowdhury and Lobaz, 2019). During critical illness; the requirements of certain micronutrients are altered and have to be provided in increased amounts. The acute phase response in critical disorders leads to redistribution of micronutrients due to release of pro-inflammatory cytokines (Blaauw et al, 2019). Further, deficiencies of micronutrients like thiamine, pyridoxine, folate, ascorbic acid, zinc and copper, are found to be higher in critically ill patients undergoing continuous renal replacement therapy. Thus, more prospective studies are needed to evaluate their effect on the metabolic and clinical efficacy of micronutrients in critically ill ICU patients (Kamel et al, 2018). Certain trace elements are considered essential in PN to maintain health like copper, chromium, zinc, manganese, selenium, iron, iodine, molybdenum and fluoride (Jin et al, 2017). The minimum basic requirements of these trace metals for PN in adults is provided by various guidelines listed in Table 3. However, their doses need to be adapted in proportion to the other macronutrients and with regard to the underlying diseased condition as suggested by both ASPEN and ESPEN (Ridley et al, 2018b; Singer et al, 2009).

PARENTERAL NUTRITION FORMULATIONS

Parenteral nutrition administration to each patient requires monitoring of clinical and metabolic changes depending upon the condition of the patient. Each formula has to be tailored according

to the needs of the critically ill patient. However, the commercially available PN regimens consist of several substrates like proteins, carbohydrates and lipids in definite ratio according to the established clinical guidelines. They are available either as premixed multi-chamber PN formulations or have to be compounded under aseptic conditions in the hospitals. The compounded PN formulations (manual or computerized) are customized according to the patient's need but there are more chances of error as well as infections in such formulations which are still debatable. The chances of error have been tried to reduce by technological advancement in compounding and has proved to be effective (Curtis et al, 2018). The premixed formulations are commercially available as single chamber or two-in-one (dextrose-amino acids formulation) or three-in-one (dextrose, amino acids and intravenous lipid emulsion) chamber bags which are promoted as safer and effective delivery modes for macro and micronutrients as compared to the traditional compounded formulations. Several clinical guidelines have suggested the use of premixed multi-chamber bags for PN for uncomplicated patients (Boullata et al, 2014; Singer et al, 2019). However, Boullata et al (2020) found both the systems i.e multi-chamber bags or compounded PN to be valuable but the choice depends on multiple factors including availability of products, expertise, processes or economic considerations.

Several studies have been conducted to compare such modes of PN for its effect on clinical outcomes, safety and cost, the determining factors for finalization of the mode of PN. Maximum numbers of errors were found to be associated with compounding or dispensing the PN regimen which led to significant adverse events even fatality in one study (Guenter et al, 2017). Further, a systematic review suggested that use of multi-chamber bags was associated with fewer infections, reduced length of hospital stay and safer than compounded bags. However, they also concluded that the safety is reduced if further additions are made in the premixed formulations in the ward under non-aseptic conditions for specialized critical patients (Alfonso et al, 2017). A prospective, randomized, single-blind study conducted in China concluded the three chamber bag PN regimen to be comparable to the compounded regimen in terms of clinical outcomes and safety. But the preparation time was significantly reduced with three chamber bags which simplify the process of PN (Yu et al, 2017). A prospective, observational, cost-accounting study evaluating 597 PN (multi-chamber bags + compounded bags) found significant reduction in cost and preparation time as well errors related to PN preparation with the use of multi-chamber bags as compared to compounded bags (Berlana et al, 2019). Another study in 688 hospitals in the United States of America concluded lower risk of infections and cost with only multi-chamber bags while multi-chamber bags with addition and compounded bags were not significantly different in these parameters (Banko et al, 2019). However, certain experts have said that these premixed formulas may not provide the required caloric, amino acid and electrolyte needs of special critical ill patients like obese, hepatic or renal failure patients. These formulas have also been criticized for high dextrose amount which may increase the risk of hyperglycaemia and infections (Boullata et al, 2014). Thus, guidelines have suggested the use of premixed PN formulas in uncomplicated critical ill patients while in specialised situations; the choice should be assessed by clinicians with expertise in nutrition support therapy.

The two-in-one or three-in-one PN formulations differ in the way of providing the lipid emulsions. The lipid emulsions are provided as separate infusion when two-in-one PN mixtures are used while three-in-one formulation have all three (dextrose, amino acid and lipid emulsion) in one container. The three-in-one formulation is preferred due to its ease of compounding, less risk of contamination, as well as cost savings. But the system has issues of emulsion destabilization and higher chances of medication incompatibility with lipid emulsion portion. In addition, the three-in-one system requires large pore size filter (1.2 μm) thus increases the risk of particulate matter including bacteria. However; studies have shown that both systems are almost comparable for the risk of infections when administered over 24 hours (Boullata et al, 2014). A

recent study have shown that olive oil based three chamber bags have shown reduced rate of infection as compared to soybean oil based compounded bags in hospitalized adult patients (Jia et al, 2019).[38] Further controlled trials are needed to confirm the superiority of one system over the other.

FUTURE PERSPECTIVES

Over the last decade, several studies have been performed to evaluate the role of nutrition support in critically ill patients. Enteral nutrition is said to be preferred over parenteral nutrition however some studies have shown parenteral nutrition to be a preferred safe alternative to enteral nutrition if taken cautiously. The actual nutritional assessment in critically ill patients is difficult and also achieving a balanced nutrition support in all critically ill patients is not possible. But reviewing several studies have suggested that nutritional support for each patient should be tailored based on their metabolism, requirements and coexisting deficiencies. Nutrition guidelines of several countries have suggested certain fixed doses of macro and micro nutrients which could be utilized as basis for stable patients and modified according to the needs of individual patient.

This review has tried to summarize the role of each component of parenteral nutrition and their effect on clinical outcomes. However, several high quality evidence based studies are lacking to justify the association between energy and protein delivery along with their amounts to be provided. The minimal and maximal amounts of carbohydrates or dextrose are also debatable and large randomized controlled trials can further clarify the situation. Several types of intravenous lipid emulsions are available recently and studied for their effects on inflammatory response and clinical outcomes in critically ill patients. However, these studies also suggest further large controlled trials to confirm their benefits clinically as well as economically. Further, there are lack of trials for investigating the optimal combinations and dosages of micronutrients to maintain the antioxidant status in critical ill patients. Lastly, recent studies and guidelines have suggested the use of multi chamber bags for the delivery of parenteral nutrition to be most safe and error free. However, there is need of further trials to confirm their full benefits.

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TABLES

Table 1: Recommended parenteral nutritional requirements of macronutrients by various guidelines for critically ill adult patients

	Recommend dose		
	ESPEN (Singer et al, 2019)	**ASPEN (ASPEN 2019)**	**Indian practice guidelines (Mehta et al. 2018)**
Energy	To be determined by indirect calorimetry – recommended hypocaloric nutrition in first week (not exceeding 70% of energy expenditure in early phase)	20-30 kcal/kg BW/day Indirect calorimetry to be used Hypocaloric dosing preferred (80% of energy needs)	25-30 kcal/kg BW/day
Protein intake g/kg/day	1.3 g/kg BW/day progressively	1.2-2.5 g/kg BW/day	1.2-2.0 g/kg BW /day
Fluid	Not mentioned	Minimal to provide adequate macronutrients	
Carbohydrate intake	≥2 g/kg BW/day but <5 mg/kg BW/min	<4 mg/kg BW/min Blood glucose levels – 150-180 mg/dL	
Intravenous lipid emulsions	<1.5 g/kg BW/day	<1 g/kg BW/day Maximum 100g/week divided in 2 doses Soy based lipids emulsions should be limited	
Mode	complete all-in-one bag	No recommendation	

Abbreviations: ESPEN: European Society for Clinical Nutrition and Metabolism, ASPEN: American Society of Parenteral and Enteral Nutrition, BW: Body weight

Table 2: Clinical studies evaluating various protein and lipid formulations for parenteral nutrition

Reference	Study Design	Objective	Results and Conclusion
PROTEIN STUDIES			
Danielis et al. 2019 - OPINiB Trial	Randomized controlled single centre trial (n = 40)	Effect of protein fortified diet on nitrogen balance in critical ill patients	Protein fortified diet (1.8 g/kg/day) strengthened the nitrogen balance in critical ill patients
Bendavid et al. 2019	Retrospective cohort study (n= 2253)	Effect of early administration of protein in critical ill patients for improving clinical outcomes	High protein delivery in the first 3 days of ICU admission showed higher 60-day survival
Koekkoek et al. 2019 - PROTINVENT Study	Retrospective single centre cohort study (n = 455)	Determination of timing and dose of protein intake for lowering 6-month mortality	Low protein delivery during first two days gradually increasing to intermediate during third to fifth day and high from sixth day was associated with lower six month mortality
de Koning et al. 2020 PROCASEPT Trial	Retrospective observational study (n=423)	Association of low, medium and high (<0.8, 0.8-1.2 and >1.2 g/kg/day respectively) protein intake and energy intake (<80%, 80%-110%, 110% of target) with long term outcomes in mechanically ventilated septic and non-septic patients during early and late phase	Late medium protein and late high energy intake was associated with better survival in septic patients and early high protein intake was associated with high mortality in non-septic patients
Stehle et al. 2017	Meta-analysis of 15 randomised controlled trials	Evaluation of glutamine supplementation in improving clinical outcomes for critically ill patients	Glutamine supplementation reduced infection rates, mechanical ventilation duration, hospital mortality rates and hospital stays in addition to providing economic benefit.

LIPID STUDIES			
Roberti et al. 2017	Case report	Comparison of four oil mixed LE to conventional soybean oil LE	The four oil mixed LE was preferred over soybean oil LE as it was less inflammatory and improves liver outcomes.
Feng et al. 2017	Pharmacoeconomic analysis	Evaluated the acquisition cost of PN with SMOFlipid emulsion rich in omega-3 fatty acid vs. standard PN	SMOFlipid emulsion PN can produce reduction in overall hospital stay, ICU stay and nosocomial infections and also reduce health care costs as compared to standard PN with a mean cost saving of US $1116 per patient.
Astapenko et al. 2019	Pilot study (n = 15)	Effect of administration of lipid emulsion on endothelial glycocalyx	The SMOF 20% lipid emulsion infusion had no injurious effects on endothelial glycocalyx
Donoghue et al. 2019	Double-blind, randomised study (n=75)	Comparison of intravenous four-oil LE (30% soybean oil, 30% medium-chain triglycerides, 25% olive oil and 15% fish oil) with 100% soybean oil LE in critically ill patients	The four oil LE was able to increase the EPA and DHA levels while reduce the omega-6:omega-3 polyunsaturated fatty acid ratio. The sequential organ failure assessments, length of ICU stay or six-month mortality were not significantly different.
Lu et al. 2017	Meta-analysis of 17 RCT	Evaluation of omega-3 supplementation in septic patients	Omega-3 supplementation can reduce ICU stay and mechanical ventilation duration
Li et al. 2018	Prospective, non-randomized, observational clinical study (n=112)	Comparison of FO based PN with standard PN in septic patients	FO based PN presented with significant reduction in all-cause mortality, APACHE II score (Acute Physiology and Chronic Health Evaluation II) and length of stay in ICU as compared to the control group receiving

			standard treatment of sepsis as per guidelines.
Wu et al. 2017	Meta-analysis of 21 RCT	Comparison of efficacy of structured triglycerides with that of physical mixture of medium and long chain triglycerides	Structured triglycerides were found to better for protein economy, liver function as well as hospital stay
Wu et al. 2017	Meta-analysis of 27 RCT	Comparison of cost of structured triglycerides with physical mixture of medium and long chain triglycerides	Structured triglycerides were found to be more cost effective

Abbreviations: n – No. of patients involved in the study, PN – parenteral nutrition, RCT – Randomized controlled trial, LE – Lipid emulsion, FO – Fish oil, SMOF - soybean oil, medium chain triglycerides, olive oil and fish oil, EPA - eicosapentaenoic acid, DHA - docosahexaenoic acid

Table 3: Recommended adult parenteral nutritional requirements of micronutrients by various guidelines

Micronutrient	**Recommend dose**			
	ESPEN (Singer et al, 2009)	**ASPEN (ASPEN 2019)**	**AuSPEN [trace element(Osland et al. 2014), vitamin(Osland et al. 2016)]**	**International consensus(Blaauw et al. 2019)**
Copper (mg/day)	< 0.48–1.27	0.3-0.5 mg	0.3–0.5	0.3-0.61
Zinc (mg/day)	> 3.27–10	3-5 mg	3.2–6.5	2.5–6.5
Chromium (µg/day)	>10-15	<1000	10–15	10–15
Manganese (mg/day)	<0.2–0.55	0.55	0.055	0.055-0.1
Selenium (µg/day)	>20–70	60-100	60–100	20–100
Iodine (µg/day)	<10–130	NM	130 (long term PN)	70–150 (if recommended)
Iron (mg/day)	1–1.95	NM	1.1 (long term PN)	1–1.2 (if recommended)
Molybdenum (µg/day)	10–25	NM	19 (long term PN)	NM
Fluoride (mg/day)	0.57–1.45	NM	NM	NM
Vitamin A (Retinol) (µg/day)	NM	990	1050	990–1050
Vitamin D (Cholecalciferol) (µg/day)	NM	5	5	5
Vitamin E (alpha tocopherol) (mg/day)	NM	10	10	10

Vitamin K (Phytomenadione) (µg/day)	NM	150	NM	Based on patient's needs
Vitamin B1 (Thiamine) (mg/day)	NM	6	3	3–6
Vitamin B2 (Riboflavin) (mg/day)	NM	3.6	4-5	3.6–5
Vitamin B3 (niacin) (mg/day)	NM	40	40-47	40–47
Vitamin B6 (Pyridoxine) (mg/day)	NM	6	3	3–6
Vitamin B12 (Cyanocobalamin) (µg/day)	NM	5	5-6	5–6
Vitamin C (Ascorbic acid) (mg/day)	NM	200	110-150 mg	110–200 mg
Vitamin B9 (Folic acid) (µg/day)	NM	600	400	400–600
Biotin (µg/day)	NM	60	69	60

Abbreviations: ESPEN: European Society for Clinical Nutrition and Metabolism, ASPEN: American Society of Parenteral and Enteral Nutrition, AuSPEN: Australasian Society of Parenteral and Enteral Nutrition, NM – Not mentioned