

Immunonutrition: a South African perspective

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Abstract

Clinical nutrition has evolved from providing nutrients to meet the patient's needs to nutrition therapy that additionally aims to provide specific nutrients, or combinations thereof, which can reduce infection and improve outcomes in critically ill patients. The value of immunonutrition in the management of critically ill, preoperative and postoperative patients is now acknowledged by many healthcare practitioners. Amid the demonstration of clinical and economic benefit in defined conditions, South African practitioners should aim to translate current knowledge to best practice in order to optimise nutrition therapy and ultimately clinical outcome in critically ill patients. For the future, a paradigm shift to pharmaconutrition has been suggested. This practice dissociates the administration of key single nutrients, in the form of requirement-based parenteral or enteral nutrition, from the delivery of pharmaconutrients in the full effective pharmacological dose, as evaluated in large, well-designed trials, in order to achieve therapeutic effects. This has been evaluated in large, well designed trials. The purpose of this review is not to provide an exhaustive overview of the available literature on immunonutrition, but rather to highlight key and recent significant studies, with a focus on energy and protein, glutamine, arginine, omega-3 fatty acids and micronutrients, and relate them to the South African context. Finally, the bigger picture should always be borne in mind, within the settings of the complexity of the acute phase response and the heterogeneity of the critical care population. As the evidence base evolves, the definition of optimal nutrition therapy should include all relevant components in the right mix, at the right time, to the right patients, to ensure optimal clinical benefit and outcome.

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Introduction

Over the last two decades, clinical nutrition has evolved from nutritional support that is intended to meet the patient's needs only (denoting a passive role), to nutrition therapy that is selected according to the patient's disease or medical condition. Currently, there is renewed interest in nutritional therapy in critical illness, particularly in the areas of immunonutrition and pharmaconutrition (or nutritional pharmacology).¹ It is now known that nutrition is much more than just delivering basic substrates or nutrients that play a role in providing a fuel source for basic metabolism and cell growth, but that there are specific nutrients, or combinations thereof, that can reduce the risk of infection and improve outcomes in critically ill patients.²

Immunonutrition has been described as the ability to modulate the inflammatory or immune response by nutrients or a specific food item that is fed in amounts above what is normally consumed through the diet alone.^{3,4} Furthermore, some nutrients, when given in higher doses, appear to serve as pharmacological agents. In the latter context, these pharmaconutrients may positively or negatively

alter clinical outcomes in a manner that is not dissimilar to the way in which any other pharmacological agent functions.^{1,5,6}

The earliest scientific evidence that implicates the role of nutrition in immune function is probably the description of thymic atrophy that was provided by Menkel in 1810.⁷ The birth of nutritional immunology (1800s) and the vitamin era (1900s) improved our understanding of the impact of nutritional deficiencies on the immune system.⁷ Some of the pioneering work in immunonutrition was carried out by Alexander at the Shriners Burns Institute. His research led to the formulation of the Shriners' burn formula, an enteral (EN) feeding solution that contained arginine, ω -3 fatty acids (FAs), and vitamins A, C and zinc.⁸ This formula resulted in reduced length of stay and reduced wound infections.⁹ Thus immunonutrition is not a new concept as it is often regarded, but rather the application thereof to new clinical settings.

The purpose of this article is not to provide an exhaustive review of the available literature on immunonutrition, but rather to highlight key and recent significant studies and relate them to the South African context. One of the restricting factors in providing state-

of-the-art health care in South African is limited available finances. Often immunonutrition is perceived to be expensive when compared with standard enteral (EN) and parenteral (PN) products. Healthcare providers need to be more aware of the evidence base that supports the benefits of immunonutrition in defined populations, and that such an approach could ultimately result in cost saving, when prescribed correctly.

The critical care patient population

The population in the intensive care unit (ICU) is heterogeneous in nature. This diverse population suffers severe physiological stress or organ failure with varying degrees of acute phase response, insulin resistance and hyperglycaemia, protein loss, impaired gut function and immune system alterations. It has been suggested that the metabolic response after injury should be divided into three distinct phenotypes: the ischaemia-reperfusion phenotype, leucocyte phenotype and angiogenic phenotype.¹⁰ This may help to determine the best nutrition therapy for patients in a specific category. Furthermore, it has been consistently documented that approximately 15-70% of patients are undernourished or malnourished on admission to hospital,¹¹⁻¹⁶ which further complicates the provision of optimal nutrition therapy. Against this heterogeneity, while the provision of nutrients to meet requirements remains of paramount importance, it might be considered simplistic that the “one nutrition therapy regimen will fit all” approach can provide optimal therapeutic support.

What is to be achieved?

In part, the goal of the nutrition therapy dietitian or practitioner could be described as supplying the best possible nutrition therapy to the patient to aid the recovery process, prevent complications and discharge a functional patient home. This encompasses screening and assessing, as well as supplying the correct amount and mix of nutrients to support and modulate the acute phase response and immune system, and maintain and improve nutritional status. Due

to high demand and cost of care, the overall objective remains minimising the duration and costs of hospitalisation, while still trying to provide optimal care. This raises the question whether or not these goals are mutually exclusive since immunonutrition is deemed to be expensive.

By preventing and managing the complications of malnutrition, nutrition therapy dietitians contribute significantly to lowering care costs. Protein-energy malnutrition (PEM) has been shown to be an independent risk factor for morbidity and mortality. PEM is associated with a significantly higher risk of complications, such as infection, increased mortality, increased length of stay in hospital and ICU, decreased quality of life and poorer prognosis, all of which have been shown to increase care costs.^{11,16-19} In this regard, despite the respective limitations of the reported studies, the consistency of the reported findings (Table I) may be more important than the actual costs, which are country-dependent. In addition, malnutrition is also associated with impaired cell-mediated immunity with changes in peripheral lymphocyte subsets, as well as increased cortisol levels and T-helper 1 to T-helper 2 cytokine shift.²⁰ Furthermore, unplanned readmission of medical patients has been shown to be associated with chronic disease, depressive symptoms and underweight.²¹

The South African scenario: hospital malnutrition

The broader incidence of adult malnutrition in South African hospitals is largely unknown. Only a few studies are available in the published literature to date (Table II). The authors are aware of ongoing studies that should provide further crucial information once such information becomes available. The study populations vary and range from groups with high incidences of tuberculosis and human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), to groups who present with lifestyle diseases. Nevertheless, the high prevalence of malnutrition is consistent and the evaluated nutritional status parameters are known to be associated with higher care costs.

Table I: Costs associated with malnutrition

Study	Outcomes
Reilly et al, 1988 ²²	Well-nourished and no complications: \$2 968 (hospital stay) Malnourished and complications: \$12 683 (hospital stay)
Chima et al, 1997 ²³	Not at risk of malnutrition: \$4 563 ± 3 702 (hospital stay) At risk of malnutrition: \$6 196 ± 4 585 (hospital stay)
Desport et al, 1999 ²⁴	Mean daily hospital cost per well-nourished patient: \$138 Mean daily hospital cost per malnourished patient: \$228
Braunschweig et al, 2000 ²⁵	Normally nourished at admission and discharge: \$28 631 ± 1 835 Patients who declined nutritionally, regardless of nutritional status at admission: \$45 762 ± 4 021
O'Flynn et al, 2005 ²⁶	Malnutrition costs the NHS in excess of £266 million annually through longer length of stay, readmissions and treatment costs
CEPTON study, 2007 ²⁷	Direct costs of under-nutrition and malnutrition amount to €9 billion/year in Germany
EuroOOPS study, 2008 ²⁸	NRS “at risk”: ↑ mortality (12%); ↑ length of stay in hospital (9 days); ↑ complications (30.6%); ↑ cost NRS “not at risk”: ↓ mortality (1%); ↓ length of stay in hospital (6 days); ↓ complications (11.3%); ↓ cost
PREDYCES study, 2009 ²⁹	Patients at risk on admission: €8 207 Patients who were not at risk on admission: €6 798 Patients who developed malnutrition in hospital: €12 237 Patients who did not develop malnutrition in hospital: €6 408

NHS: National Health Service, NRS: nutritional risk screening (NRS-2002)

Table II: Incidence of adult malnutrition in South African hospitals

Area, year	Description of malnutrition
Zululand, 1983 ³⁰	Medical patients: 93% of male and 72% of female patients: Triceps skinfold thicknesses < 60% of normal One third of patients: clinically marasmic
Durban, 1983 ³¹	Hospitalised urban black patients: Significantly reduced fat stores: 82% males
Cape Town, 1984 ³²	Medical and surgical patients: Significant body weight depletion: 20% of patients Significant fat depletion: 30% of patients Significant muscle depletion: 15% of patients
Cape Town, 1988 ³³	Tuberculosis hospital: Decreased body weight: 32.3% of patients Fat depletion: 78.8% of patients Muscle depletion: 37% of patients
Cape Town, 1997 ³⁴	Medical patients: Severe malnutrition: 17% Subclinical malnutrition: 77%
Eastern Cape, 2011 ³⁵	Burn patients: 46.3% malnourished at admission

Infection and sepsis

Approximately 5-10% of patients who are admitted to acute care hospitals acquire one or more infection, affecting two million patients each year, and resulting in approximately 90 000 deaths annually in the USA. This adds an estimated \$4.5-5.7 billion per year to the costs of patient care.³⁶

Sepsis, septic shock and the adverse sequelae of the systemic inflammatory response syndrome (SIRS) have been shown to be the 10th³⁷-13th³⁸ most common cause of death in the USA and the second most common cause of death in non-coronary ICUs.³⁷ Sepsis is often lethal. It is suggested that the mortality rate is between 20-50% in severely ill patients³⁷ or 8-90%.³⁸ Only 10% of deaths were reported to be related to underlying disease, while 25% were attributable to bacteraemia.³⁸

Costs that relate to care of a patient with sepsis have been described to be as much as \$50 000 per patient, resulting in an annual burden of approximately \$17 billion.³⁷ There are approximately 400 000-500 000 septic episodes annually in the USA.³⁸ The Centers for Disease Control and Prevention (CDC) reported a 139% increase in the incidence of sepsis over the last 10 years. This occurred despite advances in knowledge and technological support.³⁸ Sepsis accounts for \$5-10 billion of the annual healthcare costs in the USA³⁸ and is reported to be the cause of 10% of ICU stays.³⁷

Although similar statistics are not available in South Africa, it is consistently documented that patients with infectious complications or sepsis have a longer length of stay and require second- and third-generation antibiotics, both of which have major cost implications. It is reasonable to conclude that if nutrition can play a role in the management or prevention of infection and sepsis, it will ultimately benefit the patient and reduce care costs.

Immunonutrition and pharmaconutrition

Nutrition and the immune system

Nutrition and the immune system interact on various levels and four such stages of interaction have been described.⁷ Stages I (complete nutrition) and II (optimising macronutrients and micronutrients) are the so-called "passive" stages which aim to supply the immune system with essential nutrients. Stages III (active modulation of the immune system) and IV (personalised nutrition) involve modification of the immune response through immune response modifiers (IRMs) that primarily target the pathogen-associated molecular patterns (PAMP) expressed by microbial pathogen receptors in the gut and involve more active approaches in modulating immune status.⁷

Immunonutrition and pharmaconutrition in critical illness

In ancient cultures, very few patients survived 72 hours following severe illness or trauma. In the modern world, ambulances, ventilation, medication and nutrition therapy enable patients to survive serious insults and trauma that might have proved fatal. Today, some of the major challenges are sepsis and containment of the inflammatory response. Despite following strict protocols and procedures, including timely screening and assessment, early nutrition therapy and meeting nutrient requirements, there is a high incidence of complications such as infections and multi-organ failure (MOF), as well as malnutrition. The nutrition therapy practitioner is left with the question whether it is possible to influence the outcome in favour of positive clinical outcomes. Possible proposed solutions in the literature, and which are founded on a growing evidence base, include the use of nutrients to modulate the acute phase and immune response, to prevent oxidative damage, to ensure glycaemic control and to provide probiotics to alter the gut environment, as well as sufficient energy and protein. Probiotics are used to alter the gut environment. Nutrients are also used to provide sufficient energy and protein.

The targets of pharmaconutrients are the immune system, muscles and intestines. The expected benefits include preservation of lean body mass, decreased intestinal permeability, decreased proinflammatory response/SIRS, decreased nosocomial infections, shorter length of stay, decreased mortality and a decrease in care costs. Various nutrients have been suggested or have been shown to play a role as pharmaconutrients, including zinc, selenium, vitamin E, vitamin C, glutamine, arginine, ornithine- α -ketoglutarate, fibre/short-chain FAs (SCFAs), prebiotics, probiotics and synbiotics, as well as energy and protein.^{4,39}

Just as antibiotics are organism-specific, all pharmaconutrients may not be beneficial in all critically ill patient populations at a given time. The effectiveness of a pharmaconutrient may be dependent on the stage or category of the acute phase response. For instance, the septic patient is in a hyperinflammatory state with SIRS predominance, with late predominance of the compensatory anti-inflammatory response syndrome (CARS) resulting in a second round of infections, MOF and death. Typically, trauma and surgical patients display CARS predominance early on. Consequent infections result in sepsis and death. Therefore, it is clear that different nutrients will have different advantages and modulatory effects in these two states.^{20,40-42}

Energy and protein

Although energy and protein are not commonly described as pharmaconutrients, it is well known that protein and energy insufficiency results in malnutrition which is associated with an impaired immune response and impaired wound healing, both of which are in turn associated with infections.⁴³ In the South African scenario, where finances are often limited, it is imperative to first provide the patient with basic nutrition support that meets the patient's requirements. This includes meeting energy and protein requirements through EN, PN or both routes, early EN nutrition to support the gut-associated lymphoid tissue (GALT), mucosa-associated lymphoid tissue (MALT) and modulate cytokines, and ultimately optimal feeding. Although this approach will not necessarily modulate the immune response, it will at least support the immune system. Various other nutrients have been also shown to play a role in the immune system, including vitamins, minerals and trace elements. Thus, meeting basic requirements is a prerequisite for a functional immune system.⁷

Despite increased awareness and efforts, very few ICUs worldwide successfully execute the basics in terms of nutrition support. In a study which included 259 ICUs worldwide (n = 5 497 ventilated patients), it was shown that when compared with medical patients, surgical patients were less likely to receive EN (54.6% vs. 77.8%) and more likely to receive PN (13.9% vs. 4.4%) (p-value < 0.0001).

In patients in whom EN was initiated, on average, surgical patients started EN 21 hours later (57.8 vs. 36.8 hours, p-value < 0.0001) and received less of their prescribed energy from EN (33.4% vs. 49.6%, p-value < 0.0001) or from all nutrition sources (45.8% vs. 56.1%, p-value < 0.0001) than medical patients.⁴⁴ Therefore, basic principles need to be established and cemented to be able to successfully add immunonutrition and pharmaconutrition concepts when supporting such patients.

The source of protein that is used in an EN formula may also impact on immune function. Whey protein is high in branched chain amino acids, particularly leucine, which is known to play various roles, ranging from being a substrate for protein synthesis, to a modulator of insulin signaling. In addition, whey protein is high in cysteine which is the limiting amino acid for glutathione synthesis and is necessary for antioxidant defenses. Whey, a "fast" protein, preferentially stimulates protein synthesis which potentially makes it an excellent source of amino acids in critically ill patients.⁴⁵ Gastric emptying of whey-based formula is faster than similar casein-based formula⁴⁶ and may be beneficial in critically patients with motility disorders. A comparison of equal volumes of whey-based formula that had different energy densities and osmolalities indicated that they emptied at a comparable rate. This can improve nutrient delivery to patients with volume intolerance.⁴⁶ Preclinical studies reported that whey protein also facilitated protein synthesis, decreased inflammation, had antioxidant effects and reduced gut-

Table III: Glutamine for specific patient populations: clinical practice recommendations^{53,56,69}

Patient population	CCCPG	ASPEN/SCCM	ESPEN
General	No recommendation	Possible benefit (B) [*]	No recommendation
Elective and major surgery	No recommendation	No recommendation	No recommendation
Trauma	Possible benefit	Possible benefit (B) [*]	Benefit (A) ^{**}
Sepsis	No recommendation	No recommendation	No recommendation
Burns	Possible benefit	Possible benefit (B) [*]	Benefit (A) ^{**}
ALI/ARDS	No recommendation	No recommendation	No recommendation

ALI: acute lung injury, ARDS: acute respiratory distress syndrome, ASPEN: American Society for Parenteral and Enteral Nutrition, CCCPG: Canadian Critical Care Practice Guidelines, ESPEN: European Society for Clinical Nutrition and Metabolism, SCCM: Society of Critical Care Medicine

Grading (A, B) based on level of evidence: American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine⁵³ and European Society for Clinical Nutrition and Metabolism⁶⁹ grading

^{*}ASPEN: Grade B recommendation: supported by one level I [large, randomised trials with clear-cut results, low risk of false-positive (alpha) error or false-negative (beta) error] investigation

^{**}ESPEN: Grade A recommendation: (a) meta-analysis of randomised controlled trials, or (b) at least one randomised controlled trial

reperfusion injury.⁴⁷ A double-blind randomised controlled trial (RCT) compared early EN with a formula containing whey with standard EN (containing casein as the protein source) in ischaemic stroke patients, and reported that whey may decrease inflammation and increase antioxidant defenses.⁴⁸

Small peptide EN formulation may also be beneficial as a number of studies have reported that at a physiological level these formulations are easier to absorb over the gut lumen, result in less feeding intolerance and increase protein synthesis at the visceral level through increased nitrogen retention. Preclinical studies have shown a greater increase in glucagon which may have a positive trophic effect on the intestinal mucosa. Animal studies have also shown that peptide diets have higher levels of nitrogen retention, higher rates of weight gain, higher rates of tissue repair and a positive trophic effect on the small bowel mucosa, compared to free amino acid formulations.⁴⁷

However, more human data is necessary to substantiate the claims for both whey protein and small peptides based protein sources and to strengthen the evidence-base in clinical practice. It should nevertheless be noted that these substrates are currently much cheaper than pharmaconutrients, are readily available in the South African market, and should thus at least be considered in the treatment of critically ill patients in the local context.

Glutamine (cell-protective nutrients)

Glutamine is now considered by many investigators to be “conditionally essential” in critical illness.^{49,50} Deficiency can develop within 24 hours in this group of patients. It is the most abundant free amino acid in the body, but stores are rapidly depleted during injury or critical illness. Deficiency states are described in patients with trauma, sepsis, surgery and burns.^{8,50,51} Glutamine serves as a metabolic substrate for immune cells and enterocytes, supporting barrier and immune function.⁵⁰ It may also serve as a vital cell-signalling molecule in states of illness and injury.⁵² In this regard, glutamine has been shown to regulate the expression of many genes that relate to metabolism, cell repair and defense, signal transduction and activation of intracellular signalling pathways.⁵² Glutamine release could further serve as a “stress signal” to the organism to turn on genes that are vital to cellular protection and immune

regulation.⁵⁰ An example of the latter is glutamine’s potential key role in enhancing the synthesis of heat-shock proteins (HSPs), which are essential to cellular recovery following injury, and for protection against organ failure.^{2,50}

On the balance of the available evidence, glutamine supplementation in critically ill patients is currently recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN)/Society of Critical Care Medicine (SCCM),⁵³ European Society for Parenteral and Enteral Nutrition (ESPEN)⁵⁴ and the 2009 Canadian Practice Guidelines.^{55,56} A 2009 systematic review demonstrated that glutamine supplementation of total PN (TPN) reduced mortality by 29%. All EN and PN studies showed a 25% reduction in mortality.⁵⁶ In line with these findings, a recent Scandinavian study (n = 413) also found a reduction in mortality with intravenous (IV) glutamine.⁵⁷ However, the Scottish Intensive care Glutamine or seleNium Evaluative Trial (SIGNET) in 10 centres in Scotland (n = 5 02) showed no significant effect of glutamine supplementation of TPN on mortality or infectious complications.⁵⁸ The lack of effect of glutamine in the Scottish trial has been attributed to various factors, including the low dose of glutamine used (20 g/day), the short period of administration (four to five days) and late implementation. Trials with > 0.3g/kg have been shown to have better outcomes. The best results were obtained using 0.5 g/kg of IV glutamine.⁵⁹ The available literature suggests that glutamine needs to be administered early since deficiency can develop within 24 hours. The no-effect of IV glutamine on plasma glutathione⁶⁰ or the innate immune system⁶¹ may indicate that glutamine exerts its beneficial effects via mechanisms other than the immune system, such as HSP induction.

EN supplementation of glutamine has a significant beneficial effect on immunity, as shown in burn patients. In these patients, 26 g enterally supplied glutamine resulted in three times less frequent positive blood cultures.⁶² Fourteen days of glutamine supplementation via the EN route (0.5 g/kg/day) significantly increased serum glutamine levels,^{63,64} as well as plasma pre-albumin and transferrin levels.⁶⁴ In thermal injury, a setting that is associated with suppressed cellular immunity, glutamine supplementation significantly improved various measures of cellular immunity, but had no effect on humoral immunity.⁶³ Hospital stay in such patients was significantly reduced in both studies and wound healing was faster.^{63,64} EN glutamine supplementation in other groups of critically ill patients has been less

beneficial, possibly due to the low dose administered and ingested for a clinical effect to be documented, as shown by Soquel et al.⁶⁵

Considering the strength of the evidence base, the administration of glutamine in defined critical care settings (Table III) should be standard practice in the South African context. Large, multi-centre RCTs are currently underway which will provide further clarity and better define glutamine requirements in critically ill patients.⁶⁶⁻⁶⁸

Arginine (immune-modulating nutrients)

As the evidence base expanded, the hype surrounding arginine as a pharmacconutrient included initial optimism, followed by severe caution, to having a definite and appropriate place in the critical care setting. Arginine can enhance immune parameters, e.g. lymphocyte function, after trauma and surgery, and has been shown to improve wound healing.^{70,71} On the other hand, very little benefit and perhaps harm has been observed in septic patients.⁷²⁻⁷⁴ Arginine may enhance the systemic inflammatory response in septic patients. This results in increased mortality.^{72,75} This is a clear example that the “one nutrition therapy regimen will fit all” approach is not appropriate in the critical care setting.

Arginine plasma levels have been shown to be significantly reduced in surgical and trauma patients, but not in septic patients.⁷⁶ Arginase levels are only modestly increased in septic patients, as compared to the significant increase that is seen in trauma patients.^{8,77} During sepsis, there is a classic macrophage response and a maximum

increase in inducible nitric oxide synthase (iNOS), interleukin (IL)-1 and T-helper cell 1 cytokine proliferation [interferon- γ , IL-1, tumour necrosis factor (TNF)]. In trauma, the alternative macrophage response results in significant arginase increase, IL-10 and T-helper 2 cell cytokine proliferation (IL-4 and IL-13).^{70,78} Thus, clinical benefit has not been demonstrated for the use of arginine in septic patients.

Two recent systematic reviews in surgical patients demonstrated a reduction in infectious complications, length of stay and postoperative infections with arginine supplementation.^{79,80} These two reviews reported no harm in surgical patients. The Drover et al systematic review on perioperative supplementation of arginine (it included 35 trials) supports a significant treatment effect of arginine therapy following elective surgery.⁷⁹ Arginine-supplemented diets were associated with considerably reduced overall infectious complications when compared with standard formula in surgical patients [28 trials included; relative risk (RR) = 0.59, 95% confidence interval (CI), 0.50-0.70, p-value < 0.00001, I^2 = 26%]. Overall hospital length of stay, aggregated across 29 studies, was reduced in surgical patients receiving arginine-supplemented diets when compared with patients receiving standard formula [weighted mean difference (WMD) = -2.38; 95% CI, -3.39 to -1.36; p-value < 0.00001; I^2 = 87%]. Arginine-supplemented diets did not have a significant effect on mortality.

Considering the evidence-base, arginine supplementation should be standard practice where safe and appropriate (for surgery and trauma) in the South African context.

Omega-3 fatty acids (anti-inflammatory nutrients)

Fish oils decrease the production of pro-inflammatory mediators.⁸¹ The anti-inflammatory properties occur through three principle mechanisms: displacement of arachidonic acid in cell membranes, prostaglandin E3 and LTB4 production, decreased nuclear factor-kappa B (NF- κ B) and AP-1 activation.⁸¹ Omega-3 FAs (ω -3 FAs) have also been shown to decrease the production of nitric oxide (NO) via downregulation of iNOS protein expression.^{81,82} Although the inclusion of ω -3 FAs in nutrition therapy makes theoretical sense and the potential mechanisms are fairly clear, the data for the implementation of such nutrient therapy in critically ill patients are much less concrete.

Of particular interest in the critically ill patient is the effect of ω -3 FAs on the adult respiratory distress syndrome (ARDS). An EN product that contains fish oils, borage oil and antioxidants is recommended by the Canadian Practice Guidelines 2009 for the treatment of ARDS.^{55,56} Three studies with the said product as active intervention in patients with diagnosed ARDS have shown a reduction in pulmonary neutrophils, an improvement in oxygenation, decreased severity of ARDS, decreased ventilator days, decreased length of stay in ICU and length of stay in hospital and decreased lung cytokine and protein secretion.⁸³⁻⁸⁵ Despite these positive results, some concerns were raised regarding the studies. These included the fact that the control groups received high-fat formula, some studies did not have an intention-to-treat design and it was difficult to conclude whether it was the fish oil or other constituents in the formula that exerted the reported positive outcomes.

Three recent studies complicated the interpretation of findings even further. A multi-centre study in Brazil (INTERSEPT study, 14 ICUs, $n = 200$) used the same product (as described above) for seven days in patients in the early stages of sepsis and with no organ failure. Although there were significant effects on some secondary outcomes such as length of stay in hospital and length of stay in ICU (LICU), there was no effect on mortality.⁸⁶ It is important to note that the fish oil-containing product was used for prevention, and not as treatment, and that once more, the other nutrients may also have exerted beneficial effects. No benefit of the same product was found in a RCT in 11 Spanish ICUs ($n = 89$) in patients with a diagnosis of sepsis on admission.⁸⁷ The Early versus delayed Enteral Feeding (EDEN)-OMEGA study investigated whether ω -3 FAs improved ventilator free days. In this multi-centre RCT (44 centres, $n = 272$) patients received EN supplementation (twice daily) of ω -3 FAs, γ -linolenic acid and antioxidants compared with an isocaloric control, within 48 hours of developing acute lung injury (ALI). It is important to note that this was administered as a bolus, whereas in the other studies the patients received continuous EN nutrition. The supplementation did not improve the primary endpoint of ventilator-free days or other clinical outcomes in ALI, and the practice may have been harmful. Sixty-day-hospital mortality was 26.6% in the ω -3 supplemented group vs. 16.3% in the control group (p -value = 0.054). Adjusted 60-day mortality was 25.1% and 17.6% in the ω -3 and control groups, respectively (p -value = 0.11). The study was terminated early because of futility.⁸⁸ In a phase II RCT in five North American centres ($n = 89$) the addition of fish oil did

not reduce the biomarkers of pulmonary or systemic inflammation in ALI. In this case, the fish oil was supplemented as a bolus as a single nutrient [9.75 g eicosapentaenoic acid (EPA) and 6.75 g docosahexanoic acid (DHA) daily]. The researchers concluded that the results did not support the conduct of a larger clinical trial in this population with this particular agent.⁸⁹

Heterogeneity of studies investigating the supplementation of EN fish oils complicates decision-making on the part of the nutrition therapy practitioner and makes the drawing of firm conclusions difficult. Although many of these studies have robust study designs, in many cases the study design, method of administration (bolus vs. continuous) and disease (established ARDS vs. ALI vs. sepsis) differed and single or mixed nutrients were investigated. However, it seems that bolus administration of fish oils is harmful in this group of critically ill patients and should not be practised.

Guidelines with regard to the use of PN lipids differ between the North American and European organisations. ESPEN recommends the use of lipid emulsions as part of TPN,⁵⁴ while ASPEN and the Canadian guidelines recommend TPN without soy-based lipids.^{53,55,56} The difference in these guidelines can probably be attributed to the regional availability of lipid sources (ω -3 containing lipid sources is not yet available in North America). The Canadian Practice Guidelines 2009 further state that there is insufficient evidence to draw a conclusion as to the type of lipid to be used in critically ill patients on TPN.

Four small recent studies using ω -3 FA containing PN had different interventions (ω -3 FAs as part of PN or supplemented PN ω -3 FAs). Although there was some indication of a reduction in mortality, no effect on infectious complications was documented.⁹⁰⁻⁹³ A significant reduction in procalcitonin levels was found in the study by Khor et al, suggesting that fish oil attenuates the inflammatory process.⁹² A small study ($n = 16$) compared a standard PN lipid emulsion to a lipid emulsion containing ω -3 FAs in patients with ARDS. The fish oil-supplemented PN resulted in a beneficial alteration in lipid mediator profiles,⁹⁴ the clinical significance of which still remains to be confirmed. A third-generation lipid emulsion containing soybean, medium-chain triglyceride, olive and fish oils (SMOFlipid) resulted in favorable FA profiles (a desirable reduction in the ω -6/ ω -3-FA ratio)⁹⁵ and retained hepatocellular integrity.⁹⁶ Small trials showed that fish oil- (ω -3) supplemented PN had anti-inflammatory and hepatoprotective effects in hyperinflammatory disease such as sepsis,⁹⁷ a beneficial effect on PN-associated liver disease,⁹⁸ reduced the Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score II, as well as procalcitonin in sepsis.⁹² However, clearly larger trials are required to confirm the findings or form the basis for recommendations in practice. A systematic review (six trials were included) concluded that PN lipid emulsions that contain fish oil had no mortality advantage, but significantly reduced infectious complications (p -value = 0.03). There was a trend towards shortening hospital length of stay by 3.06 days (the exclusion of a heterogeneous study showed a significant reduction), and significantly reduced ICU length of stay by 2.07 days.⁹⁹ The authors of the systematic review further concluded

that although insufficient data precluded a conclusive economic advantage, the possibility of cost reduction existed,⁹⁹ a conclusion that remains to be confirmed in clinical practice.

Considering the current evolving evidence base and available guidelines, ω -3 FAs should be considered to form part of PN lipid emulsions, at least for their effect on lipid profiles and PN-associated liver disease as discussed above, but strengthening of the evidence base is needed to reach firmer conclusions. EN omega-3 FA supplementation [fish-oil derived ω -3 FAs (EPA and DHA), borage oil and antioxidants] administered in the context of an immune-enhancing diet is currently recommended specifically for patients presenting with ALI and ARDS by ASPEN/SCCM (Grade A recommendation),⁵³ ESPEN (Grade B recommendation)⁶⁹ and the 2009 Canadian Practice Guidelines.⁵⁶

Micronutrients

Critical illness is associated with increased production of reactive oxygen species and oxidative stress, and low levels of most micronutrients, with resultant diminished endogenous antioxidant defenses.¹⁰⁰ The inherent antioxidant potential is overwhelmed in critically ill patients, resulting in cell damage, the SIRS response and increased morbidity and mortality in critically ill patients.⁸¹ Micronutrient supplementation is thought to be beneficial to critically ill patients by ameliorating oxidative stress and by improving clinical outcomes.

Research on micronutrient supplementation in the critically ill has focused mainly on five micronutrients: selenium, zinc, copper, vitamins C and E. Individual studies have investigated the vitamin B group.¹⁰⁰ The aims of supplementation can be described as provision of basic nutritional support (bearing in mind the increased requirements due to hypermetabolism and wound healing), the prevention and correction of deficiencies and modulation of the APR and immune responses through reinforcement of endogenous antioxidant defenses.

Trials in patients with thermal injury have focused mainly on selenium, zinc and copper, after low blood concentration of these micronutrients had repeatedly been shown in this patient population, as well as the known uniqueness of this group of patients in terms of the extensive cutaneous losses of these micronutrients.¹⁰¹⁻¹⁰⁴ Berger et al consistently demonstrated in a series of well controlled trials that trace element supplementation reduces infectious complications in burn patients. Supplementation (IV) of copper 2.5-3.1 mg/day, selenium 315-380 μ g/day, and zinc 26.2-31.4 mg/day for eight to 21 days resulted in a significant reduction in the number of infections. This related to a significant reduction of nosocomial pneumonia (p-value < 0.001) and of ventilator-associated pneumonia (p-value = 0.023).¹⁰⁵ This is in agreement with the authors' previous data which showed that trace element supplementation resulted in a significant reduction in bronchopneumonia infections and consequent shorter hospital length of stay.¹⁰⁶ Patients receiving 59 μ mol Cu, 4.8 μ mol

Table IV: Supplemented antioxidant nutrients, vitamins and trace elements^{53,54,56}

CCCPG	ASPEN/SCCM	ESPEN
Based on three level I, and 13 level II studies, the use of supplemental combined vitamins and trace elements should be considered in critically ill patients.	Combination of antioxidant vitamins and trace minerals, specifically including selenium, should be provided to all critically ill patients receiving specialised nutrition therapy.	All PN prescriptions should include a daily dose of multivitamins and trace elements. (Grade C recommendation)
Insufficient data to make a recommendation regarding IV/PN zinc supplementation in critically ill patients.	(Grade B recommendation)	RDA vitamins, minerals and trace elements.
Insufficient data to make a recommendation regarding IV/PN selenium supplementation alone, or in combination with other antioxidants, in critically ill patients.		Thiamine 100-300 mg/day for the first three days (deficiency states). (Grade B recommendation)

ASPEN: American Society for Parenteral and Enteral Nutrition, CCCPG: Canadian Critical Care Practice Guidelines, ESPEN: European Society for Clinical Nutrition and Metabolism, IV: intravenous, PN: parenteral nutrition, RDA: recommended dietary allowance, SCCM: Society of Critical Care Medicine

Se, and 574 µmol Zn per day (IV) demonstrated a significantly improved clinical course, including better graft take and fewer infectious complications. Supplementation was again associated with a significant reduction in infectious complications, especially bronchopneumonia.¹⁰⁷

A growing body of evidence is emerging that demonstrates the potential benefits of micronutrient and specifically antioxidant

micronutrient supplementation in critically ill patients. A recent systematic review included 15 RCTs involving 1 714 participants (primary objectives) and 18 RCTs involving 1 849 participants (secondary objectives).¹⁰⁰ This updated review concluded and supported previous findings¹⁰⁸ that micronutrient supplementation in the critically ill may be associated with a decrease in overall mortality [RR 0.78, 95% CI 0.67-0.90, I² = 0%, p-value = 0.0009]

and more specifically in 28-day mortality (RR 0.75, 95% CI 0.63-0.88, I² = 0%, p-value = 0.0006). Micronutrient supplementation in this updated review was not associated with a decrease in infectious complications, similar to the findings of Heyland et al.¹⁰⁸ This finding could possibly indicate that the observed mortality effect was mediated by other mechanisms, e.g. increased organ function. The updated review was the first to report on LICU and length of stay and concluded that these outcomes were unaffected by micronutrient supplementation. A sensitivity analysis of combined micronutrient supplementation indicated a significant reduction in mortality (RR 0.69, 95% CI 0.54-0.90, I² = 2%, p-value = 0.006). Although in contrast to the findings of the previous systematic review¹⁰⁸ (i.e. single nutrients were associated with a significant decrease in mortality, combined micronutrients were not), this new finding of the updated review supports prior hypotheses and the rationale underlying the use of combinations of micronutrients, namely the biochemical properties of the endogenous antioxidant network and micronutrients' interdependence for regeneration of antioxidant defenses.¹⁰⁹ This updated systematic review did not find clear evidence that PN was superior to EN administration in terms of clinical outcomes. The authors recommended that future studies could investigate the use of PN and EN administration of micronutrients to maximise the opportunity of demonstrating a treatment effect, if

Table V: Approximate ICU costs per day*

A. Standard high care postoperative costs (12 hours)			
High care bed (R7 000.00/day)			3 500.00
Enoxaparin	40 mg SC	X 1	76.80
Morphine	15 g	5 amps	23.96
Metoclopramide	10 mg	1 amp	2.50
Paracetamol	1 g	2 amps	130.00
Cefazolin	1 g	2 amps	25.60
TOTAL (High care bed and medication)			R3 758.86
B. ICU costs and medication (treatment of complication)			
ICU bed only, excludes ventilation			10 000.00
Phenylephrine	(10 mg/ml) 1 ml	X 30	1 807.00
Enoxaparin	40 mg SC	X 1	76.80
Esomeprazole	40 mg IV	X 1	186.57
Caspofungin	50 mg IV	X 1	2 401.22
Imipenem-cilastatin	500 mg IV	X 8	1 982.05
Linezolid	600 mg IV	X 2	997.92
Amiodarone	200 mg NGT	X 3	51.63
Morphine	15 g	10 amps	47.93
Metoclopramide	10 mg	3 amps	7.50
Remifentanyl	5 mg	X 5	2 508.00
TOTAL (ICU bed and medication)			R20 066.62
C. Enteral nutrition + IV glutamine			
Semielemental feed	2 litres	X 1	511.64
IV glutamine	200 ml	X 1	738.81
TOTAL (Enteral nutrition + IV glutamine)			R1 250.45

* These are approximate costs in one setting (Gauteng private hospital; 2012) used as an example only (R20 066.62 x 3 days = R60 199.86)

one really exists. The secondary outcomes of this review confirmed that timing, duration and dosing are key factors to ensure optimal clinical benefit.¹⁰⁰

The latest systematic review, including 21 trials, regarding antioxidant micronutrients in the critically ill confirm the mortality, length of stay and LICU findings by Visser et al,¹⁰⁰ and additionally report a significant reduction in duration of mechanical ventilation (WMD in days = -0.67, 95% CI -1.22 to -0.13, p-value = 0.02) with antioxidant supplementation.¹¹⁰ Furthermore, antioxidants were associated with a significant reduction in overall mortality in patients with higher risk of death (> 10% mortality in control group) (RR 0.79, 95% CI 0.68-0.92, p-value = 0.003), whereas no significant effect was observed for trials of patients with a lower mortality in the control group.¹¹⁰

The Cochrane Database Systematic Review by Avenell et al (updated 2007) investigating the effects of single-nutrient supplementation, specifically selenium supplementation, including the selenium-containing compound ebselen, concluded: "There is limited evidence to recommend supplementation of critically ill patients with selenium or ebselen".¹¹¹ They found no significant differences for overall mortality and infectious complications and no clear evidence of the benefits of such supplementation for ventilator days, LICU, length of stay or quality of life. However, they did find that the evidence was more suggestive of a benefit on mortality in the first month for

general ICU patients when compared with those with severe pancreatitis (p-value = 0.02). The more recent SIGNET trial⁵⁸ found that 500 µg selenium daily as part of PN in critically ill patients significantly decreased new infections in a subset of patients who received the supplement for ≥ 5 days, but it did not affect mortality. When the SIGNET trial data⁵⁸ for selenium supplementation were entered into the current Cochrane systematic review,¹¹¹ the random effects risk ratio for mortality changed from 0.75 (0.59-0.96, I² = 0%) to 0.86 (0.74-1, I² = 0%), and the risk ratio for new infections changed from 1.22 (0.67-2.23, I² = 0%) to 0.93 (0.79-1.09, I² = 0%).¹¹¹

In one older study, high-dose vitamin C administration during resuscitation (66 mg/kg/hour) was shown to attenuate lipid peroxidation and reduce resuscitation fluid requirements, as well as post-burn oedema. The length of mechanical ventilation was also significantly reduced and improved early respiratory function was observed.¹¹²

Other micronutrients that have received attention in recent years include vitamin D and vitamin B₁₂. Vitamin D deficiency states have been described in patients with severe sepsis and other critically ill populations^{113,114} with low levels of vitamin D-binding hormone being reported.¹¹⁵ Studies of vitamin D replacement studies in the critically ill have mainly considered short-term outcomes and have generally led to increases in vitamin D levels.^{116,117} Whether the latter translates into meaningful clinical outcomes remain to be seen. It is unclear whether low levels of vitamin D contribute to critical

illness or are just a marker of illness severity. The outcomes of large clinical trials that investigated vitamin D supplementation are currently awaited. It is proposed that future studies should examine vitamin D as well as important metabolites of vitamin D, their binding proteins and parathyroid axis. The potential benefit of IV vitamin B₁₂ supplementation as a pharmaconutrient in critically ill patients has been described,¹¹⁸ but clinical intervention trials studying vitamin B₁₂ as a pharmaconutrient strategy in the critical care setting are awaited. One recent observational study indicated an increased mortality rate in patients with Vitamin B₁₂ levels over 900 pg/ml (p-value < 0.0002).¹¹⁹ Nutrition therapy practitioners should always bear in mind that “much more is not necessarily better” and that some micronutrients have or may have a narrow therapeutic window when high-dose supplementation is being considered. Furthermore, in this group of patients the potential exists for the creation of a pro-oxidant microenvironment with deleterious patient outcomes. This should always be borne in mind.

Establishing exact micronutrient requirements in the critically ill has proven to be notoriously difficult. Various general sets of guidelines are available (Table IV). Despite these guidelines, little consensus exists as to what to use when, and many questions remain regarding required doses, routes and timing of replacements or supplementation.

Providing micronutrients to include the full range of trace elements and vitamins is an integral part of nutritional support. In practical terms in the South African context, it is clear that micronutrients should be provided at least at the current available recommended doses to prevent overt clinical deficiencies. For other claims, indications and higher doses, the literature consistently indicates that the ratio of risk (adverse effects) to benefit (mortality) may be favourable, and if such higher doses are used in practice, it should be within the dose range that the current experience covers, and for the clinical settings studied only.

Finally, the bigger picture should always be considered, bearing in mind the complexity of the acute phase response and the vast heterogeneity of the critical care population. Optimal nutrition therapy includes all relevant components, including attention to energy, protein, carbohydrates, lipids, fluids, fibre and the discussed immunonutrients and pharmaconutrients, in the right mix, at the right time, to the right patients, to ensure optimal clinical benefit and outcome.

Cost considerations

Considering the evidence base, sets of guidelines are available for the implementation of immunonutrition and pharmaconutrition in appropriate circumstances. But often, and specifically also in the South African setting, the final verdict regarding implementation is determined by cost. The available evidence on the benefits of and cost containment by nutrition therapy should not only be seen within the context of the limitations of the studies being reported and the regional variation of costs, but also within the context of the consistency of the reported benefits.

Basic nutrition therapy costs have been reported to be US\$20-40 per day (EN nutrition), while PN nutrition costs US\$55-200 per day. In addition, antibiotic therapy has been reported to amount to approximately US\$65-US\$1 345/day.¹²⁰

Already in 1997, it was shown that an immune-enhancing formula containing arginine not only significantly reduced late postoperative events in patients undergoing gastric surgery, but also reduced the costs of treating complications (83 563 Deutsche Mark in the experimental diet group vs. 122 430 Deutsche Mark in the control group, resulting in a cost-reduction of 38 867 Deutsche Mark).¹²¹ In a more recent study, the projected investment and cost savings using arginine-containing formula for 1 000 well-nourished surgery patients, with a 20% base infection rate, was US\$45 000 and US\$1 442 000 respectively. The projected investment and cost savings using arginine-containing formula for 200 malnourished surgical patients, with a 20% base infection rate, was US\$44 000 and US\$272 400 respectively. Finally, the projected investment and cost savings using arginine-containing formula for 200 trauma patients, with a 60% base infection rate, was US\$35 000 and US\$759 400 respectively.¹²²

Recently, a simulation study, incorporating outcome rates from 200 Italian ICUs for over 60 000 patients, was conducted to determine whether PN alanyl-glutamine supplementation (compared to standard TPN) in critically ill patients had the potential to partially or totally offset its own costs by reducing the consumption of other medical resources. The glutamine-supplemented TPN resulted in a reduced mortality rate ($26.4 \pm 1.6\%$ vs. $34.5 \pm 2.1\%$), reduced infection rate (13.8 ± 2.9 vs. $18.8 \pm 3.9\%$) and reduced hospital length of stay (24.9 ± 0.3 days vs. 26.0 ± 0.3 days). More importantly in this context, it resulted in a lower total cost per patient (€23 409 \pm €3 345 vs. €24 161 \pm €3 523). The treatment cost was completely offset by savings on ICU and antibiotic costs.¹²³

A comparison of conventional vs. preoperative immunonutrition in gastrointestinal cancer patients resulted in a total nutrition cost of €3 407 in the conventional group and €14 729 in the supplemented or preoperative group. In patients without complications, the in-hospital routine care was similar, but the mean cost of complication per patient in the conventional group was €6 178, compared to €4 639 in the preoperative group (p-value = 0.05). The total cost of patients with complications was €535 236 in the conventional group and €334 148 in the preoperative group. Cost-effectiveness (analysis performed by dividing per-patient costs of clinical nutrition and costs of treating postoperative complications with the percentage of complication-free patients; thus, the cost of achieving one complication-free patient per group) was €6 245 in the conventional group and €2 985 in the supplemented group.¹²⁴

To the authors' knowledge, there are no comparative cost data in South Africa. A simple approximate cost calculation rather than an economic analysis, (only including ICU bed and medication but excluding the cost of ventilator support, IV fluids and medical and allied professional fees) was undertaken (as an example) to determine the cost of one day for a high care (no complications), a critically ill patient in the ICU (with complications) as well as the

approximate cost of one day of enteral feeding with a semielemental formula plus 200 ml IV glutamine (Gauteng private hospital setting protocols and costs) (Table V). The costs were calculated for an elderly, well-nourished patient, who had a knee replacement and developed complications (sepsis and atrial fibrillation; treated with second- and third- generation antibiotics and an antifungal agent), who needed ventilation. Standard costs, if the patient did not develop complications for 12 hours in a high care unit (standard protocol) would have been R3 758.86 (Table V, Section A). In this example and in comparative terms, the standard (semielemental) feed as well as specialised (glutamine) nutrition therapy, alone or in combination (Table V, Section C), can be seen as relatively “minor” compared to the costs, in the same patient, of medication necessitated by the complication described in the example (Table V, Section B). If the assumption was also to be made that preventive nutrition support/therapy would have significantly reduced the risk of the complication that was encountered for a total costs of R5 009.31 (Table V, Sections A and C), the approach would have still achieved significant costs containment in comparison to the costs of treating the specific complications in the example used.

Bearing in mind that some studies have indicated that LICU can be shortened by two to three days with IV glutamine, when needed, the authors compared the cost of seven days of IV glutamine ($R\ 738.81 \times 7 = R\ 5\ 171.67$) vs. three extra ICU days ($R\ 20\ 066.62 \times 3 = R\ 60\ 199.86$) in order to highlight the cost containment a

pharmaconutrient-based nutrition therapy approach has to offer in the appropriate setting (the authors concede the theoretical nature of the example and the assumptions made therein).

Amid a growing and strengthening evidence base supporting benefit, and clear indications of outcome benefits, as well as potential cost savings, critical care nutrition guidelines have been developed to help busy practitioners decide how to feed their critically ill patients. Despite good adherence to some recommendations, large gaps exist between many current recommendations and actual practice in ICUs, and consequently, nutrition therapy is still suboptimal.¹²⁵ Knowledge-to-action models need to be explored and implemented to optimise nutrition therapy at the bedside.¹²⁶

Conclusion

The value of immunonutrition formula in the management of critically ill and preoperative and postoperative patients is now acknowledged by many nutrition therapy and medical practitioners. Amid the demonstration of clear clinical and cost-containment benefit in defined conditions, South African practitioners should also aim to close the knowledge-to-best-practice gap to optimise nutrition therapy and ultimately, clinical outcome in critically ill patients. It is clear that continued clinical research is necessary for an even better understanding of immunonutrition and pharmaconutrition approaches. Specifically, large, multi-centre, prospective RCTs that evaluate each immune-modulating nutrient individually, as

well as in various combinations, at various doses, and in defined patient populations, would lead to better evidence-based practice guidelines.¹²⁷ A few such trials are already underway. In future, a paradigm shift to pharmaconutrition is gaining momentum, a practice which dissociates the administration of key single nutrients in the form of requirement-based PN or EN nutrition from the delivery of pharmaconutrients in the full effective pharmacological dose, as evaluated in large, well designed trials, in order to achieve therapeutic effects.¹ The current use of clinical pharmacology, molecular biology and clinical research principles in the study of pharmaconutrients should provide further answers on how to administer the right nutrients, in the right doses, at the right time, in critically ill patients.²

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