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Nutrition in ICU

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OVERVIEW OF NUTRITION

Nutritional support in the Intensive care represents a challenge, but it is fortunate its delivery and monitoring can be followed closely.

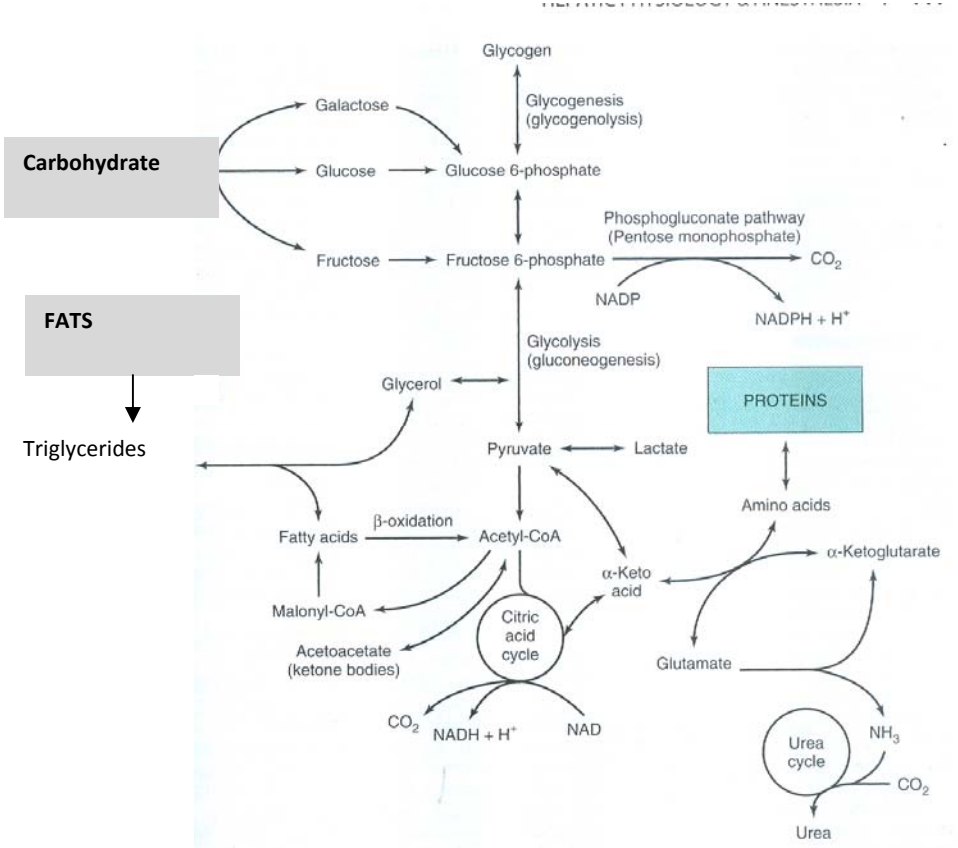
During acute illness patients experience a degree of hyper inflammation, cellular immune dysfunction, oxidative stress and mitochondrial dysfunction. Depending on the severity and duration of these disturbances in metabolism, multi-organ failure and death may occur.

As a result of stress response and inability to maintain normal oral intake, patients can develop nutrient deficiencies and altered immune status is well known. Deficiencies are associated with increased risk of developing infectious complications, organ failure and death. Consequently, artificial nutritional therapy via enteral or parenteral route is considered an integral part of standard patient care.

Energy is normally derived from dietary or endogenous carbohydrates, fats, and protein[1]. Metabolic breakdown of these substrates yields the ATP required for normal cellular function. Dietary fats and carbohydrates normally supply most of the body energy requirements.

Dietary proteins provide amino acids for protein synthesis; however when their supply exceeds both essential and non-essential amino acid requirement s, they also function as energy substrates. Excess carbohydrates are stored as glycogen in the liver and skeletal muscle. When glycogen stores are saturated (200-400g in adults), excess carbohydrate is converted to fatty acids stored as triglycerides primarily in fat cells .

Nutritional support in the critically ill population has 3 main objectives: to preserve lean body mass, to maintain immune function and to avert metabolic complications. Nutritional modulation of the stress response to critical illness includes early enteral nutrition, appropriate macro and micro nutrient delivery.



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METABOLIC ALTERATION DURING STARVATION

Protein content of essential tissues is spared. As blood glucose concentration begins to fall during fasting, insulin secretion decreases while glucagon increases. Hepatic and to a lesser extent, renal glycogenolysis and gluconeogenesis re-enhanced. Because glycogen supplies are depleted within 24hrs, gluconeogenesis becomes increasingly important. The liver uses chiefly deaminated amino acids (alanine and glutamine) as precursors for glucose synthesis.

Only tissue, renal medullary cells and erythrocytes continue to utilise glucose, in effect sparing tissue proteins. Lipolysis in adipose tissue is enhanced, so that fats become the principal energy source. Glycerol from

the triglycerides enters the glycolytic pathway while fatty acids are broken down to Acetyl-CoA. Excess Acetyl-CoA results in the formation of ketone bodies (ketosis). Some fatty acids can contribute to gluconeogenesis. If starvation is prolonged, the brain, kidneys and muscle also begin to utilize ketone bodies efficiently[1].

METABOLIC ALTERATION DURING CRITICAL ILLNESS

During critical illness there is a marked activation of the hypothalamic-pituitary adrenal axis, with adrenergic stimulation and cytokine activation. The pro-inflammatory is characterised by marked proteolysis and loss of lean body tissue. There is evidence that skeletal muscles cannot utilise blood-borne substrates for oxidative phosphorylation during critical illness, and therefore cannabilize their protein stores for branched amino acids. Ubiquinin breaks down intra-cellular protein and during sepsis there is up regulation of mRNA coding for ubiquitin[6].

Perioperative critical illness are usually characterised by tissue injury, a neuroendoctrine stress response and starvation. The response to injury involves increases in the secretion of catecholamine, cortisol, glucagon, thyroxin, angiotensin, aldosterone, and growth hormone, ACTH, ADH and TSH. Insulin secretion is at least initially decreased but may subsequently rise due to increasing levels of growth hormone.

Catecholamines, glucagon, thyroxin, and growth hormone promote glycogenolysis, while glucagon and cortisol induce gluconeogenesis[1]. Hyperglycaemia is characteristic and reflects increased hepatic production as well as decreased utilisation by peripheral tissues. Decreased tolerance to glucose loads occurs as a result of decreased insulin secretion and peripheral resistant to its actions. The effects are due to increased catecholamine secretion which enhances lipolysis. Both protein synthesis and breakdown are increased, but the latter exceeds the former, so there is a net loss of tissue protein. During sepsis, muscle utilisation of fat and carbohydrate is impaired resulting in increased protein breakdown. Cells appear to rely on branched chain amino acids. Circulating levels of glutamine are decreased .Moreover, rapidly proliferating cells, such as those of the immune system and the GI utilise amino acid as an energy source[1].

Glucose administration during acute illness fails to suppress protein breakdown. An adequate intake of calories and proteins can decrease but not prevent protein catabolism in a stressed patient

Table 1. ***(Reference 6.)***

	STARVATION	CRITICAL ILLNESS
Mediator activation	Low	High
Metabolic rate	Decreased	Increased
Fuel	Glucose/fat	Mixed
Cetabolism	Decreased	Increased
Ketogenesis	Increased	Slightly increased
Ureagenesis	Unchanged	Increased
Gluconeogenesis	Increased	Markedly increased
Catecholamines	Unchanged	Increased
Glucagon	Increased	Markedly increased
Insulin	Decreased	Increased
Cortisol	Unchanged	Increased
Growth hormone	Increased	Increased
Visceral proteins	Normal	Decreased
Cytokines	Variable	Increased
Immune function	Normal	Impaired

NORMAL ENERGY REQUIREMENTS

Total energy requirements vary widely and depend on the Basal metabolic rate, specific dynamic action (energy required for digestion of meals) , and a person's activity level. BMR is energy expenditure measured after the last meal, and in a state of thermal neutrality. Clinically, basal energy expenditure in kilocalories can be estimated by Harris-Benedict equation, using weight in kilograms, height in centimetres and age in years:

Males: BEE = 66 + {13.7 X weight (kg)} + {5 x height (cm)} – (6.8 x age} 1
Where BEE is basal energy expenditure in kilocalories per day, H is height in centimetres. W is weight in kilograms and A is age in yrs

Females: BEE = 655 + {9.6 X weight (kg)} + {1.8 x height (cm)} – (4.7 x age) 1
Where BEE is basal energy energy in kilocalories per day, H is height in centimetres, W is weight in kilograms, and A is age in years.

Adjusted body weight: Adjusted body weight = [(actual weight – ideal weight) * 0.25] + ideal weight.

A stress multiplication factor is applied ranging from 1.2 to 1.6 to determine the actual energy expenditure, as the BEE from the equation is determined in the fasted resting non-stressed state.

The above equations are based on population based analysis or by metabolic gas analysis.

BEE is increased by temperature, (13% per degrees Celsius) and degree of stress.
Indirect calometry measures inspired and expired oxygen, carbon dioxide and nitrogen concentrations as well as the minute ventilation and using the Weir formula calculating the resting energy expenditure.

REE = 3.9 X VO2 + 1.1 X VCO2 – 2.8 x UUN
Alternate and easier way is to remember that most patients in ICU will require between 25-30 kcal/kg/day in males and 25-29 kcal/kg per day in females of non-protein per day[9]. Patients with extensive burns and severe sepsis, caloric requirements may be as high as 30-35kcal/kg/day.

Protein intake should be between 1.2 and 1.5 g/kg per body weight per day[9]. Guidelines from the European Society of Parenteral and Enteral Nutrition (ESPEN) recommend 20-25kcal/kg/day during acute phase of critical illness and 25-30kcal during the anabolic flow phase. Trace elements and vitamins play an important role in various enzyme catalyzed key reactions[9].

NUTRITIONAL ASSESSMENT

Evaluation of nutritional status is central to nutritional support of critically ill patients. Nutritional assessment allows the identification of those patients who need nutritional interventions and helps in monitoring the efficacy of nutritional support.

History taking to detect weight loss, dietary habits and symptoms of hypoproteinaemia and examining the patient for evidence of loss of skeletal mass or fat stores, oedema or jaundice. Anthropometric measurements, cutaneous hypersensitivity tests and laboratory tests to classify a patient's degree of malnutrition.

However, it is unclear how the nutritional status of the critically ill patient can be precisely assessed as body weight of critically ill can fluctuate erratically due to oedema, thus making anthropometric measurements inaccurate. Biochemical parameter such as pre-albumin, transferin, and retinol binding protein reflect hepatic synthetic activity and can serve as a guide to assessment of nutritional status. Albumin has a long half life and can become depleted after infusion of large volumes of fluid, and this is not an accurate marker during acute illness.

TECHNIQUES USED IN NUTRITION SUPPORT[15]:

a) Enteral

1. Oral nutritional supplements
2. Gastric
   - Nasogastric tubes; allow gastric residuals to be checked, suitable for shorter term enteral feeding (< 6 weeks).
   - Pharyngostomy
   - Oesophastomy
   - gastrostomy tubes; requires that gastric emptying is present and contra-indicated by gastro-oesophageal reflux and absence of gag reflex.
   - jejunostomy tubes ; allows feeds to be delivered in a continuous fashion because small bowel doesn't tolerate bolus feeds.
3. Duodenal
   - Nasoduodenal
   - Extended gastrostomy
4. Jejunal
   - Nasojejunal
   - Percutaneous jejunal
   - Surgical jejunostomy

b) Parenteral: Central venous catheter

- Peripheral venous line
- Peripheral inserted venous catheter

ENTERAL NUTRITION

The GIT is the route of choice for nutritional support when its functional integrity is intact. It is simpler, cheaper, less complicated and associated with fewer complications.

Before initiation of feeding, assessment should include evaluation of weight loss and previous nutrient intake prior to admission, level of disease severity, co-morbid conditions and function of the GIT.

Enteral nutrition supports the functional integrity of the gut by maintaining tight junctions between the intra-epithelial cells, stimulating blood flow and inducing release of trophic endogenous agents.

Structural integrity of villous height is maintained and supporting the mass of secretory IgA-producing immunocytes which compromise the gut associated lymphoid tissue (GALT) and in turn contributes to mucosal associated lymphoid tissue at distant sites such as the lungs, liver and

kidneys. The adverse changes associated with gut permeability from loss of functional integrity are a dynamic phenomenon. The consequences of permeability changes include increased bacterial challenge (engagement of GALT with enteric organisms), risk for systemic infection and greater likelihood of multi-organ dysfunction syndrome.

Specific reasons for providing early EN are to maintain gut integrity, modulate stress and the attenuate disease severity.

The importance of promoting gut integrity with regard to patient outcome is being strengthened by clinical trials comparing critically ill patients fed by EN to those receiving standard therapy**.**

In a recent meta-analysis, in elective GIT Surgery and Surgical critical care, patients who were given early post-operative EN experienced significant reduction in infection (relative risk {RR} = 0.72; 95 % Confidence interval 0.54-0.98; P = .03, hospital length stay (mean 0.84 days); P =0.001. In a meta-analysis of patients undergoing Surgery for complications of severe acute pancreatitis, those placed on EN 1 day post op showed a trend toward reduced mortality compared to controls randomised to standard therapy. (RR=0.26; CI 0.06- 1.09; P = .06)[5]. The most consistent outcome effect from EN is reduction in infectious morbidity.. In many studies, further benefits are seen from reduction in hospital length of stay, cost of nutrition therapy, and return of cognitive function.

Enteral feeding should be started early within 24-48hrs following admission[5]. The feeding should be advanced toward goal over next 48-72hrs[5]. Attaining access and initiating EN should be considered as soon as fluid resuscitation is completed and the patient is haemodynamically stable. A window of opportunity exists in the first 24-72hrs following admission or the onset of the hypermetabolic insult. Feedings started within this time frame (compared to feedings started after 72hrs) are associated with less gut permeability, diminished activation and release of inflammatory cytokines, (tumour necrosis factor and reduced systemic end toxaemia).[5]

During hemodynamic compromise, EN should be withheld until the patient is fully resuscitated and stable. EN is being provided to patients who are prone to GIT dysmotility, sepsis and hypotension and thus are at increased risk for subclinical ischeamia[5]. More complications are associated with nasojejunal tubes.

EN may be provided with caution to patients into stomach or bowel with low doses of pressor agents, but any signs of intolerance (abdominal distension, increasing NG Output or gastric residual volumes, decreased passage of stool and flatus, hypoactive bowel sounds, increasing metabolic acidosis) should be viewed as early signs of gut ischaemia.

The literature supports the concept that bowel sounds and evidence of bowel function are not required for initiation of enteral feeding. GIT dysfunction in the ICU setting occurs in 30-70 % of patients depending on diagnosis, pre-morbid condition, ventilation mode, medication and metabolic state[5]. Mechanisms of post-operative GIT dysfunction are: mucosal barrier dysfunction, altered motility, atrophy of the mucosa, and reduced mass of GALT.[5]

Critically ill patients should be fed via enteral access tube placed in the small bowel if at high risk for aspiration or after showing intolerance to gastric feeding. Multiple studies have evaluated gastric vs. jejunal feeding in various medical and surgical ICU settings. Level 2 studies (Small randomised trials with uncertain results, moderate to high risk of false positives or false negative), comparing gastric vs. jejunal feeding showed significant less gastro-oesophageal reflux with small bowel feeding.[5]

Types of Enteral formulae

Broadly classified into polymeric and pre-digested formulas. The polymeric formulas contain nutrients in a high molecular weight form which requires a normal digestive and absorptive ability. Pre-digested formulas contain 1 or more partially digested macro nutrients, which facilitates the absorption of nutrients in ICU patients who have impaired digestive and absorptive function

Table2. ***(Reference 6)***

POLYMERIC	PRE-DIGESTED	IMMUNOMODULATING
Ensure	Alitraq	Arginine
Fresubin	Perative	Glutamine
Nutren 1.0	Vital	Omega 3 fatty acids
Nutrison Std	Peptamen	RNA Nucleotides
Osmolite	Nutrison Pepti	

Products available for enteral nutrition

Typical formulas contain 1-2kcal/ml and 30-60 g of protein per litre**.**

Formula 1000ml	Energy KJ	Energy KCal	Protein g	CHO g	Fat g	Content of clinical interest	Osmolality mOsm/kg H_2O	Cost
Jevity®	4430.8	1060	44.3	154.7	34.7	Fibre 14.4g	300	R33.94
Jevity Plus®	5016	1200	55.5	171.5	39.3	Fibre 12g, FOS	450	R40.70
Ensure®	4210	1000	36.9	135.7	32.5	FOS	443	R17.14
Fresubin energy DRINK®		900	56	188	58		440-480	R53.75
Nutren Fibre®	4200	1500	40.1	126.5	38	Fibre 12g	360	R22.44
Osmolite ® (low residue feed)	4452	1060	37.1	151.1	34.7		300	R40.70
Perative® (Semi-elemental)	5434	1300	66.6	177.2	37.4	Arginine	385	R73.19
Suplena®	8380	2004	30	256	95.8		600	R92.62
Alitraq® (Elemental)	4180	1000	52.5	164	15.3	Glutamine 15.5g	575	R19.71
Glucerna SR®	3880	930	46.5	111	33.8	Fibre 7.6g	470	R56.47
Peptamen® (Semi-elemental)	4200	1000	39.8	123	38.7		375	R59.34
Modulen IBD®	4200	1000	36	110	47		370	R60.05

Immunomodulating diets

The concept of pharmaconutrition is greater than the provision of nutrients alone[3]. The quantity of nutrients delivered is dependent on provision of an adequate enteral formula. The administration of key nutrients should be dissociated from the provision of parenteral or enteral nutrition so their full dose can be delivered either parenterally or enterally.

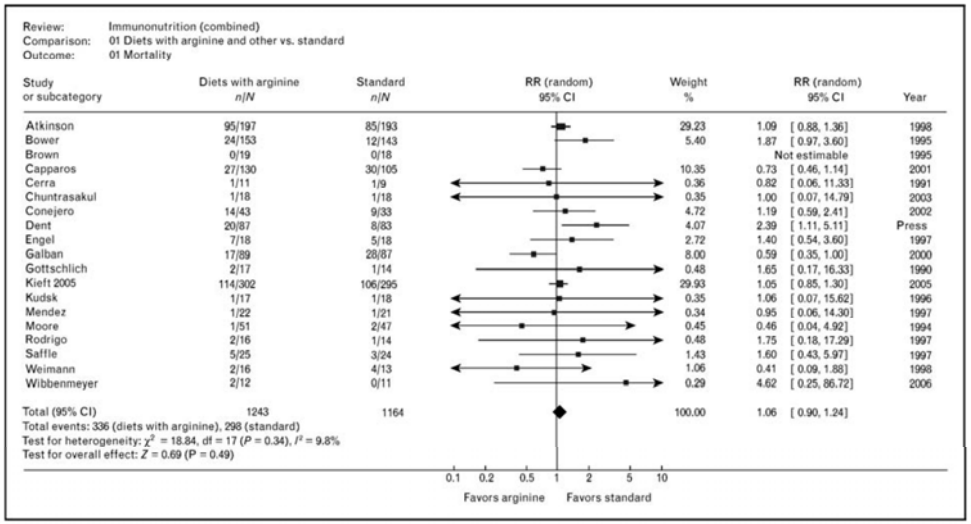
Immune-modulating enteral formulations (supplemented with agents such as Arginine, glutamine, nucleic acid, omega-3 fatty acids and anti-oxidants should be used for the appropriate patient population (major elective surgery, trauma, burns, head and neck cancer and critically on mechanical ventilation with caution in patients with severe sepsis[5].

A large body of data suggest that adding pharmaconutrients to enteral formulations provide even further benefits on further benefits on patient outcome than use of standard formulations alone. Studies from have provided a rational for the mechanisms of beneficial effects seen clinically. The myeloid suppressor cells are capable of causing states of severe arginine deficiency which impact production of nitric oxide and negative effect on microcirculation. Immunomodulating diets containing arginine and omega-3 fatty acids appear to overcome the regulatory effect of myeloid suppressor cells. Agents such as RNA nucleotides increase total lymphocyte count, lymphocyte proliferation and thymus function. Glutamine, considered a conditionally essential amino acid, exerts a

mydriad of beneficial effects on anti-oxidant defences, immune function, production of heat shock proteins, and nitrogen retention. Addition of agents such as Selenium, ascorbic acid and Vitamin E provides further anti-oxidant protection.

Multiple meta-analysis have shown that use of immune-modulating formulations is associated significant reductions in duration of mechanical ventilation, infectious morbidity and hospital length of stay compared to use of standard enteral formulations.

Figure 1 Risk ratio (RR) and associated 95% confidence intervals (CIs) for the effect of immunonutrition on mortality in critically ill patients



n/*N*, number of patients that die/total number of patients in group.

Reference 3

Argininine

Stimulates release of growth hormone, prolactin, and insulin, and increases the number of T-cells and enhances T-cell function. During catabolic disease arginine serum levels decrease due to a reduced dietary intake, increased uptake in endothelium, liver and intestine and increased metabolism.

During development of sepsis, arginine levels begin to increase[3].Depending on underlying pathophysiology, there is an up-regulation of different enzymes and therefore different metabolism of Arginine. It can be metabolised through nitric oxide synthetase enzymes to nitrogenous compounds like nitric oxide or metabolised via arginase to urea and

ornithine. An increased expression of arginase, leads to a depletion of arginine, decreased T-cell activation, and increased risk of infection. It is hypothised that arginine supplementation may inhibit arginase and prevent negative sequelae[3]. Benefit of sequalae have been demonstrated in elective Surgery[3]

However there have been signals from studies that arginine supplementation may be associated with harm in infected or septic critically ill. The potential toxic effect may be due to its role as a substrate for inducible nitric oxide synythase (iNOS). iNOS is up regulated during inflammatory states resulting in an increased production of nitric oxide, contributing to impaired microcirculation and organ dysfunction.

Glutamine

The amino acid has many essential metabolic functions. It plays a role in nitrogen transport within the body; it is a fuel for rapidly dividing cells e.g. lymphocytes, enterocytes and clonocytes; most important substrate for renal ammoniagennesis and a pre-cursor to glutathione resulting in depletion of glutamine stores protects structural and functional integrity of intestinal mucosa and augments cellular immune functions especially associated with cell mediated immunity.

During metabolic stress, the requirement for glutamine exceeds glutamine synthesis and supply from proteolysis. Lower levels of glutamine have been associated with immune dysfunction and increased mortality[3]

Glutamine supplementation during illness may enhance gut barrier and lymphocyte function, preserve lean body mass and protect against damaging effects of oxidative stress .

It protects against septic shock. Recent animal and human studies have demonstrated that glutamine may enhance tissue Heat Shock Protein-HSP expression which is vital to cellular and tissue protection after stress or injury.

A recently updated meta-analysis examined the relationship between glutamine supplementation and clinical outcomes in critically ill patients and revealed a significant reduction in mortality (RR 0.75, p=0.02)

Reference: 14

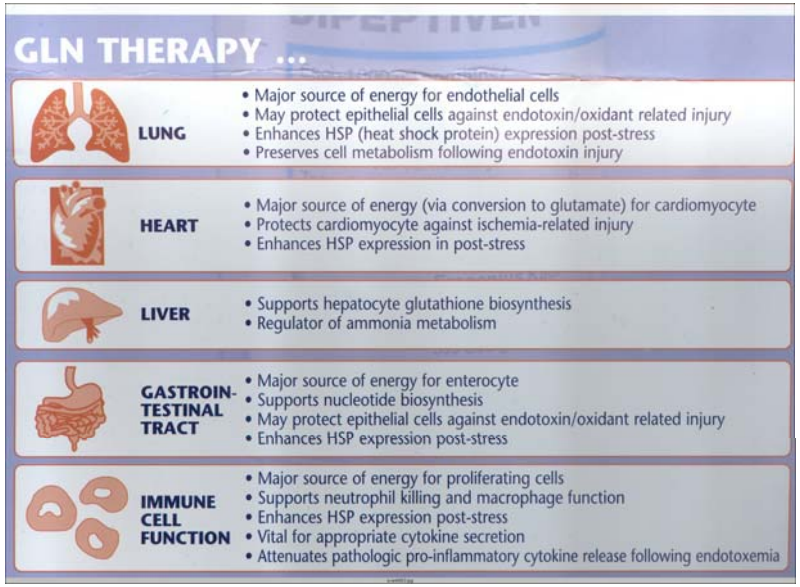
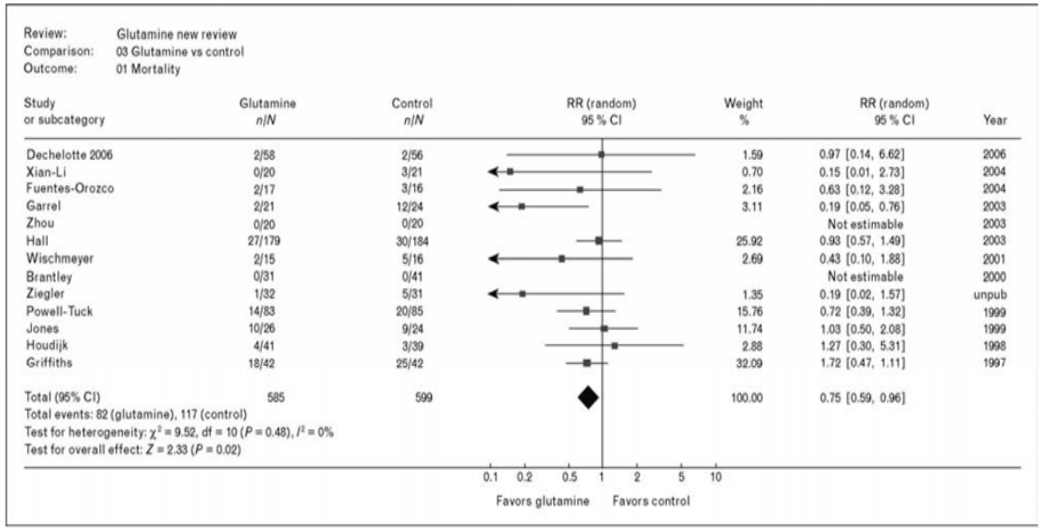


Figure 2 Risk ratio (RR) and associated 95% confidence intervals (CIs) for the effect of glutamine supplementation (enteral and parenteral) on mortality in critically ill patients



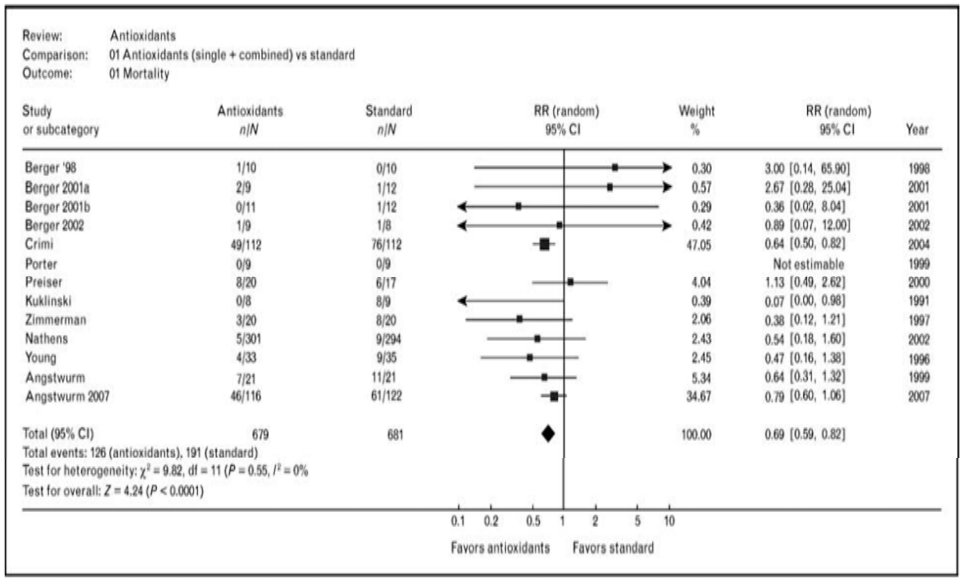
n/N, number of patients that die/total number of patients in group.

Anti-oxidants

Anti-oxidants are part of a complex defence system designed to protect tissues from damaging effects of oxidative stress caused by excessive amounts of ROS and reactive nitrogen-oxygen species. There is evidence that oxidative stress is central to the underlying pathophysiology of critical illness including organ failure development.

In critically ill patients, there are reduced stores of anti-oxidants which are associated with an increase in free radical generation, an augmentation of systemic inflammatory response, cell injury, increased organ failure and higher mortality. Thirteen studies were identified most studied the effects of Selenium either alone or in combination with other trace elements and vitamins while others looked at the effects of Zinc and Vitamins A, C and E. When the results of all the trials were targeted, overall anti-oxidants were associated with a significant reduction in mortality (RR 0.90, P= 0.51[3])

Figure 3 Risk ratio (RR) and associated 95% confidence intervals (CIs) for the effect of antioxidant supplementation on mortality in critically ill patients

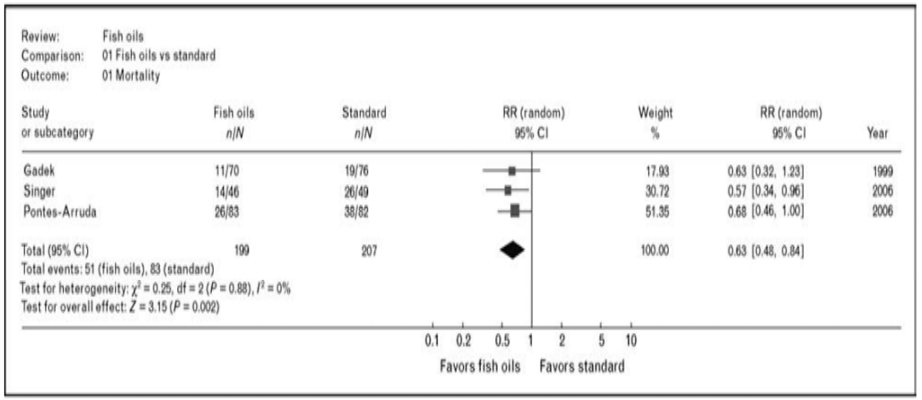


n/N, number of patients that die/total number of patients in group.

n-3 fatty acids

The biological effects of n-3 fatty acids or fish oils during illness is related to their steady incorporation into inflammatory cell membrane phospholipids often at the expense of n-6 arachidonic acid. The n-3 fatty acids antagonise the production of pro-inflammatory eicosanoids from n-6 arachidonic acid (leukotriene B4, thromboxane A2 , prostaglandin E2 and are pre-cursors for less inflammatory eicosanoids (eg. Thromboxane A3, prostaglandin E3, leukotriene B5) resulting in anti-inflammatory effects. A recent meta-analysis aggregating the results of 3 studies demonstrated that enteral formula enriched with fish oils reduces mortality (RR 0.63 95% CI 0.48, 0.84, P = 0.002)and tended to reduce ICU length of stay[3].

Figure 4 Risk ratio (RR) and associated 95% confidence intervals (CIs) for the effect of enteral formulas enriched with fish oils, borage oils and antioxidants on mortality in patients with acute respiratory distress syndrome



n/N, number of patients that die/total number of patients in group.

Dosing of Enteral feeding

Clinicians should clearly identify the goal of EN, as determined by energy requirements. There are over 200 predictive equations including Harris Benedict equation which has been published in the literature. Energy requirement may be calculated as 25-30kcal/kg/day or indirect calorimetry may be used. Efforts to provide > 50-65% of goal calories should be made in order to achieve the Clinical benefit of EN over the first week of hospitalisation[5]. The impact of EN on patient outcome appears to be dose-dependent effect. > 50-65% of goal calories may be required to prevent increases in intestinal permeability in burn and bone marrow transplant

patients, to promote faster return of cognitive functioning head injured patients **(Supported by Level 2 and Level 3 study{ nonrandomised contemporaneous controls})** where increases in percent goal calories improved clinical outcome. If unable to meet energy requirements (100% of target goal calories) after 7-10days by enteral feeds alone, initiation of supplemental parenteral nutrition should be considered. In patients with BMI < 30, protein requirement should be in the range of 1.2-2.0 g/kg actual body weight per day and may be higher in burn or multi-trauma patients. In critically ill patients, protein requirements are higher than energy requirements.

In critically ill obese patient, permissive underfeeding or hypo caloric feeding with EN is recommended, for all classes of Obesity where BMI > 30. The goal of EN regimen should not exceed 60-70% of target energy requirements or 11-14kcal/kg actual body weight per day[5]. Protein should be provided in a range > or equal to 2.0g/kg ideal for BMI (30-40) or > 2.5 g/kg ideal weight per day for Class 3[5].Severe obesity adversely affects patient care in ICU and increases risk of co-morbidities (eg. Insulin resistance, sepsis, infection, deep vein thrombosis, organ failure). Achieving some degree of weight loss may increase insulin sensitivity, improve nursing care, and reduce co-morbidities.

Monitoring of EN Therapy

Patients should be monitored for tolerance of EN and inappropriate cessation of EN should be avoided. Holding EN for gastric residual volumes < 500ml in the absence of other signs should be avoided. Patients placed on EN should be assessed for risk of aspiration. Steps to reduce risk of aspiration should be employed. These measures reduce risk of aspiration: Head end of the bed elevated 30-45 degrees. , agents to promote motility such as prokinetic drugs or narcotic antagonists should be initiated where clinically feasible, diverting level of feeding by post-pyloric tube placement should be considered, use of chlorhexidine mouth-wash twice a day should be considered to reduce risk of ventilator-associated pneumonia.

Complications of EN Therapy

EN generates complications related to mechanical or to metabolic effects. Grossly adverse complications occur if nutrients are infused outside the gastro-intestinal tract, particularly on the airways. Bronchial aspiration may occur[3].

Non-occlusive bowel necrosis has emerged as a devastating complication. The incidence is less than 0.3% but the mortality rate greater than 50% [6].

Diarrhoea

This is the most common complication in the Intensive care, but there are many possible factors causing it.

Other causes of diarrhoea include Medications (particularly those containing Sorbitol or Magnesium), lack of fibre in the tube feeding formulae, physiological factors associated with stress or critical illness itself, disturbances in gut flora, caused by antibiotics, reduced gut motility and antacids[1].

The administration of enteral feeding can be pump driven or controlled by gravity, continuous or intermittent which affects the incidence of diarrhoea. The use of pump-driven infusion dramatically reduced the incidence of diarrhoea compared to gravity-controlled infusion[11]. Composition of certain enteral formulas has been associated with an increased incidence of diarrhoea, including the amount of carbohydrate, fat, high Osmolarity and bacterial contamination.

Although there are many different possible causes of diarrhoea in critical illness, consistent management of diarrhoea can be improved by the use of standardised protocols[10].

PARENTERAL NUTRITION

Total parenteral nutrition is indicated if GIT cannot be utilised or if absorption is inadequate. TPN formulas utilize hyperosmolar solutions of amino acids and glucose mixed together. The hypertonic. nature of these solutions requires central venous access, but peripheral venous access may be considered for low Osmolarity (850mOsmol/L) mixtures designed to cover a proportion of nutritional needs[2]. All patients who are not expected to be on normal nutrition within 3 days should receive

PN within 24h-48h if EN is contra-indicated or if they cannot tolerate EN. There has been no study that has evaluated the best timing for PN initiation in ICU. **Heyland's meta-analysis evaluated 26 randomized trials of 2211 patients in terms of clinical outcome for patients having received PN vs. standard care. There was no influence of PN on mortality rate was found (Risk ratio1.03), but there were fewer complications in patients with malnutrition was identified[2].**

PN Mixtures

PN Regimens contain many different components, including water, macronutrients, electrolytes, micronutrients and other additives which can be administered in separate containers or using an all-in-one bag. All in-one bag cost is lower.

PN Components

During acute illness, the aim should be to provide energy as close as possible to the measured energy expenditure in order to decrease negative energy balance. In the absence of calorimetry, ICU patients should receive 25kcal/kg/day increasing to target over next 2-3 days[2]. No study has demonstrated an advantage to any measurement technique or predictive formula. All patients receiving less than their target enteral feeding after 2 days should be considered for supplementary parenteral nutrition. The minimum amount of carbohydrate required is about 2g/kg of glucose per day[2]. Hyperglycaemia (glucose > 10mmol/l) contributes to death in the critically ill patient and should also be avoided to prevent infectious complications. Reductions and increases in mortality rates have been reported in ICU patients when blood glucose is maintained between 4.5 and 6.1 mmol/l. Glucose is the main metabolic fuel for the human body. The brain, peripheral nerves, renal medulla, leukocytes, erythrocytes and bone marrow use glucose as the main source of oxidative energy.

Lipid emulsions should be an integral part of PN for energy to ensure essential fatty acid provision in long term fatty acid provision in long term ICU patients. Fatty acids serve a function of acting as energy sources, contribute towards the structure and physical properties of cell membranes, act as precursors of bioactive lipid metabolites such as prostaglandins and regulating cell responses including gene expression. Many fatty acids can be synthesized within the human body but 2 (linoelic acid, 18 carbon omega-6 fatty acid, and alpha-linoelic acid cannot. These fatty acids must be supplied to humans and are referred to as the essential fatty acids.

The typical ICU patient requires 9-12g/day of linoelic acid and 1-3g/day of alpha linoelic acid. The essential fatty acids are synthesized in plants and are found in high amounts in plant oils (eg. Corn, sunflower, soybean) They are metabolised to longer chain, less saturated fatty acids such as arichidonic acid (omega 6) and eicosapentanoic acid and decosahexaenoic acid. Fatty acids can influence inflammatory and immune processes through effects on cell membrane structure and function, modification of inflammatory mediator profile and alteration in gene expression.

Thus, the nature and quantity of lipid supplied to critically ill patients may have an important role in determining clinical outcome. Lipid formulations used in parenteral nutrition are composed of triglycerides with phospholipids as emulsifiers eg. : Soybean oil based, soybean LCT and medium chain triglyceride from coconut oil, Triglyceride mixtures in which each glycerol, mixtures of soybean and olive oil mixture of lipids including fish oil.

Amino acid mixture should be infused at approximately 1.3-1.5g/kg ideal body weight per day in conjunction with adequate energy supply[2]. The principal goal of protein/amino acid administration in critical illness is to provide precursors for protein synthesis in tissues with high turnover and to protect skeletal muscle mass and function. Glutamine participates in protein and glucose metabolism as a carrier for nitrogen and carbon between organs, is connected with other amino acids and with protein synthesis as a pre-cursor off or nucleotide, cellular protection through glutathione and heat shock proteins. And is a regulator of ammonia and acid base balance.. Under normal circumstances it is not an essential amino acid, but has an endogenous production rate of 50-80g/24hrs. In critically ill there is increased demand for its utilisation (increased immune activity and repair) is not adequately met over a sustained critical illness and plasma levels fall. A low plasma level is associated with worse outcome.

All Parenteral nutrition prescriptions should include a daily dose of multivitamins and trace elements. Many trace elements and vitamins are essential in anti-oxidant defence. The FDA approved trace element formulation results in high levels of Copper and Manganese which may be associated with toxicity during prolonged home PN. Critically ill patients are characterized by increased oxidative stress which is proportional to the severity of the condition. Consequences of acute trace element deficiency are not immediately detected as the full clinical picture requires weeks to develop, but the biochemical alterations appear within 3-5days.

ICU patients are generally hyper metabolic, with increased macro-nutrient, trace element and vitamin requirement). When PN is prolonged, and if the patient remains critically ill, determination of plasma concentrations on a monthly basis enables detection of gross deficiencies, which should be corrected by the individual trace element. In patients with major burns, they have large exudative losses of Copper, Selenium and Zinc. Randomised clinical trials have shown clinical benefit from doses calculated to compensate these losses.

Thiamine and Vitamin C deficits pose a special risk. Thiamine supplements to the level of 100mg-300mg/day should be provided during the first 3 days in the ICU patients with possible thiamine deficiency. Some patients have specific substitution requirements that should be considered separately from PN requirements

Critically ill patients are prone to fluid and sodium overload, and renal dysfunction is frequent. The highly variable requirements should instead be determined by plasma electrolyte monitoring.

Table 1
Conflicting meta-analysis results regarding the benefits of PN in different ICU populations.

	Number of studies included	Type of nutrition studied and Specific population	RR (95% CI)	Conclusions
Simpson [2]	11	vs. EN		PN improves outcomes
Gramlich [14]	13	vs. EN in terms of infection	0.64 (0.46–0.87)	EN better but no difference in mortality, length of ventilation, or diarrhea
Dhaliwal[14]	5	Combination of PN and EN vs. EN alone		No effect of PN on mortality, infection, length of ventilation or length of stay
Brauschweig[15]	27	vs. EN	0.64 (0.54–0.76)	Standard better than PN
Brauschweig[15]	7	vs. standard nutritional care in the malnourished		
		Mortality	3.0 (1.09–8.6)	PN improves
		Infection	1.17 (0.88–1.56)	PN might improve

Reference 2.

Complications of parenteral nutrition

PN allows delivery of essential nutrients and prolongation of life in patients with non-functioning intestinal tracts. Severe complications of PN have been recognised and some of them life-threatening. PN complications are associated with increased mortality and affect the quality of life of PN patients. The complications are divided into:

1. Mechanical (related to insertion and care of central venous catheter)
2. Infectious (related to catheter associated infections
3. Metabolic (refer to high or low serum levels of PN solution, liver disease and metabolic bone disease)

Mechanical complications

Complications that occur when placing vascular access catheter or device can develop early post-procedure or delayed post-procedure.

Early complications are related to injury of surrounding vital structures or malpositioning of the catheter tip:

Pneumothorax
Arterial puncture
Haemothorax
Hydrothorax
Cardiac temponade
Air embolism
Line malposition
Blocked catheter

Delayed complications are;

Venous thrombosis (Risk factors include underlying disease e.g. patients with Cancer, and type and location of the catheter

Infectious complications

The Centres for Disease control and prevention guidelines of Intravascular catheter related infections estimate 5 per 1000 catheter infection annually. Mortality is estimated to be 12% to 25% for each infection[4]. The most prevalent organisms cultured include coagulase-negative staphylococci, Staphylococcus Aureus and Klebsiella pneumonia

Metabolic complications

1. **Hyperglycaemia**
   The most common cause of hyperglycaemia is excess Dextrose infusion. Uncontrolled hyperglycaemia from Dextrose overfeeding can lead to immune system dysfunction and increased susceptibility to infections.

2. **Hyperlipidaemia**
   Impaired lipid clearance is usually responsible for PN induced hyperlipidaemia. Obesity, diabetes, sepsis, pancreatitis and liver disease predispose to hypertriglyceridemia because of decreased lipids clearance[4]

3. **Hypercapnia**
   Overfeeding of total calories and Dextrose can result in excess of Carbon Dioxide production during Carbohydrate metabolism[4].

4. **Re-feeding Syndrome**
   Rapid nutritional repletion in severely malnourished individuals can result in severe fluid and electrolyte disturbances including hypernataemia, hypophosphataemia, hypokalaemia and hypomagnesemia. Severe hypophosphataemia can cause weakness, convulsions, respiratory failure and cardiac decompensation leading to death[4] . The most important steps are to identify patients at risk for developing re-feeding syndrome, provide nutrition support cautiously, correct and supplement electrolyte and vitamin deficiencies to avoid re-feeding syndrome.

5. **Selenium deficiency**
   It has been reported in patients receiving long term-PN. In some studies done, the findings were suggestive of impaired renal homeostasis of Selenium conservation[4]Selenium levels should be monitored periodically in patients receiving long term PN.

6. **Gastro-intestinal Complications:**
   Numerous animal studies have demonstrated intestinal villous atrophy when PN is provided due to lack of stimulation from luminal nutrients. Abnormal gastric motility has been reported in patients on PN therapy[4]. Hepatobilliary disorders- steatosis, steato-hepatitis, fibrosis, cirrhosis, gallstones, cholestasis, cholecystitis.

7. **Renal Complications:**
   Renal disorders associated with PN include hyperoxaluria, hypercalcuria and tubular renal defects. TPN associated nephropathy is characterised by decline in creatinine clearance and impaired tubular function has been reported in children and adults receiving long term PN.

8. Bone disease:
   PN associated bone disease was first reported in 1980[4]. Klein and colleagues described insidious onset of severe bone pain and hypercalciuria ain adults receiving PN for more than 3 months[4].

9. Manganese toxicity

CATHETER-RELATED	METABOLIC	HEPATO-BILIARY	GIT CHANGES
Mechanical e.g. central vein thrombosis,haemo/pneumo/ hydrothorax, air-embolism.	Hyper /hypoglycaemia	LFT elevations, hyperbilirubinaemia	Atrophy of intestinal mucosa.
Sepsis. S.epidermis, Candida. Septic venous thrombosis is life threatening.	Electrolyte and acid base abnormalities	Steatosis, steatohepatitis	
Occlusion	Vitamin deficiencies	Hepatomegaly, cirrhosis, liver failure	
Superior vena caval syndrome	Trace element deficiencies	Related to nutrient deficiencies	
	Re-feeding syndrome		

EARLY vs DELAYED FEEDING

Timing of nutrition should be tailored to the individual critically ill patient. There is no good data to show improvement in relevant outcomes in early initiation of enteral nutrition. Experts favour the view that critically ill patients who are haemodynamically stable and have a functioning GIT tract, should be fed as early as possible[6].

Advantages and risk of early enteral nutrition[6]

ABSOLUTE BENEFITS	RELATIVE BENEFITS	RELATIVE RISK
Improved caloric intake	Promotes bowel mucosal integrity	Pulmonary aspiration
Avoid TPN related complications	Prevents translocation	Diarrhoea
Cost-effective	Decreases infectious complications	Metabolic complications
	Reduces lipid per oxidation	Intestinal ischemia and necrosis
	Reduces hospital length of stay	

NUTRITIONAL SUPPORT DURING ORGAN FAILURE

Renal Failure:
ICU patients with acute renal failure or acute kidney injury should be placed on standard enteral formulations and Standard ICU recommendations for protein and calorie provision should be followed. If significant electrolyte abnormalities develop, a special formulation designed for renal failure (with appropriate electrolyte profile may be considered. Patients receiving haemodialysis or continuous renal replacement therapy should receive increased protein, up to 2.5g/kg/day[2]. At least 1 randomised prospective trial has suggested an intake of 2.5g/kg/d is necessary to achieve positive nitrogen balance in this patient population. There is an appproximate10-15g/day of amino acid loss during continuous replacement therapy.

Hepatic Failure:
Traditional assessment tools should be used with caution in patients with Cirrhosis and hepatic failure, as these tools are less accurate and less reliable due to complications of ascites, intravascular volume depletion, oedema, portal hypertension and hypoalbuminaemia. Enteral nutrition has been associated with decreased infection rates and fewer metabolic complications in liver disease and after liver transplant when compared to Enteral nutrition.

Protein requirements should be same manner as for the general ICU patient. Branched chain amino acid formulation should be reserved for the rare encephalopathic patient who is refractory to standard treatment. There is no evidence to suggest that formulation enriched in BCAA improves patient outcomes.

Findings from Level 2 Randomised Outpatient trials suggest that long (12 and 24 months) nutritional supplementation with oral BCAA granules may be useful in slowing the progression of hepatic disease/ failure and prolonging event free survival.

Acute pancreatitis
On admission, patients with acute pancreatitis should be evaluated for disease severity. Patients with severe acute pancreatitis should have a naso-enteric tube placed and Enteral nutrition initiated as soon as fluid volume resuscitation is complete.

3 meta-analysis of varying combinations of ten level 2 randomised trials showed that the use of EN compared to PN reduces infectious morbidity. (RR=0.46; 95% CI ; P= 0.001[2].

The need to initiate EN early within 24-48hrs of admission is supported by the fact that out of six level 2 studies done, only in patients with severe acute pancreatitis, 5 studies which randomised and initiated EN within 48hrs of admission all showed significant outcome benefit.

Tolerance to EN in patients with severe acute pancreatitis may be enhanced by: minimizing the period of ileus after admission by early initiation of EN, displacing the level of infusion of EN more distally in the GIT, changing the content of EN delivered from intact protein to small peptides and long-chain fatty acids to medium-chain triglycerides or fat free elemental formula, switching from bolus to continuous infusion. For patients with severe acute pancreatitis, when EN is not feasible, use of PN should not be initiated until after the first 5 days of hospitalisation.

Patients with mild to moderate acute pancreatitis do not require nutrition support therapy unless an unexpected complication develops or there is failure to advance to oral diet within 7 days.

Pulmonary Failure
Patients with ARDS and severe acute lung Injury should be placed on Enteral formulation characterised by an anti-inflammatory lipid profile (i.e. Omega-3 fish oils, borage oil) and antioxidants.

In 3 Level 1 studies involving patients with ALI, ARDS and sepsis use of enteral formula fortified with omega 3-fatty acids and anti-oxidants shown to significantly reduce length of stay in the ICU, duration of mechanical ventilation, organ failure and mortality compared to use of a standard enteral formulation.

Fluid restricted calorically dense formulations (1.5-2kcal/ml) should be considered for patients with acute respiratory failure that necessitates volume restriction[2].

Serum phosphate levels should be monitored closely and appropriately replaced when needed. Phosphate is essential for the synthesis of ATP and 2.3-diphosphoglycerate, both of which are critical for normal diaphragmatic contractility and optimal pulmonary function.

Nutrition therapy in end of life situations:
Specialised nutrition therapy is not obligatory, in cases of futile care or end of life situations. Provision of EN or PN has not been shown to improve outcome[2].

CONCLUSION

Nutritional support of critically ill patients is a challenging, rapidly evolving field with new products and supplements now available. Good ICU management requires that processes must be in place to ensure that nutritional support is delivered adequately to improve outcomes in critical illness.

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