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EATING TO LIVE-NUTRITION IN ICU

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INTRODUCTION

Nutrition is essential to life. Good nutrition is essential to health. Maslow's hierarchy of needs demonstrates that in medicine we are mostly involved in base, physiological needs, and while we are very concerned with maintaining organ function in our patients we rarely stop to bother about nutritional health. Nutrition is often overlooked, deemed the zone of dieticians. Perhaps it is due to the fact that most of our theatre work involves ensuring that patients have not eaten or trying to avoid consequences of a patient that is not "Nil Per Os" .In ICU our focus must shift, ensuring proper nutrition, has a dramatic effect on mortality and morbidity in ICU. Malnutrition has been linked to increased length of ICU stay, duration of mechanical ventilation, risk of infection, muscular weakness, impaired wound healing and mortality (1, 2, 6). Nutrition is inextricably linked to outcomes in ICU.

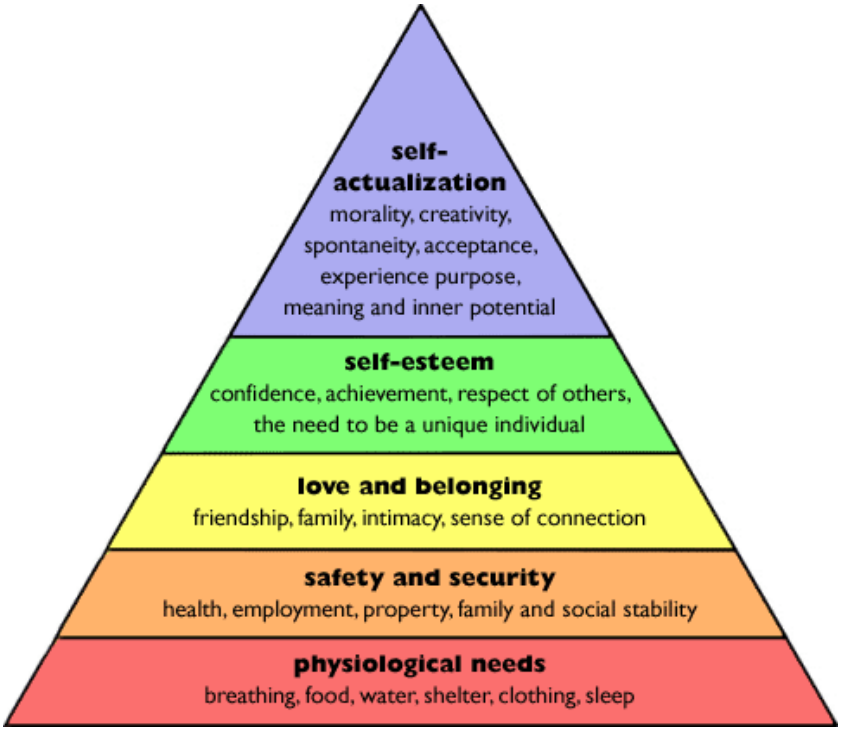


Fig 1: Maslow's Hierarchy of needs

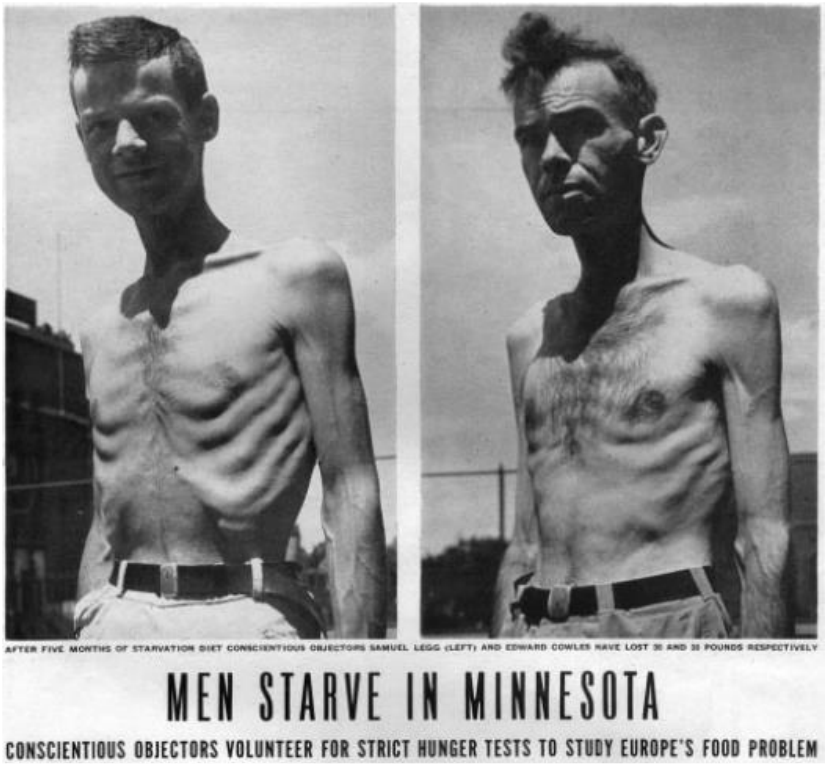
WHY IS NUTRITION IMPORTANT IN ICU?

Critical illness is a catabolic state (3). Increased metabolic demand, often coupled with periods of starvation, promotes loss of lean body mass and micronutrients. This catabolism is a response to severe pathological stressors which encourages proteolysis, gluconeogenesis and lipolysis. Surges in stress hormones have been reported including cortisol, adrenocorticotropic hormone (ACTH), adrenaline and glucagon. Proinflammatory cytokines such as interleukin 6, interleukin 1 and tumour necrosis factor alpha (TNF) increase the magnitude of this response. In addition, 50% of ICU patients have pre-existing nutritional deficiencies which compound this problem (4). Poor nutrition in ICU has long reaching consequences, post ICU discharge; patients reported 18% weight loss and persistent functional limitations at one year post discharge. Muscle wasting and weakness were noted to be causative factor (5)

Further evidence for feeding in ICU includes the fact that enteral nutrition supports the functional and structural integrity of the gastrointestinal tract (GIT) by stimulating blood flow to the gut. The intestinal tract is able to maintain tight junctions in luminal cells as well as initiating release of trophic endogenous substances (gastrin, cholecystokinin). It allows for the preservation of villi height and supports GALT (gut-associated lymphoid tissue) (12). Enteral nutrition also allows for the modulation of stress response to critical illness and acts as a preventative against stress ulceration.

ICU-acquired malnutrition

The Minnesota starvation experiment was conducted during World War 2 in 1944. It involved the participation of 36 healthy young men who were subjected to semistarvation and then refeeding. The purpose of this trial was to learn about starvation physiology. As allied forces entered German-occupied Europe they encountered many starving civilians and medical staff had very little idea of how to adequately treat them. The trial involved a year-long internment period involving 3 months of standardised normal nutrition followed by 6 months of semistarvation and 3 months of refeeding. During the semi-starvation period calories were restricted to 25kcal/kg/day. Interestingly this 25kcal/kg/day is the standard nutritional calorie allowance in ICU; our patients are being prescribed what is essentially a semi-starvation diet. During the experiment all volunteers were expected to walk 35km/week. Upon refeeding it was noted that despite increasing daily calories to normal limits these volunteers still continued to lose weight and only when the calorie allowance was increased to supranormal values that rebuilding occurred and loss of tissues subsided. Conclusions from the trial found that diet alone had a profound effect on blood pressure, cholesterol level and resting heart rate. The participants reported a decreased tolerance to cold, dizziness, extreme tiredness, muscular pain and reduced coordination (44).The correlation between this and ICU is that it mirrors the nutrition and energy challenges of the ICU patient.


AFTER FIVE MONTHS OF STARVATION DIET CONSCIENTIOUS OBJECTORS SAMUEL LEGG (LEFT) AND EDWARD COWLES HAVE LOST 30 AND 32 POUNDS RESPECTIVELY

MEN STARVE IN MINNESOTA

CONSCIENTIOUS OBJECTORS VOLUNTEER FOR STRICT HUNGER TESTS TO STUDY EUROPE'S FOOD PROBLEM

WHY DO WE UNDERFEED?

Underfeeding is a complex and multifaceted process. The average feeding in critically ill patients provides 50-95% of requirements. Factors related to underfeeding consist of:

- Patient-related factors
  - Type of illness
  - Severity of illness
- Feeding method factors
- Type of feed used(energy dense vs. standard feeds)
- Feeding tube location (gastric vs. small intestine).
- Feeding process factors
  - Time to initiation
  - Time to goal
- Underprescription
- Interruption of feeds

Repeated interruptions in feeds occur 2.3-7 hours per day (45).Underprescription is a major problem, in a study by Mclave et al prescriptions were around 65.6% of requirements and only 78% of what was prescribed was given. Thus the simple act of underprescribing can impact in major underfeeding.

Table 4 Type of interruption for enteral nutrition

Author	Year	Sample size		Type of interruption									
				Feeding tube problem	GR	GI intolerance	Procedure	Surgery	Radiology	Nursing care	Hemodynamic	Airway	Other
McClave et al [6]	1999	44	% of patients affected	41	45	[a]		[39]	27	30	[a]	NR	31
			% of total interruption time	7.7	15.1	[a]		[35.0]	4.6	1.4	[a]	NR	36.2
			% of avoidable	67	70	[a]		[80]	52	99	[a]	NR	52
Boivin and Levy [24]	2001	40	% of total interruption events	19	17	NR	NR	13	23	11	4	12	NR
Roberts et al [9]	2003	50	% of patients affected	NR	38	28	NR	NR	NR	NR	NR	NR	NR
Elpern et al [32]	2004	39	% of total interruption time	2.7	11.5	9.2		[35.7]		NR	13.5	NR	11.2
Rice et al [14]	2005	55	% of total interruption events	3	4	5		[41]		2	6	15	3
O'Leary-Kelley et al [7]	2005	60	% of patients affected	24.9	21.7	15.0	15.0	23.3	13.3	33.3	NR	30	21.6
			% of total interruption time	11.1	6.6	13.2	1.4	23.4	6.9	2.5	NR	28.8	5.9
Reid [19]	2006	32	% of total interruption events	5	14	7		[8]	3	16	NR	21	12
Petros and Engelmann [33]	2006	61	% of total interruption events	6.0	31.9	9.6		[30.7]	10.8	NR	NR	NR	10.8
O'Meara et al [12]	2008	59	% of total interruption events	17.3	9.7	NR	10.9	5.2	4.5	24.8	2.1	14.2	11.3
			% of total interruption time	25.6	13.3	[a]	7.9	7.7	5.0	2.3	3.7	11.7	22.8
Kim et al [34]	2010	47	% of patients affected	NR	8.7	6.5	4.3	6.5	4.3	NR	6.5	19.6	15.2
			% of total interruption events	NR	6.5	4.0	4.0	24.2	1.6	NR	10.5	25.8	23.4

Other: transfer, high blood sugar, high bilirubin, dialysis, medication, GI bleeding, equipment/formula problem, ICU doctors, dietitian.
NR indicates not reported.
[a] Categorized into "other" in original article, although categorized into a specific type of interruption in this review.

Table 1: Causes of enteral feed interruptions (45)

WHEN SHOULD I FEED?

Enteral nutrition has been advocated within 24hrs of ICU admission although ESPEN guidelines state that feeds can be commenced with 3 days if oral intake is not anticipated in the time period (11).

ASPEN guidelines reported a metanalysis of 21 RCTs which looked at early vs. late enteral feeding reported mortality reduction (RR=0.70; 95% CI, 0.49-1: p=0,05) and decreased infection risk (RR=0.74:95% CI, 0.58-0.93; p=0.01), they suggest starting feeds within 24-48 hours. It is also suggested that patients at high risk (NRS 2002>5, NUTRIC

Score>5) should be progressed to goal feeding as soon as possible, preferably within the first 48-72 hours (12).

Patients at risk

ASPEN guidelines recommend determination of nutritional risk to further stratify patients as to whether feeds should be started earlier or later. Two scoring systems may assist with risk stratification: the NUTRIC score (Fig 2), and the NRS (nutritional risk screening) 2002 (Fig 3). Both scoring systems include the nutritional status of the patient and the extent of disease.

It is noted that certain patients may require enhanced nutritional support in ICU such as more rapid introduction of feeds and increase to near-goal feeds in a short period. In a study by Alberda et al, an increase in daily calories by one thousand reduced mortality (odds ratio 60 day mortality 0.76, 95%CI (0.61-0.95), P=0,014) however beneficial effect was only observed in patients with BMIs <25 or >35 (7).This drew the hypothesis that baseline nutritional status has an effect on intake of energy and outcomes and that malnourished patients would most likely benefit the most from increased energy intake. These 2 scores hope to further stratify the “at risk” patients as BMI is often inaccurate/inappropriate in the ICU.

The Nutric score devised by Heyland involved a secondary analysis of a prospective observational study to evaluate a novel biomarker for sepsis. It should be noted that nutritional care was not standardised. Collected data included age, baseline apache II score, baseline SOFA score, comorbidities, days from hospital admission to admission into ICU, and serum interleukin 6. Other variables investigated although not included in the score, were a BMI>20, estimated percentage of oral intake in the previous week, weight loss in last 3 months, procalcitonin and CRP. Each variable was assigned points based on association strength.

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NUTRIC Score[1]

The NUTRIC Score is designed to quantify the risk of critically ill patients developing adverse events that may be modified by aggressive nutrition therapy. The score, of 1-10, is based on 6 variables that are explained below in Table 1. The scoring system is shown in Tables 2 and 3.

Table 1: NUTRIC Score variables

Variable	Range	Points
Age	<50	0
	50 - <75	1
	≥75	2
APACHE II	<15	0
	15 - <20	1
	20-28	2
	≥28	3
SOFA	<6	0
	6 - <10	1
	≥10	2
Number of Co-morbidities	0-1	0
	≥2	1
Days from hospital to ICU admission	0 - <1	0
	≥1	1
IL-6	0 - <400	0
	≥ 400	1

Table 2: NUTRIC Score scoring system: if IL-6 available

Sum of points	Category	Explanation
6-10	High Score	➢ Associated with worse clinical outcomes (mortality, ventilation). ➢ These patients are the most likely to benefit from aggressive nutrition therapy.
0-5	Low Score	➢ These patients have a low malnutrition risk.

Table 3. NUTRIC Score scoring system: If no IL-6 available*

Sum of points	Category	Explanation
5-9	High Score	➢ Associated with worse clinical outcomes (mortality, ventilation). ➢ These patients are the most likely to benefit from aggressive nutrition therapy.
0-4	Low Score	➢ These patients have a low malnutrition risk.

*It is acceptable to not include IL-6 data when it is not routinely available; it was shown to contribute very little to the overall prediction of the NUTRIC score.[2]

[1] Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Critical Care. 2011;15(6):R268.
[2] Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool. Clin Nutr. 2015. [Epub ahead of print]

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Fig. 2 Nutric Score

NRS 2002

The NRS score contains two constituents, namely, nutritional criteria and severity of disease. Variables analysed included BMI, mid-arm circumference, weight loss and change in intake. Kondrup et al then validated the score by performing a retrospective analysis of 128 RCTs including inpatient and outpatient populations. The evaluated sensitivity and specificity of the score to identify patients at risk for poor nutritional-related outcomes were 75% and 55 % respectively (18).

Nutritional Risk Screening 2002 (ESPEN guideline)			
Impaired nutritional status		**Severity of disease** (≈ requirement/stress-metabolism)	
Mild **Score 1**	Wt loss >5% in 3 mths Or Food intake <50-75% of normal requirement in preceding week.	Mild **Score 1**	Hip fracture (9). Chronic patients, in particular with acute complications: cirrhosis (11), COPD (12). *Chronic hemodialysis, diabetes, malignant oncology.*
Moderate **Score 2**	Wt loss >5% in 2 mths Or BMI 18.5 - 20.5 + impaired general condition Or Food intake 25-50% of normal requirement in preceding week	Moderate **Score 2**	Major abdominal surgery (13-15). Stroke (16). *Severe pneumonia, malignant hematology.*
Severe **Score 3**	Wt loss >5% in 1 mth (≈ >15% in 3 mths (17)) Or BMI <18.5 + impaired general condition (17) or Food intake 0-25% of normal requirement in preceding week	Severe **Score 3**	Head injury (18, 19). Bone marrow transplantation (20). *Intensive care patients (APACHE>10).*
Score: +		**Score:** = **TOTAL SCORE:**	

Fig. 2 NRS SCORE

HOW MUCH SHOULD I FEED?

Predictive equations

The simplest option is to use a weight-based calorie intake formula which states that in acute illness calories should be restricted to <20-25 kCal/kg/day. This is due to evidence suggesting that increased caloric delivery may be associated with less favourable outcomes. Calories in the recovery period should increase to 25-30kCal/kg/day. (11)

This may not be sufficient for all patients, especially patients at extremes of weight. Other ways to obtain energy requirements are utilising predictive equations. There are a multitude of equations that can be utilised. One of the most popular is the Harris-Benedict equation which calculates basal energy expenditure using weight, height, age, sex, activity and stress factors.

Men: 66.47 + (13.75 x weight) + (5 x height) – (6.78 x age)

Women: 65.55 + (9.56 x weight) + (1.85 x height) - (4.68 x age)

Variables – gender, weight (kg), height (cm), age (years)

Daily calorie requirement = BEE x activity factor x stress factor

Injury	**Stress factor**
Minor surgery	1.0 to 1.1
Long bone fracture	1.15 to 1.3
Cancer	1.1 to 1.3
Peritonitis / sepsis	1.1 to 1.3
Severe infection / multi trauma	1.2 to 1.4
Multi-organ failure	1.2 to 1.4
Burns	1.2 to 2.0
Activity	
Confined to bed	1.2
Out of bed	1.3

Fig 4 Harris benedict equation

It should be noted that the Harris-Benedict equation is derived from testing normal volunteers and thus may not be accurate, even with the addition of a stress factor(8). Additional equations have been tested using inpatient populations like the Penn state or Ireton-jones equations. However neither has been shown to be more accurate than the Harris-benedict equation (14).

Indirect Calorimetry

The gold standard for deriving nutritional requirement is indirect calorimetry due to its ability to calculate energy expenditure and thus the energy requirement. Indirect calorimetry involves the measurement of inspired and expired gas volumes, flows and concentrations of oxygen and carbon dioxide. It thus measures oxygen consumption and carbon dioxide production and calculates the respiratory quotient (VCO2/VO2). The abbreviated Weir equation is then used to calculate resting energy expenditure:

Resting energy expenditure= (3.94xVO2) + (1.1xVCO2)

Indirect calorimetry is not without shortcomings. Different monitors of indirect calorimetry produce differing estimates of energy expenditure (9). Results may also be inaccurate in the following settings: high fractional inspiratory oxygen requirements, intercostal chest drains, use of nitrous oxide, haemodynamic instability and ventilator modifications or disconnections (10).

TICACOS (the tight calorie control) trial was prospective, nonblinded, randomised controlled trial which evaluated indirect calorimetry vs. a fixed provision of 25kcal/kg/day. Evidence showed that patients whose nutrition was guided by indirect calorimetry received

a higher mean protein and energy intake than the control group. The intervention showed a trend toward reduced mortality (32% vs. 47%, p=0.058) but also showed a significant increase in the duration of mechanical ventilation (16.1±14.7 days vs. 10.5±8.3 days, p=0.03) and length of stay (17.2±14.6 days vs. 11.7±8.4 days, p=0.04) (13).

Table 1. Recommendations to Improve Indirect Calorimetry Measurements.

Step	Recommendation
1.	Adequate warmup of the calorimeter for some of the devices
2.	Precise calibration
3.	Eliminate patients with chest tubes, air fistulas, or other leaks
4.	Partial fraction of oxygen should be below .60 (<0.70 if using M-COVX; GE Healthcare, Helsinki, Finland)
5.	Patient should be stable without recent fluctuations in respiratory status
6.	Nitric oxide administration should preclude measurement
7.	No recent change in the setting 1–2 hours before the indirect calorimetry measurement
8.	Measurements are allowed if the patient is hemodynamically stable
9.	Measurements are allowed if temperature is stable
10.	Avoid measurements if the patient is ventilated with positive end-expiratory pressure >12.

(10)

Bodygem, an Indirect Calorimeter

WHAT SHOULD I FEED?

The three macronutrient groups include proteins, fats and carbohydrates. Daily calories are estimated using one of the methods mentioned above i.e. derived equations or indirect calorimetry. Protein requirements are subtracted from total energy requirements to determine the non-protein energy requirement. One gram of protein provides 4kcal of energy. Non-protein energy is divided amongst carbohydrates and fats with the usual division being 60% carbohydrates and 40% fats. Carbohydrates provide 4kCal/g and fats 9kCal/g.

Protein requirements

Protein requirements vary from 1.3-1.5g/kg/day for moderate stress to 1.5-2g/kg day for severely stressed patients (burns, albumin<21g/dl) (17). Protein is considered the most important macronutrient in the critically ill; it has an essential role in maintaining skeletal muscle function and mass, sustains the immune system and has a significant role in the healing of wounds (17). The ICU patient thus has a greater requirement for protein then the normal population. Methods to determine adequate protein intake are currently not available. Nitrogen balance may be used as a substitute. Nitrogen acts as a surrogate for protein as nitrogen is a component of amino acids and urea. Nitrogen balance is the net balance between intake and output, with the nitrogen equilibrium generally noted to be +/- 4 to 5g/day. There are limitations to this method of protein measurement as protein redistribution cannot be accounted for. Nitrogen loss is measured by urinary urea nitrogen content. Unfortunately total urinary nitrogen content cannot be analysed by most laboratories. Thus 2g/day is added to account for non-urea urinary nitrogen loss; an additional 2g/day is added for other losses including insensible, gastrointestinal and integumentary losses. Disappointingly this still underestimates the nitrogen loss in the critically ill as non-urea nitrogen losses (ammonia, creatinine, uric acid and amino acids) increase in these patients. Additional GIT losses may also occur in diarrhoea and patients

with thermal injuries will have increased integumentary losses. In addition, there is a lack of large prospective randomised trials evaluating nitrogen balance therapy. Lack of evidence and the fact that it is a non-practical measurement means that simpler weight-based equations are frequently used instead (16). Biochemical measurement of serum protein like albumin, prealbumin, and transferrin have not been validated for determining adequate protein intake and thus should not be used in such a manner (12).

Carbohydrate requirements

ESPEN recommends 2g/kg of glucose per day. It should be noted, there is no definitive evidence that carbohydrates are essential nutrients (15). Glucose maybe synthesised from amino acids, lactate and glycerol in the liver and kidneys and thus the exogenous need for glucose is questionable. Carbohydrates, however, are seen to be an innocuous, cheap, an expedient source of energy and a good source of plant fibre. Carbohydrates also seem to have specialised properties including use in anaerobic metabolism, being a very efficient substrate in aerobic metabolism and providing Kreb Cycle intermediaries. It is also important to note that glucose is the primary energy substrate of cells lacking mitochondria including erythrocytes, renal medulla cells, many leukocytes and the transparent tissues of the eye. Brain tissue predominantly uses glucose as a substrate but lactate and ketones may be used as a substitute.

The ESPEN recommendation of 2g/kg/day can be based on the need for baseline glucose (50g) which is necessary to prevent ketosis; a further 100g is used by the brain daily and another 20-30g by non-CNS tissues. It is important to note if glucose is not provided, gluconeogenesis occurs via skeletal muscle catabolism which has a detrimental effect in ICU patients. Glucose therapy may also result in hyperglycaemia which is known to be proinflammatory and worsens infection and organ dysfunction (15).

Hypocaloric feeding

Arabi conducted the PERMIT trial which looked at permissive underfeeding (40-60% of caloric requirements) compared to standard enteral feeding (70-100% of goal) for 14 days while maintaining the same protein intake in both groups. There was no difference in the primary outcome of mortality at 90 days or any secondary outcomes (infection, ICU length of stay). It should be mentioned that most of these patients were young (mean age 51 years) and were not noted to be at nutritional risk (BMI 29.3) so the validity of this study in patients at increased nutritional risk is questionable (46).
It is noted if PN is used <20kcal/kg/day or 80% of requirements is advocated (12).

Glycaemic control

ASPEN recommends targeting moderate glycaemic control with blood glucose of 7.7-10mmol/l. The VISEP trial (the efficacy of volume substitution and insulin therapy) looked at 535 patients in 18 ICUs and showed an increased incidence of severe hypoglycaemia and no mortality benefit in the tight glucose control group (19). The COIITTSS trial in 509 patients was a multicentre trial looking at Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock. The tight glucose control group showed more hypoglycaemic

episodes and trend towards higher mortality (20). Finally, the NICE-SUGAR trial (normoglycaemia in intensive care evaluation and survival using glucose algorithm regulation) was a large RCT that compared tight glucose control (4.4-5.5mmol/l) vs. moderate glucose control (<10mmol/l). Patients in tight glucose control group had higher risk of death at 90 days (27.5% vs. 24.9%, p=0.02).Taking all this evidence into account current recommendations are for moderate glucose control with a value of less than 10mmol/l

Lipids

Fatty acids form part of the essential macronutrients. Many can be synthesised in body but linoleic acid and alpha-linoleic acid need to be sourced exogenously. These essential fatty acids are found in plant and animal-based products. The plant-based sources include corn, sunflower and soya beans. These plant-based fatty acids are metabolised into omega 6 (arachidonic acid) and omega 3 (eicosapentaenoic acid {EPA} and docosahexaenoic acid {DHA}) fatty acids. Fish oils contain both omega 3 fatty acids (17).

Omega 3 appears to be helpful as a constituent of cell membranes and as an immune modulator and an antinflammatory. In 2011 Rice et al, conducted a double- blinded, multicentre RCT, evaluating the use of omega 3-enriched enteral nutrition in acute lung injury. The study was stopped early due to futility. The primary outcome was ventilator-free days and they concluded that patients receiving omega 3 had fewer ventilator-free days (14 vs. 17.2; p=0.02) but a trend towards higher mortality was also noted (26.6% vs. 16.3%, p=0.054) (21). In a systematic review in 2014, Chen et al reported that omega 3 supplementation had no significant effect on mortality [RR 0.82, 95% CI (0.62-1.09), p=0.18] (22).

ASPEN thus does not recommend the use of enteral formula enriched with omega 3 in patients with ARDS/ALI or medical patients while consideration maybe made for surgical or patients with traumatic brain injuries.

Prebiotic and probiotics and rationale for usage

In the critically ill there is rapid invasion of the gastrointestinal tract with pathogenic organisms. This is encouraged by multiple factors including the use of broad spectrum antimicrobials, gut ischaemia and reperfusion, stress ulcer prophylaxis, use of vasopressors, and reduced or absent enteral feeding. This pathogenic invasion has been linked to GIT infections resulting in diarrhoea and impaired nutrition, bloodstream infections, nosocomial pneumonia and VAP (ventilator associated pneumonia). Mechanisms for VAP include frequent micro-aspiration which occurs in intubated patients.

Methods to combat this invasion include Probiotics, Prebiotics and Synbiotics

Prebiotics

Prebiotics are non-digestible, fermentable soluble fibre additives which promote survival of probiotics such as bifiddobacteria and lactobacillus. They have been linked to decreased diarrhoea episodes (12).

Probiotics

The World Health Organisation defines probiotics as “viable organisms that, when digested in adequate amounts, can be beneficial for health”. Probiotics that are administered are either bacteria or yeasts. Most commonly used probiotics include lactobacillus and bifidobacterium with different subtypes being used. Common yeasts that are utilised include saccharomyces.

Methods by which probiotics function have been postulated to include: acting as a competitive inhibitor to pathogenic strains, inducing release of bacteriocins to inhibit microbial growth, generating antioxidative effects, stimulating mucus production, potentiation of antigen degradation, suppression of immune cell proliferation, modulation of apoptosis of epithelial cells, and immune modulation (25). However, there seems to be a lack of compelling evidence as to whether there is a benefit in the ICU patient. This therapy is noted to not be benign as blood stream infections of lactobacillus rhamnosus and saccharomyces boulardii have been identified (26).In fact in a systematic review by Watkinson et al, including 8 RCTs with 999 patients, there was no significant change in length of ICU stay, hospital mortality and nosocomial infection rate(26). This was later reassessed in a meta-analysis by Barraud et al which looked at 13 trials of 1439 patients. They showed that probiotics did not significantly reduce ICU mortality (OR, 0.85; 95% CI, 0.63-1.15) or hospital mortality (OR, 0.90; 95% CI, 0.65-1.23) however it did reduce ICU-acquired pneumonia (OR, 0.58; 95% CI, 0.42-0.79) (27).

Synbiotics

Synbiotic is the term used when probiotics and prebiotics are administered together.

Currently ASPEN guidelines suggest usage of prebiotics as a soluble fibre supplement in all haemodynamically stable patients on enteral feeds; their rationale included a small study of patients with SIRS and feeding intolerance, whose stool analysis showed lower amounts of anaerobes including commensal organisms (23). ASPEN does not make a recommendation for the usage of probiotics in the general ICU population, but says that consideration of usage in selected patient populations (trauma, pancreatectomy and post liver transplant) can be undertaken as safety and benefit is better established.

Immunonutrients

Antioxidants

Antioxidants include vitamin C, vitamin E, vitamin A and trace elements such as zinc, copper, selenium and manganese. Critical illness is a proinflammatory state resulting in widespread oxidative stress and cellular dysfunction. Reactive oxygen and nitrogen species are formed which overwhelm the innate antioxidant supply. This inflammatory response can result in multi-organ dysfunction, organ failure and death. Trace minerals are required for the action of glutathione peroxidase and superoxide dismutase which directly counteract free radicals (28). Vitamin C is able to decrease the formation of, as well as scavenge, oxygen free radicals. It allows preservation of the endothelial glycocalyx and plays a focal role in immune system defence (29). Critical illness is associated with low levels of all these antioxidants due to prior malnutrition, haemodilution, increased capillary permeability and possibly due to renal replacement therapy.

ASPEN advises use of antioxidants in certain patient populations although it does concede that evidence quality is low for this recommendation. They looked at 15 trials and found a reduced mortality (RR=0.8; 95%CI 0.7-.092; p=0.001) (12). Manzarnares et al conducted a meta-analysis including 21 RCTs which focused on antioxidant minerals. They looked at combinations of copper, manganese, zinc, iron and selenium and excluded studies containing glutamine and arginine. A significant mortality reduction was noted (RR=0.82 95%CI 0.72-0.93; p=0.002) as well as a reduction in duration of ventilation (weighted mean difference in days=-0.67, 95%CI -1.22 to-0.13, p=0.02). A subgroup analysis was completed regarding the effect of selenium but here there was only a trend toward a reduction in mortality (RR=0.89; 95% CI 0.77-1.03 p=0.12) and infections (28).

ESPEN recommendations with regard to antioxidants suggest that all parenteral nutrition should include daily allowances of trace elements.

Glutamine

Glutamine is a conditionally essential amino acid, meaning that it becomes essential in critical illness. It is the preferred energy source of enterocytes, lymphocytes and neutrophils. Glutamine usage increases during critical illness, this results in an impaired response to infection when glutamine stores are low. Lower glutamine levels have been associated with higher mortality rates (12). Supplementation is thought to maintain gastrointestinal integrity and ensure a more robust immune response. Initial trials showed promising results with regards to mortality and infection reduction, however, recent trials showed contrary results. The REDOX (Reducing deaths due to oxidative stress) trial looked at 1223 critically ill patients. It was a multi-centre RCT with a 2x2 factorial design and divided patients into 4 groups: placebo, glutamine (parenteral and enteral), antioxidants and lastly glutamine and antioxidants. They found a trend towards increased mortality at 28 days in the glutamine group (OR1.28 95%CI 1.00-1.64; p=0.05) and significantly higher in-hospital mortality and mortality at 6 months (29). Criticisms of this trial include: high dose glutamine used in both enteral and parenteral routes, feeding of unstable patients and glutamine supplementation in patients in hepatic and renal failure. The METAPLUS trial(High-Protein Enteral Nutrition With Immune-Modulating Nutrients vs. Standard High-Protein Enteral Nutrition and Nosocomial Infections in the ICU) found no significant difference in new-onset infections and a significant increase in 6 month mortality in the medical subgroup in the immune-modulating arm (54% vs. 35%;p=0.04) . Of note METAPLUS looked a combinations of glutamine, arginine, omega 3 fatty acids, selenium and antioxidants (30).The SIGNET trial (Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients) showed no difference in usage of glutamine across all clinical outcomes.

ASPEN currently suggests glutamine should not be used routinely in critically ill patients. While ESPEN, which is a slightly older guideline, supports use in burn patients. This is based on a small RCT by Garrel et al.

HOW TO FEED

Parenteral Nutrition (PN) vs. Enteral Nutrition (EN)

Beneficial effects of enteral nutrition include continuation of the physiological process of feeding, allowing the gut to digest food. It also supports structural and functional integrity of the GIT. Its advantages as compared to parenteral nutrition include its significant economic benefit and that it does not require invasive central line access. The incidence of pneumonia and infection has been shown to be reduced in enteral nutrition. Six meta-analyses compared EN and PN. Significant reductions in infectious morbidity with EN use has been demonstrated however other outcomes such as mortality and length of stay were not significantly different.

If adequate EN (>60% of energy and protein requirements) is not established within 10 days following admission, supplementation with PN is advised. Parenteral nutrition should be withheld in patients at low nutritional risk (NRS 2002 <3, NUTRIC <5) in the first seven days if enteral nutrition is not possible. In high risk patients (NRS >5, NUTRIC>5) PN should be commenced as early as possible following ICU admission.

Gastric vs. jejunal feeding

While the rate of pneumonia has been less with jejunal feeding, the quantity of feed tolerated is the same via both routes.

Guidelines differ with ESPEN recommending use only after intolerance to gastric feeds or when jejunal tubes may be placed easily i.e. post abdominal surgery. ASPEN recommends the usage of jejunal tubes in patients noted to be high aspiration risks. However it is important to note that the most pertinent measure against aspiration is to ensure 35-40 degree head-up tilt.

WHEN NOT TO FEED

Haemodynamic instability

Feeding during periods of haemodynamic instability is not recommended as there is an increased risk of ischaemia and reperfusion injury to the bowel. However patients who are on chronic stable low dose vasopressors may continue or proceed with nutrition, with caution. Feeds should not to be instituted or continued when mean arterial pressure is less than 50mmHg or when escalating doses of catecholamines are necessary.

Gastric residual volume (GRV)

Estimating feed tolerance can be a complex process especially in ICU. It involves the absence of abdominal distension, the passage of flatus and stool as well as confirmatory radiological studies. Feed intolerance can thus be estimated by opposing findings as well as the presence of diarrhoea, high gastric outputs and high gastric residual volumes.

It has been noted that feeding interruptions secondary to perceived feed intolerance (as measured by gastric residual volumes) is significant and resulting in 33% of total

interruptions. The justification for measuring gastric residual volumes involves the apparent correlation between GRV and regurgitation leading to aspiration and pneumonia.

ASPEN states that no such correlation exists and even GRVs of 250ml did not correlate to the action of gastric emptying itself. They concluded that even when GRVs are substantial it does not increase any adverse outcomes and that measurement of GRVs leads to increased rates of tube obstruction, wastage of nursing time and most importantly inappropriate stoppage time leading to significantly less EN delivery.GRV should therefore not be used to estimate feeding intolerance.

HOW TO MONITOR FEEDS

Enteral feeding protocols

Nurse driven protocols enable greater nutritional delivery. Daily volumes should be targeted and if goals are not met, increased rates for short periods or bolus feeds should be instituted to prevent undernutrition.

Prokinetics

Delayed gastric emptying is a common feature of ICU patients (32-34). Prokinetics like erythromycin (3-7mg/kg/day) and metoclopramide (10mg 6hrly) have been shown to decrease GRVs and possibly feeding intolerance (35). Feeding intolerance is associated with worse outcomes secondary to malnutrition. However important clinical sequelae such as mortality and infection rate are not affected by this intervention and neither of these drugs are innocuous (12). Adverse effects with erythromycin include cardiac arrhythmias, QT prolongation, hypotension, antibiotic resistance and tachyphylaxis. While the maximal length of use of metoclopramide is 12 weeks as licensed via the FDA (US food and drug administration), the EMA (European medicines agency) suggests usage for only 5 days, due to neurological adverse effects including convulsions, dystonia, dyskinesia, and extrapyramidal effects (35). It may also cause QT prolongation. Alternative prokinetic agents have been studied; this includes experimental work in use of naltrexone and naloxone, which is thought to directly counteract the effect of opioid-induced gastroparesis. Use of prokinetics in ICU patients with feed intolerance is thus supported but surveillance for potential serious adverse events should be undertaken.

ICU POPULATION SUBSETS

Pulmonary failure

Nutrition in respiratory failure requiring ventilation concentrates on altering the ratio of energy delivery to provide higher fat to carbohydrate ratios. The theory behind this is that due to the differing respiratory quotients of the two fuel sources, a diet high in fat would produce a lower CO_2 which would be helpful in patients with problems of CO_2 retention. Unfortunately this theory has not be shown to be a feasible one as CO_2 production does

not appreciably increase depending on the energy source if feeding demands are met and it is only when overfeeding occurs that CO_2 production increases to significant amounts.

Energy dense feeds are advocated in patients with fluid overload, including those in respiratory failure complicated by pulmonary oedema. Energy dense feeds have a higher kCal/ml (1.5-2 kCal/ml) then normal feeds (1kcal/ml).

Renal Failure

Use of specialised enteral nutrition (low in potassium, phosphate) in patients with renal failure may be of use but standard feeds have also been advocated, if electrolyte abnormalities are not problematic. Patients on renal replacement therapy have higher protein requirements due to higher protein losses and thus protein intake should be increased to an upper limit of 2.5g/kg/day. Protein should not be withheld from patient at risk of renal failure in hopes of decreasing incidence as evidence has not bourne out this theory.

Hepatic Failure

If energy requirement equations are being used to determine nutritional goals, care needs to be taken when it comes to the patient with hepatic failure as these patients are often fluid overloaded and feeds should be calculated using premorbid weight or anthropometric measures. Protein restriction to reduce the possibility of hepatic encephalopathy is unnecessary and detrimental (24). The utilisation of Branched-Chain Amino Acid (BCAA)-enriched formulae in patients with hepatic encephalopathy is controversial as, while it may improve clinical outcomes in advanced cirrhosis, when compared to other therapies to prevent hepatic encephalopathy (lactulose and antibiotics) it does not seem to have an additive effect (12, 36). Enteral nutrition is preferred over the use of TPN as TPN may increase adverse hepatic effects.

Acute Pancreatitis

Energy requirement in acute pancreatitis can fluctuate depending on severity and stage of the disease. Frequent reassessment is needed to meet the metabolic demands of the patient (12). Enteral nutrition is advocated in these patients as first-line therapy but if not tolerated PN may be used. ESPEN supports the use of glutamine when parenteral nutrition is needed. If TPN is used best practice recommendations support lipid infusions but advise to temporarily withdraw if persistent hypertriglyceridemia ensues (>12 mmol/l). Patients with severe pancreatitis have discernable micronutrient insufficiencies but presently there is inadequate evidence to support supranormal micronutrient supplementation (37).

Surgical Patients

Immune modulating formula may be considered in traumatic brain injury and general trauma patients. A meta-analysis by Marik et al involving 372 trauma patients, found no difference in those receiving immune-modulating formula and standard nutrition in with regard to infections, hospital length of stay and mortality (38).

Patients with open abdomens have increased protein needs as loss occurs via the high protein exudate from the large open abdominal wound (39).

Burns

Burns patients require high protein due to high protein loss from injured dermis (40). Early feeding (within 4-6hours of injury) is advised by ASPEN (12) this is based on numerous small trials in which beneficial effects range from lower catecholamine and glucagon levels (41), lower endotoxin and TNF alpha concentrations (42). A study by Vicic et al looked at 102 burn patients on early oral diet and showed significant decreases in pneumonia and sepsis (43), although it must be mentioned that this effect was not seen in the previously mentioned studies. Small studies show promising results with regard to enteral glutamine supplementation and thus this should be considered (12).

Sepsis

Immune modulation in sepsis appears to be detrimental and use is not advised (11, 12).

Terminal Nutrition

Once care is deemed futile or terminal a decision regarding continuation of nutrition is required. No evidence exists in this subset but it is noted that the use of artificial nutrition and hydration is not mandatory and in some instances may prolong suffering and cause distress. Treatment should be individualised and liaising with family is of paramount importance.

CONCLUSION

Nutrition is vitally important to clinical outcomes in ICU. A great disparity lies in the fact that this intervention is frequently neglected, as other components of critical care, such as haemodynamic and respiratory support, are deemed more important. (45). It is often easy to overlook nutrition as poor nutrition has insidious and often late consequences. Patients post discharge from ICU report marked morbidity relating to poor and undernutrition in hospital. Ensuring patients receive appropriate nutrition, early nutrition and have minimal stoppage times (in terms of feeding) is of fundamental significance and concentration on variables that oppose this is paramount.

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