The impact of nutrition in the acutely ill patient

This symposium explored the role that proper nutrition can play in the care of acutely ill patients following trauma, sepsis or the effects of major surgery. The meeting, which was held at the 2014 European Society of Intensive Care Medicine (ESICM) congress was chaired by Professor Rupert Pearse (Barts, London School of Medicine and Dentistry) and Professor Jean-Daniel Chiche (Paris Descartes University). All types of acute harm are characterised by inflammation which is often followed by a decline in organ function and increased mortality. Speakers at the symposium looked at the link between nutrition and outcomes in acutely ill patients, with a particular focus on those staying for extended periods in the ICU, and those with traumatic brain injury. The available evidence in this area overwhelmingly points to the role that proper nutrition can play in minimising long-term damage and improving outcomes in patients who experience a traumatic event.

Nutritional interventions improve QoL

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Significant acute inflammation is a common factor in all types of acute harm whether it is caused by trauma, sepsis, surgery or disease. As clinicians, we spend a lot of time managing inflammation and its consequences, as well as the acute event, yet our knowledge of the underlying processes is still not complete. Molecular biology is constantly evolving and developing tools to understand the long-term consequences of inflammation. One of the most convincing theories suggests that patients who do not make a simple recovery from injury suffer from a prolonged, dysregulated immune-inflammatory state.1

In a US study investigating surgical mortality in Medicare hospital, it was found that mortality 30 days after discharge for surgical procedures, without re-hospitalisation, was 2%. At one year the mortality rate had doubled to 4%.2 It is clear that there can be appreciable mortality after discharge even though the patient appears to have made a full recovery.

The morbidity associated with surgery may not always be easy to identify. In the VISION study (Canada 2012) investigating recovery from non-cardiac surgical procedures, peak post-operative fourth generation troponin T (TnT) was measured in around 15,000 patients in the first three days after surgery.3 It was found that mortality 30 days after discharge, without re-hospitalisation, was 1.9% in the whole group and was significantly associated with peak post-operative TnT measurement. Myocardial injury following non-cardiac surgery is clearly occurring even in the absence of clearly diagnosed myocardial infarction (MI) or other cardiac events.4

The process of surgery itself causes the myocardium to leak, implying that it has suffered an insult. The mortality associated with these troponin elevations is actually greater than for patients that present to hospital with acute chest pain. Although it is difficult to understand why this takes place, a likely explanation is that the elevated troponin is related to the significant inflammatory response caused by surgery. The risk from inflammation is not confined to the site of injury; the acute period of inflammation is also known to cause injury to other organs such as the lung, gut, kidney and liver. A whole range of organ systems and conditions such as acute lung injury, delirium, sepsis related myocardial injury and muscle function can be affected by the period of acute inflammation the patient experiences during surgery, trauma or other stress.

Even though a patient may survive a complication, an acute event such as a wound infection experienced in the ICU can subsequently bring about a dramatic reduction in long-term survival.5 The way in which patients are managed in the ICU can have an impact which lasts for many years: it is possible to see a continued separation in survival curves up to 15 years after the initial intervention.6 Although the intervention itself is bound to have an effect, survival is also strongly affected by the occurrence of complications.

To study these phenomena in more detail it is useful to look for example at patients with acute kidney injury (AKI) as this is an area where there is a lot of good quality data. Although it may seem obvious to state that patients with more severe AKI are much more likely to progress to chronic kidney disease it may be less obvious that AKI is one of the most important causes of chronic kidney disease. The stepwise deterioration in kidney function with continued acute events, leads to a corresponding stepwise loss of nephron and kidney function until the patient becomes dependent...
on external haemodialysis. As long-term patient well-being cannot be divorced from acute episodes we do need to think more carefully of the long-term effects of an acute complication.

Acute episodes of kidney injury steadily reduce not just renal function but also survival with an incremental increase related to the level of injury.1 The effect of kidney disease is confined not just to the kidneys, but also has a powerful impact on cardiovascular health. Long-term mortality following cardiac surgery is strongly affected by kidney health2 and it has been shown that long-term coronary events can be significantly affected by underlying kidney disease.10

Rising insulin levels secondary to the stress, and insulin resistance negate the ability to mobilise adipose stores, leading to catabolism following utilisation of stores of carbohydrate. Muscle serves as the source of gluconeogenic substrates for gluconeogenesis in the liver to preserve the function of the brain, red blood cells and parenchyma. In these highly catabolic patients there is a “perfect storm” with multiple mechanisms operating to break down lean body tissue: the patient is traumatised, hyper-dynamic and immobilised. Simultaneously there is a decrease in synthesis of muscle protein as amino acid substrates are diverted to gluconeogenesis, while multiple separate cellular mechanisms break down lean tissue.13,14

However, providing adequate protein feed does not appear to completely reverse the situation. A study looking at tissue loss found that within 10 days of admission of hyper-dynamic ventilated patients to the ICU, 10% of the cross-sectional area (CSA) of the rectus femoris muscle had been lost, along with 17.5% of the CSA of muscle fibres following biopsy and the ratio of protein to DNA decreased by 29%.15

Inactivity is associated with an “anabolic resistance” to essential amino acids (EAA): immobilisation of one leg in healthy volunteers induced a 27% decline in post-absorptive myofibrillar protein synthesis. Infusion of additional amino acids reduced the decline but did not abolish it.16

Despite general agreement that energy and protein deficits are associated with poor outcome, there is less consensus on patient selection, timing and amount of feed. Current thinking suggests that where possible enteral feeding should be employed due to the additional non-nutritional benefits that accrue, including maintenance of gut integrity, early immune benefits and attenuation of the metabolic response to stress.17 In the gut, mucosal atrophy is prevented, as is loss of the gut barrier while normal growth of gut bacteria is maintained.

Enteral feeding appears to have systemic effects: the inflammatory response to stress is attenuated as enteral delivery activates the cholinergic anti-inflammatory pathway.18-21 Activation of vagal efferents through a cholinergic mechanism results in down-regulation of pro-inflammatory cytokine mediators in the gut wall. Enteral feeding also attenuates the hyper-dynamic response to endotoxaemia. Healthy volunteers who were given a purified E coli endotoxin as well as a high protein, high fat enteral feed showed a lowering of inflammatory cytokines, increase of anti-inflammatory cytokines and less mucosal damage compared to a fasted group.22

As the evidence base has increased, the clinical benefits of early EN have become more noticeable. Early meta-analyses found reductions in infection rate and length of stay, while the latest meta-analysis reports a decrease in mortality.23 Numerous prospective randomised studies also testify to the safety of early enteral feeding with most papers reporting 85% to 90% success.

The safety and success of early enteral feeding has been confirmed in the most challenging patients.23 In 100 ICU patients with open abdomen following surgery, time to closure was reduced along with the rate of pneumonia in patients fed immediate EN. Finally, ventilated ICU patients requiring pressors were found to benefit from EN given within the first 48 hours of admission, displaying lower mortality than those fed after 48 hours.25

A number of papers suggest there is little difference in outcome between full and trophic feeding. In a study of 1000 acute lung injury patients on mechanical ventilation, there was no difference in mortality, ventilator-free days, multiple organ failure, or infection between patients who achieved 85% of goal calories and those who received...
only 25%. Other studies in medical or surgical ICU patients also found no difference in mortality or length of stay between trophic and full feeding. Perhaps this suggests that in the first week, the non-nutritional benefits are of more benefit than the number of calories.

Regarding feed content, anti-inflammatory, immuno-modulatory and cytoprotective effects have been claimed for many agents but the most important compounds are probably EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid) and certain amino acids.

Berger et al (2013) investigated the role of fish oils in modulating the inflammatory response in patients undergoing open heart surgery. There was a trend to better SOFA and APACHE scores, improved glycaemic control, decreased lactate and IL-6 in the group receiving a 2-hour peri-operative infusion of fish oils.

We now know that DHA and EPA generate specialised pro-resolving mediators (SPMs) such as Resolvins, Lipoxins, Protecins and Maresins that promote the active resolution of inflammation through interaction with various cellular targets such as neutrophils, macrophages, dendritic cells, vascular smooth muscle cells and the endothelium.

There at least 17 SPMs which are endogenously produced by-products of the administration of DHA and EPA. Different series of SPMs act on different cell types, pre-resolving to different tissues – providing a possible explanation for the variable clinical responses reported in the literature.

The role of arginine has been controversial. Nitric oxide synthase (NOS) catalyses the breakdown of arginine to citrulline plus nitric oxide suggesting that arginine should not be used with septic shock patients or those with refractory hypotension as the additional NO would function as a vasodilator. However, this theory ignored the complexity of arginine metabolism and the tight regulation of NOS.

A number of clinical studies in sepsis demonstrated that a high ratio of arginine to ADMA (asymmetric dimethylarginine) increases cardiac output. Furthermore, no adverse effects were seen in sepsis. In eight ICU patients, different doses of IV arginine were associated with a net decrease in whole body protein breakdown, and there was no difference in gastric perfusion, PAP (pulmonary arterial pressure) or MAP (mean arterial pressure), while stroke volume increased, and arterial lactate decreased.

Arginine deficiency rapidly develops following injury or surgery due to an increase in arginase, therefore post-operative arginine deficiency must be remedied to avoid loss of T cell function. In persistent inflammatory / immunosuppression catabolism syndrome (PICS) there is a rapid rise of myelo-derived suppressor cells (MDSCs), the major producers of arginase, preventing maturation and proliferation of arginine and causing dysregulation of the immune system. Chronically critically ill patients can be locked into this syndrome with persistent inflammation and poor survival: 44% of patients aged over 60 in the ICU for more than 14 days will be dead within a year.

Finally, delivery of protein alone is not enough; multiple studies have shown exercise is also helpful in protecting LBM. Resistance exercise can help to improve muscle protein synthesis and restore protein balance, attenuating the loss of LBM in critically ill patients, even in the absence of nutritional supplementation.

We have to look at each individual patient, taking into account the severity of their injury, the haemodynamics and oxygenation, ongoing morbidities, tolerance and ability to exercise. Nutrition can improve outcome and decrease healthcare costs through reductions in DVTs, pneumonia, ventilator time, length of stay, mortality and infections while attenuating the metabolic response to stress. Specific nutrients appear to exert many beneficial effects but we are only just learning how these agents function.
Nutrition options in neurocritical care

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Patients in neurocritical care are critically ill by any accepted criteria. Traumatic brain injury patients (TBI) are also at the highest risk of delayed gastric emptying and feed intolerance, the incidence of which can be as high as 80%. Unfortunately a lack of good quality evidence has impaired the development of robust guidelines on the management of these patients.

Current Brain Trauma Foundation guidelines can only recommend that severe TBI patients receive nutritional support by day 7 of injury. While there is some data to indicate a reduction in mortality and morbidity with early nutrition there is a lack of guidance for the post-acute rehabilitation period.41

Acute brain injury patients typically have hyper-metabolic and hyper-catabolic responses related to the severity of injury (Glasgow Coma Scale). A large observational study in nearly 800 patients, unfortunately not included in guidelines, found a 30 to 40% increase in mortality for every 10 kcal/kg of cumulative deficit in the first 5 days after injury.42 This important finding should be investigated in a prospective trial.

Due to the lack of robust studies in this area, a recent systematic review of nutrition in TBI patients included non-randomised prospective studies as well as RCTs.43 Sixteen studies were included but most were under-powered to demonstrate real differences in endpoints such as mortality and functional recovery.

The comparison of early against delayed feeding was confounded by the poor tolerance in these patients to gastric enteral feeding. However, there was a clear signal in favour of early feeding regarding mortality, with older and non-randomised studies showing a greater treatment effect. Small sample size and date of publication increased the risk of over-reporting positive results.

The review also compared early PN with delayed EN and early PN with early EN in this population of brain injured patients. There was nothing to suggest that one regimen was better than any other and only a trend in favour of PN. Again, heterogeneity was associated with the year of publication with older studies being more heterogeneous. There was also no evidence favouring either type of feeding on the development of infectious complications.

There is little data to confirm how effective we are at delivering nutrition to these patients. A 2011 study looked at over 100 severe TBI patients with a potential of over 1000 feeding days and found that 88% of patients were fed by day 3, with enteral nutrition being used in 97%.44 However the nutrition goals were only around 33% of target. Gastric intolerance was the factor most commonly associated with unsuccessful nutrition.

Countries including Spain have produced their own guidelines for the management of neurocritical patients.45 These include recommendations for the proportions of calorie intake that should be supplied by glucose, fat and protein in order to meet the increased protein requirements of these patients.

Other issues to bear in mind include the use of anti-convulsant medications such as phenytoin, given that standard polymeric enteral preparations are known to affect the absorption of phenytoin.46 Previous practice was to interrupt nutrition for two hours before delivery of phenytoin. Kitchen et al (2001) maintain that the best approach is to use IV administration of phenytoin with daily monitoring and dose adjustment.47

TBI is also often associated with heavy alcohol consumption that in turn is associated with thiamine deficiency. In such cases, thiamine delivery should be commenced before carbohydrate in order to avoid precipitation of Wernicke-Korsakoff syndrome and severely impairing chances of recovery.48

There is on-going interest in other interventions such as omega-3 PUFA (poly-unsaturated fatty acids), glutamine, vitamin D and zinc therapy. These appear plausible but so far there has been no evidence to suggest they improve outcomes.49

Therapeutic hypothermia is commonly used along with sedation to manage acute brain injury. The on-going Eurotherm study aims to investigate the role of titrated therapeutic hypothermia in the management of intra-cranial pressure (ICP).

However, hypothermia – along with sedation and muscle relaxant – has a significant effect on nutrition requirements. Hypothermia can exacerbate gastric intolerance and high residual volume but a 2011 study suggests that even during hypothermia there is sufficient GI function to enable enteral nutrition to be absorbed without an increase in vomiting and that patients can achieve a positive feed balance.49

In the absence of indirect calorimetry the Harris-Benedict equation is used to calculate basal energy expenditure (BEE) in kcals per day. The respiratory quotient (RO) gives an indication of the substrate usage (fat, carbohydrate, protein etc). Ideally the body would metabolise fat rather than lean body mass (LBM) with an RO of around 0.7.

In a study of energy expenditure in ischaemic stroke patients treated with moderate hypothermia, indirect calorimetry was used to measure total energy expenditure (TEE) during three days of hypothermia.50 The ratio of TEE to predicted BEE decreased significantly during hypothermia by 25%, whereas the Q10 calculation would have predicted a 30% or 40% reduction in BEE for a 5 degree temperature reduction, suggesting that feeding based on calculations would increase the risk of underfeeding.

Sedation is necessary in therapeutic hypothermia. However, it has been established that the low energy expenditure seen in hypothermia is due only to the lower temperature and not sedation.51 On the other hand, sepsis significantly increases energy expenditure independently of fever.
Due to the massive increase in energy requirements that shivering brings about it is important to monitor and to try to prevent this where possible.\textsuperscript{52}

The optimal temperature for administration of therapeutic hypothermia is widely accepted to be about 350C.\textsuperscript{53} Beyond this, only a very modest further reduction in energy expenditure and oxygen consumption can be achieved. Oxygen delivery undergoes a linear reduction below 35 degrees. In this study, patients were heavily sedated to tolerate hypothermia and to prevent shivering. They were therefore receiving an additional 800 to 1000 kcal/s from the lipid emulsion in which the propofol sedative was delivered.

In conclusion, nutritional support is probably sub-optimal in neurotrauma and neurocritical care. Early initiation is recommended with the small bowel being used in preference to gastric feeding. The main challenge is to deliver EN because of the high risk of gastric intolerance and large residual gastric volumes. There is only weak evidence to suggest that PN may be preferable and if therapeutic hypothermia is to be used, the TEE may not be reduced as much as standard equations would predict.

**Nutritional challenges with long staying ICU patients**

In most institutions, patients who stay beyond 10 days in the intensive care unit consume a significant part, if not the majority, of the ICU budget, yet their nutritional needs have not been well characterised.

When muscle data from various studies carried out by our working group was aggregated it was clear that the protein:DNA ratio varied widely even in healthy volunteers, but long-stay patients in particular, experience a huge loss over time. The main nutritional goal in these patients is to attenuate losses in lean body mass (LBM). Unfortunately guidelines are not helpful in making decisions on nutritional interventions, as they have largely been constructed with the small bowel being used in preference to gastric feeding. The main challenge is to deliver EN because of the high risk of gastric intolerance and large residual gastric volumes. There is only weak evidence to suggest that PN may be preferable and if therapeutic hypothermia is to be used, the TEE may not be reduced as much as standard equations would predict.

In the Krishnan study (2003) comparatively few individuals were available after two weeks: 45 compared to 187 at the beginning.\textsuperscript{56} The conclusions may therefore be more applicable to short- than long-stay patients. The EPaNIC study found no difference in mortality rates related to the route of administration of nutrition but it is difficult to apply these results with confidence to long-stay ICU patients as, after two weeks only 350 patients remained in each group from a starting point of over 2000.\textsuperscript{57} A similar problem arose with the EDEN study (2012) where the number of critically ill patients declined from nearly 500 in each group to 100 after two weeks.\textsuperscript{58} Similarly, in a study by Doig et al (2013) on the role of early parenteral nutrition in critically ill patients, the original cohort declined by over 50\% to 300 patients by day seven.\textsuperscript{59} In the Scandinavian Glutamine Trial (2011) fewer than 50 of the original 200 patients were still in the study by day 14.\textsuperscript{60}

None of this should be taken as a criticism as it is very difficult to predict at an early stage which patients in the ICU will be there for a long period, and to monitor their nutrition accordingly.

As this brief review demonstrates, the past decade has generated evidence for the role of nutrition in the ICU patient, but the long-stay patient is still poorly characterised, making it difficult to take evidence-based decisions on nutrition after the first one or two weeks. This is all the more surprising since these patients consume a significant proportion of hospital and ICU resources.

Units should attempt to assess their long-stay patients and their response to nutrition. Expensive equipment is not necessarily required; in the absence of indirect calorimetry energy expenditure in patients on mechanical ventilation may be roughly estimated by the CO2 production as reflected by the end-tidal CO2 if stable. Measurement of whole body protein turnover is not practical in routine clinical practice but studies can provide knowledge that is useful in the ICU. In a recent study it was found that healthy controls given total parenteral nutrition (TPN) moved from negative to positive protein balance as evaluated using leucine (Leu) and phenylalanine (Phe).\textsuperscript{61} Critically ill patients with multiple organ failure had a greater whole body protein turnover (synthesis and breakdown), if fed correctly, but the increase in synthesis and degradation was not uniform throughout the body.
In muscle, protein synthesis in critically ill patients is usually within the normal range of 1.25 to 2.25% per 24 hours, and the different fractions involved in muscle protein synthesis (myosin, actin and mitochondrial) tend to function at a normal level. The overall loss of muscle tends to be due to increased degradation of muscle fibres, usually via increased activity of the proteasome and lysosomal proteolytic systems. In critically ill patients, synthesis in the liver of albumin and other proteins is enhanced. In the presence of inflammation, overall plasma levels of albumin decrease, not because of a drop in synthesis but because of increased turnover.

In the absence of sophisticated equipment, the oxidation of protein can be used to assess whether patients are being fed adequately. In a feeding study on ICU patients (Berg et al 2013) isotopically labelled N nutrition was given to head trauma patients randomized to receive either 50% or 100% of measured energy expenditure during 24 hours. At the end of the period whole body protein turnover was measured using labelled d-5-Phe and 13C-Leu tracers. Whole body protein synthesis was lower during hypocaloric (50%) feeding but protein degradation and amino acid oxidation were unaltered, leading to more negative protein balance. In conclusion, long-stay patients are most likely to benefit from properly designed and delivered nutrition. However, at this stage it is not wise to uncritically rely on published guidelines as long-stay patients are not fully incorporated in the studies upon which they are based. Repeated assessments—including energy expenditure (easily measured through carbon dioxide elimination), protein status (urine analysis) and the status of vitamins and trace elements—are necessary to ensure that proper nutrition is being delivered for long-stay patients.

Guidance is hard to come by, but clinicians should take an interest in this group given the amount and proportion of resources these patients consume.