Review Article

Parenteral nutrition in adult intensive care

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Introduction

A healthy person deprived of food will starve to death in approximately 2 months; severe trauma or major surgery reduce that time to about one month. A loss of more than about 12% of total body nitrogen or of more than 33% of body weight is generally fatal. Lesser degrees of protein/calorie malnutrition, via respiratory muscle weakness, reduced hypoxic drive and decreased tissue oxygenation, contribute to postoperative pneumonia and difficulty in weaning from ventilators. Nutritional impairment of cardiac function and frank cardiac failure also occur. Bacteraemia from increased gastrointestinal permeability, decreased resistance to infection, and impaired wound and bone healing are concurrently disadvantageous. Although critically ill patients should benefit from nutritional support, the ideal constituents, timing and routes of intervention remain to be established. There is a dearth of major trials of intravenous nutrition in the critically ill, and inadequate appreciation of the changing metabolic status of patients at different stages of illness. In combination with the more obviously varying requirements between patients, these factors have resulted in discordant advice on nutritional intervention, and often in subsequent suboptimal management.^{1,2}

The nutritional physiology of the ITU patient

Patients in ITU (intensive therapy unit) belong to one of two broad metabolic groups.³ The first comprises cachectic, malnourished patients with decreased basal metabolic rate. They have elevated levels of glucagon and reduced insulin, and initially mobilize protein and fat to provide energy. Subsequently, ketones produced from fat become a chief source of energy. Their relatively modest nitrogen losses are critical as they are superimposed on already diminished body protein content.

The second group, with sepsis and/or organ failure, have high levels of circulating catechol-

amines and glucocorticoids compared to patients malnourished *ab initio*. An early nutritional 'ebb' phase – usually provoked by initial circulatory insufficiency – lasts 24–60 hours and is associated with relatively low circulating insulin and glucagon. It is followed (with resuscitation) by the 'flow' phase in which there is insulin resistance, and high glucagon levels. Energy expenditure and nitrogen excretion increase because of generalized catabolism despite a net increase in hepatic protein synthesis. Gluconeogenesis is accelerated and is not inhibited by exogenous glucose supplements. Ketogenesis is limited, particularly in comparison with the initially malnourished patient. There are complex changes in growth hormone, with abolition of normal cyclical oscillations, but often an elevated baseline level of an extent inversely proportional to age.^{4,5} Although this may be enhanced by nutritional support in the young, it is unaffected by feeding in the elderly and in obesity. As growth hormone is important in the promotion of lipolysis and the liberation of energy substrates, these changes have nutritional significance. It is probable that the indirect anabolic effects of growth hormone are mediated by insulin-like growth factor (IGF-1) which also attenuates the hyperglycaemic effect of growth hormone. IGF-1 levels are low in severe illness and are not affected by conventional nutritional support. Nitrogen losses in the flow phase may be increased further by low ambient temperature and inactivity. Active mobilization and work, for example, through physiotherapy, however, usefully conserve muscle protein.

Nutritional assessment and energy expenditure

The existence of nearly 200 different equations using clinical and laboratory parameters to assess the nutritional status of acutely ill patients attests to their shortcomings.⁶ Assessments by experienced observers using simple means will rarely be much improved upon by laboratory data. However, more precise measurements of nutritional requirements are needed if the most appropriate nutritional support is to be provided. Indirect (hood) calorimetry at the bedside provides accurate

and noninvasive data on basal and total energy expenditure. The several machines now available at reasonable cost should be used more widely.⁷

Septic and severely injured patients have been thought to have a resting energy requirement (REE) of at least 1.2–1.5 times their basal requirement in health, and severely burned patients perhaps more than twice basal levels. Use of indirect calorimetry at the bedside shows that this is rarely the case and that REE differs little from anticipated levels in health. Although energy expenditure does sometimes rise transiently by as much as 40% above basal, for example, during intermittent haemodialysis, total energy expenditure is normally only 5–10% above resting expenditure in ITU patients.⁸

Prolonged use of hypocaloric glucose as sole nutritional support of critically ill patients leads to glycogen depletion and utilization of fat as the principal energy source, and is reflected in a decrease in the respiratory quotient (RQ).^{*} However, when these patients are given hypertonic, hypercaloric glucose and amino-acid solutions, although the RQ rises, there is also an associated increase in oxygen consumption. This indicates that fat is still used preferentially but that an increasing conversion of glucose to glycogen occurs.^{9,10}

Moreover, generous provision of energy and amino acids may not allow endogenous protein preservation in catabolic patients. A careful study using a tritiated water dilution technique confirmed weight gain over a 10-day period, but despite an average gain of 2.2 kg of fat and/or glycogen there was nevertheless a mean loss of 1.5 kg (12.5%) of body protein (and a loss of about 12 litres of body water).¹¹

An increased dependence on lipid as fuel is characteristic of the seriously ill. Fat utilization is improved by administration of exogenous lipids, and it appears that a large carbohydrate load rather than improving nutritional support, may actually cause physiological stress by increasing energy expenditure. Excessive nutritional provision may prove just as harmful as short- to medium-term starvation. 'Hypermetabolic' ITU patients should accordingly have their energy requirements mea-

sured, and receive nutritional support comprising a balance of carbohydrate and lipid calories adjusted to their energy expenditure.¹²

The components of parenteral nutrition

Macronutrients

For the reasons outlined above, the conventional provision of 20–30% of non-nitrogen calories as fat should be amended to nearer 50% in intensive care practice. This change receives further support from the problems of insulin resistance and glucose intolerance which are found particularly in the early part of the ebb phase. Insulin is often given with carbohydrate and has some anabolic effect, but also permits glucose utilization for lipogenesis with subsequently increased CO₂ production (and potential respiratory acidosis). An increased fat:glucose ratio may be more beneficial than added insulin. It is reasonable to commence with an insulin-free regime in which fat constitutes 40% of total calories, but carbohydrate provision may thereafter be adjusted according to the patient's tolerance.

The ratio of nitrogen (in grams) to calories (in kcal) is conventionally set at between 1:100 and 1:150 and this will normally be appropriate. Convincing evidence for amino-acid regimes other than those generally available is lacking, but glutamine supplementation (see below, 'Specific agents to promote anabolism') may prove important. Nitrogen administration in hepatic and renal failure is also discussed below. Adequate levels of essential fatty acids will be provided by any regime which includes commercially available lipid solutions.

Electrolytes, trace elements and vitamins

Serum concentrations of electrolytes and trace elements are relatively easy to measure and correct, but the relationship between normal serum values of the latter and tissue needs is unclear and especially so in ITU practice. Potassium and calcium (measured daily) should be provided as necessary, as should magnesium, deficiency of which is often overlooked in patients with excessive gastrointestinal losses (fistulae, high jejunal stomas, paralytic ileus, etc). It is common to find that the serum phosphate falls (sometimes precipitously) in the first few days of intravenous nutrition; although this is mainly the result of shift into cells, it is potentially dangerous and should be anticipated – most ITU patients will need at least 33 mmol per day.¹³

It is reasonable to give estimated daily requirements of trace elements on a routine basis, using preparations such as Addamel and Additrace,

^{*}The respiratory quotient (RQ) is the ratio between CO₂ production and O₂ consumption, and reflects substrate use. Pure fat metabolism gives a respiratory quotient of 0.7. An RQ of 1.0 usually reflects 100% carbohydrate use, which also represents a 30% higher increase in CO₂ production and need for a 40% greater minute volume. Protein metabolism has little effect on the respiratory quotient. Lipogenesis increases the RQ, potentially up to 1.3. An RQ of greater than 1.0 therefore suggests that carbohydrate intake is in excess of energy needs.

without undue concern for monitoring unless parenteral feeding is necessary for more than 3–4 weeks.

Provision must be made for vitamin supplementation. Thiamine deficiency must be anticipated, especially when a relatively carbohydrate-rich feeding regime is utilized and when prior malnutrition is known or suspected; this is particularly important in the alcoholic who will have increased requirements as well as prior deficiency. Beri-beri and serious neurological toxicity precipitated by imperfect parenteral nutrition should be considered iatrogenic with the attendant medicolegal implications. No ideal vitamin supplements exist in the UK, but Multibionta® and Solivito N® given on alternate days, with Vitlipid N® daily, supply water- and fat-soluble vitamins, and are suitable for most patients. The vitamin A content of Multibionta is undesirable in patients with liver disease in whom Parentrovite® may be alternated with Solivito N (with advantageous increase in thiamine provision).

Specific agents to promote anabolism

The deficiency of IGF-1 and deranged growth hormone metabolism in critically ill patients has prompted their therapeutic use. IGF-1 levels can be increased by up to a factor of five, malnourished patients, those with liver failure or on a high fat regime perhaps needing IGF-1 rather than growth hormone alone. Early trials in septic critically ill patients suggest that large doses of growth hormone may decrease protein catabolism, enhance wound healing, improve skeletal muscle function, and accelerate recovery, without clinically obvious adverse effects.¹⁴ More definitive studies are awaited.

Glutamine, the most abundant circulating amino acid, becomes conditionally essential in the critically ill.¹⁵ Changes in the free glutamine pool may therefore contribute a disproportionate component to negative nitrogen balance, not helped by its current omission from commercial amino-acid solutions because of its instability. The reduced mucosal enzyme activity, increased intestinal permeability, villous atrophy, and presumably associated bacteraemia seen in patients on exclusive parenteral nutrition are incompletely explained. Animal studies have, however, confirmed that glutamine is a major mucosal metabolic substrate with a role in the promotion of intestinal integrity. The synthesis of stable glutamine-containing dipeptides has allowed therapeutic trial of glutamine supplemented parenteral nutrition. Permeability, and villous height are normalized. The most beneficial way to maintain gut mucosal integrity remains nonetheless the reintroduction of some element of enteral nutrition at the earliest opportunity.¹⁶

Supplemental branched-chain amino acids have not proved to be useful, while clear roles for short-chain fatty acids or ketoacids, and/or taurine remain to be substantiated.¹⁷

Administration

There is a good case for providing intravenous nutrition through peripheral cannulae if possible, given the infrequent but potentially serious mechanical complications of central lines. Peripheral fine-bore silicon lines now have a typical useful life of around 130 hours (3.5 times that of Teflon), and thrombophlebitis is minimized by avoiding solutions of high osmolality or low pH. Cutaneous vasodilator patches appear beneficial, but additional improvement from hydrocortisone or heparin in the infusions is absent or minor.¹⁸

For long-term intravenous feeding, and especially when a carbohydrate-based high osmolality, low pH feed is indicated, central venous feeding is required. Subclavian lines have significantly lower associated infection rates and last longer than lines placed in other sites. If, as is often the case, the patient requires other central venous access, a second venous entry site should be employed and multiple lumen lines avoided.¹⁹ The question of whether feeding lines in ITU should be tunnelled is as yet unresolved, although it is of definite benefit in parenteral nutrition in general. Even though the catheter's hub and not its skin (or vein) entry site seems to be the major focus of infection, we favour tunnelling whenever possible. Feeding lines, whether central or peripheral, should be entered as infrequently as possible and always using stringent aseptic techniques. Enteral feeding by mouth, nasogastric or percutaneous gastrostomy tube should be recommended as soon as possible.

It is important to be aware that the planned intake of nutrients is achieved on only 50% of ITU patient days, mainly due to logistic problems. A strategy needs to be devised to overcome this, and to ensure, when the feed is discontinued for any reason, that a 'catching up' period follows. Close liaison with and between members of an established nutrition team, including pharmacist, nutrition nurse, dietician and clinician, may be the key.

Metabolic complications of parenteral feeding

The glucose intolerance of the seriously ill may allow glucose-based intravenous nutrition to provoke hyperosmolarity and non-ketotic hyperglycaemic coma, and also rebound hypoglycaemia following its abrupt withdrawal. The lipid balanced

regimes discussed above avoid these problems and often do so without recourse to insulin.

Regimes with a major lipid component have been associated with hepatic, respiratory and renal toxicity, acute pancreatitis, thrombocytopaenia, coagulation disorders and depressed immune function. In the majority of patients the very clear advantages of lipid administration will outweigh the potential for (mostly idiosyncratic) adverse reactions. Not even in pancreatitis are there more than anecdotal data to support energy provision predominantly as carbohydrate. However, if any of the above develop whilst on parenteral nutrition, withdrawal of lipid should be considered at least temporarily.

Liver enzymes often rise after starting intravenous nutrition, typically reaching a peak at 1–4 weeks. This is usually the result of mild hepatic steatosis. In patients in whom energy provision has been based on measurement of requirements, this benign side effect probably stems from carbohydrate/nitrogen mismatch with subsequently decreased lipoprotein synthesis and intrahepatic accumulation of triglycerides. Other causes may include essential fatty acid and carnitine deficiency, and the absence of as yet unidentified dietary protective factors. However, the main cause of steatosis is still the provision of energy in excess of requirements (and/or of utilization capacity) in patients whose energy requirements have been estimated rather than measured. Protection from and treatment of steatosis is conferred by an isocaloric regime with *at least* 10% lipid calories. The use of supplementary glutamine and cyclical rather than continuous feeding are probably beneficial, and the reintroduction of enteral feeding is usually curative. Cholestasis is less common and in the ITU context is usually associated with multiple organ failure: exogenous lipids are not strongly implicated.²⁰

Specific conditions and parenteral nutrition in ITU

Renal failure

Nutritional regimes in acute renal failure are largely empirically based. Relatively low volume feeds of high-energy density (that is, lipid-containing) with restricted electrolytes as necessary, form a conventional approach. Excessive provision of nitrogen occasionally leads to hyperammonaemia and exacerbation of uraemia, but this is rarely a major problem. Amino-acid clearance is increased by dialysis (continuous or intermittent) and nitrogen restriction can then be relaxed to nutritional advantage. Calcium/vitamin D status requires particular attention.

Pancreatitis

Mild pancreatitis is not helped by intravenous nutrition, but in moderate to severe pancreatitis, intravenous nutrition (which does not stimulate pancreatic exocrine secretion) has an important therapeutic role.²¹ It should be started early and should include *at least* sufficient fat to provide the essential fatty acids. As soon as possible it should be replaced by enteral feeding ideally delivered distal to the ligament of Treitz.

Hepatic failure

In acute hepatic encephalopathy, short-term benefit in mental status is reported from branched chain fatty acids but meta-analysis reveals potentially increased mortality when increased proportions of branch-chain amino acids are given.¹⁷ As the gut is still functioning, enteral feeding is usually possible in patients with liver failure – even in those in the perioperative phase of transplantation – but when intravenous nutrition is necessary, some modification of standard regimes is required. Because of the avid sodium retention, an effectively sodium-free regime is needed; volume restriction can be safely accommodated by the use of lipid calories providing up to 50% of total energy.

Other conditions

Patients with the short gut syndrome will almost always require parenteral nutrition initially. The very major losses from high output stomas include sodium (best measured by measuring urine sodium levels) and magnesium, which need appropriate replacement. Fortunately, intestinal adaptation occurs. If more than 1.5 m healthy small bowel, or more than 1 m small bowel and residual colon remain, the early and persistent use of enteral feeding ($\pm$ glutamine) to maximize small intestinal absorptive function will permit the majority to be weaned from parenteral nutrition.

Immune-deficient patients often have an abnormal amino-acid profile and may be zinc and selenium deficient. As these alter *in vitro* immunological response it is logical to correct them. Lipid has been considered to impair immune response, but the benefit of a balanced intravenous regime almost certainly exceeds the theoretical hazard (which is probably avoided entirely by slow lipid administration).²² Patients can, however, usually be fed enterally in this context.

Intravenous nutrition in the acute phases of aggressive 'curative' chemotherapy for malignancy is questionable as there is inadequate understanding of how intravenous nutrition influences the impact of the chemotherapy. Parenteral nutrition generally prolongs but does not increase survival in

gastrointestinal malignancy and AIDS; use in this context is more an ethical than a nutritional issue.

Conclusions

Intravenous feeding regimes can be tailored to the needs of all critically ill patients, but this should not lead to neglect of the enteral route which is preferable whenever possible. Feeding regimes should be based on calculated energy expenditure. Catheter placement and care is of paramount

importance in preventing septic complications. Problems arising from intravenous nutrition are less likely if each unit has a formal protocol for intravenous nutrition supervised by a nutrition team; this is of proven cost-effectiveness.

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