Clinical nutrition

Artificial nutritional support - what are the options?

By A. Murphy, MSc, MRPharms and A. Scott, BSc, SRD

This month's special feature is on clinical nutrition. The first part discusses the indications for artificial forms of feeding and reviews measures intended to reduce complications which might arise. The second part discusses managing drug therapy in patients receiving enteral and parenteral nutrition.

Since the discovery of intravenous nutrition by Dudrick et al\(^1\) about 35 years ago, the ability to support life by artificial nutrition has developed considerably. In tandem with an increased understanding of the requirements and metabolism of both macro and micro nutrients, there has been an improvement in delivery systems, such that the safety and efficacy of nutrition support and its cost-effectiveness are now well established in certain patient groups.\(^2,3,4\) In spite of this, the incidence of malnutrition in hospitals is well documented, reports indicating an occurrence of 30 to 35 per cent.\(^5\) The King's Fund Report for 1992 demonstrated the cost benefits of treating malnutrition.\(^6\) Assuming 10 per cent of hospital admissions were properly fed, their hospital stay could be reduced by five days. This would represent a national saving of £266 million based on 544,000 admissions. The main findings of this report were that malnutrition increased morbidity and mortality and reduced quality of life.

Since the first line of nutritional intervention is oral diet, it would seem obvious that food provided should not only be palatable, but also meet the Health of the Nation nutrition guidelines for hospital catering.\(^7\) However, where oral nutrition is inadequate or not possible, the following questions can be helpful in determining if artificial nutritional support is indicated, and if so, what type:

- Does the patient have a functioning gut?
- Has the patient's intake been assessed by the dietitian, and is the patient able to meet his or her nutritional requirements?
- Has the patient lost 10 per cent or more of his or her body weight in the past three months?

If artificial nutrition is deemed to be necessary, it can be given enterally and/or parenterally, according to the situation.
**Nutritional assessment**

Basal metabolic rate (BMR) can be assessed by various prediction formulae, for example, Harris Benedict and Schofield. These are based on age, sex and the patient's weight. However they should be used with caution as they are based on an assessment of groups of healthy individuals. They also rely on the patient's weight which may be affected by oedema or ascites. Furthermore, modifications have to be made by the assessor for activity, stress factors (such as trauma and burns) and repletion, if indicated. This undoubtedly introduces observer bias.

In practice, the Schofield prediction formula is used and additional factors are added as appropriate. For example, in the estimation of the energy requirements for a 75-year old female, weighing 55kg, six weeks after a cerebrovascular accident, who has just started to mobilise but has no stress factors, then if:

<table>
<thead>
<tr>
<th>BMR calculation</th>
<th>1151kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress factor</td>
<td>&gt;Nil</td>
</tr>
<tr>
<td>Activity factor, 15 per cent</td>
<td>173kcal</td>
</tr>
<tr>
<td>Total daily energy requirement</td>
<td>1324 kcal</td>
</tr>
</tbody>
</table>

Her daily nitrogen requirements can be calculated if her catabolic status is known.12

<table>
<thead>
<tr>
<th>Status</th>
<th>Nitrogen requirements g/kg/day</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>0.17</td>
</tr>
<tr>
<td>Moderately catabolic</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypercatabolic</td>
<td>0.3</td>
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</tbody>
</table>

Estimated daily nitrogen requirements (assuming normal status) 9g

It is important at this stage to consider mitigating factors that could influence the assessment process. They include fluid losses which could be due to fistulae or diarrhoea. Other factors such as blood biochemistry and fluid balance should also be considered and it is at this juncture that a multidisciplinary team approach can be invaluable.

**Giving enteral feeds**

Enteral nutrition refers to nutrition support delivered via a tube to the patient's gastrointestinal tract.

Pump-assisted delivery is the administration method of choice and commencement with full strength feed at a low rate (25 to 30ml per hour) is standard practice at University College London hospitals (UCLH). A protocol for administration that is adopted as standard ensures delivery of prescribed feed.8 Table 1 shows some indications for enteral feeding. The choice between intermittent or continuous infusion should preferrably be
discussed with the patient, along with the nursing staff. The choice also depends on whether the patient is ambulatory and the quantity of oral intake. There is good evidence to suggest that overnight feeding can increase supplementary oral intake in the day by 50 per cent. This is a useful intervention when patients are being weaned off artificial nutrition support.

There are a number of feeding tubes available on the market and the choice is generally based on efficacy, cost benefit ratio and estimated period of feeding. For short term feeding, that is, up to two weeks, a fine-bore nasogastric tube is generally used and for longer term feeding, percutaneous endoscopic gastrostomy (PEG) tubes are the preferred option.

### Table 1: Diseases in which enteral feeding may be indicated

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Conditions</th>
</tr>
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<tbody>
<tr>
<td>Hypermetabolism</td>
<td>Major surgery, Sepsis, Trauma, Burns, HIV/AIDS</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>Cerebral vascular accident, Motor neurone disease, Multiple sclerosis, Head injury</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>Oesophageal obstruction, Inflammatory bowel disease, Short bowel syndrome, Pancreatic insufficiency</td>
</tr>
<tr>
<td>Cancer</td>
<td>Head and neck cancer, After chemotherapy or radiotherapy, Surgery</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>Anorexia nervosa, Severe depression</td>
</tr>
<tr>
<td>Organ system failure</td>
<td>Respiratory failure, Renal failure, Hepatic failure, Cardiac failure</td>
</tr>
</tbody>
</table>

*This table was adapted from Current perspectives in enteral nutrition in adults, BAPEN 1999*

### Types of enteral feeds

There is a wide range of feeds available on the market. For the most part, these are nutritionally complete and can be used as a sole source of nutrition. They provide protein, fat, carbohydrate, electrolytes, vitamins, minerals, trace elements and water. The standard polymeric formulae where the above nutrients are present in their intact form may be used for the majority of patients.
Diarrhoea is a complication of enteral feeding. It is a frequently cited problem associated with an incidence of 10 to 25 per cent and may necessitate discontinuing the feed (after eliminating drug therapy and infectious causes). There are some feeds on the market which are supplemented with soluble fibre, which has been advocated for the treatment of diarrhoea. The soluble fibre provides a substrate for colonic microflora to produce short-chain fatty acids. These fatty acids act in the ascending colon to promote absorption of water and sodium and therefore have a possible role in preventing diarrhoea. The recent development of feeds with fructo-oligosaccharides or prebiotics that are undigested in the small intestine but pass to the colon where they are fermented is another aid in preventing diarrhoea. Moreover, they also selectively promote the growth of bifidobacteria and therefore reduce colonisation by Escherichia coli and Clostridium difficile. Examples of these feeds are Jevity Plus and Fresubin Isofibre. There are also some feeds in which the nutrients are already hydrolysed, which means less enzyme activity may be required for digestion. Such formulae are indicated in short gut syndrome, radiation enteritis or malabsorption syndrome. Examples of such products are Perative, Emsogen and Peptamen. Other types of feeds have a modified mineral and electrolyte content (eg, Nepro, Suplena, Nutrison low sodium, Nutrison low protein low minerals) which may be useful in renal or hepatic insufficiency. Finally, there is a range of specialist feeds which are immunomodulating. They include Impact, Alitraq, Stresson and Reconovan. These feeds contain nutrients in pharmacological doses and are purported to confer immunological benefits to the host. They contain a range of nutrients, including glutamine, arginine, omega-3 fatty acids and antioxidants.

**Glutamine** Glutamine is a non-essential amino acid, which is used as a preferential fuel by enterocytes and cells of the immune system. It is believed that conditions of stress or trauma increase the requirement for this amino acid, thus rendering it conditionally essential. Most feeds contain 5 to 10g glutamine and this has traditionally been considered sufficient, but there is evidence to suggest that this dose is insufficient under conditions of stress.15,16

**Arginine** Like glutamine, arginine is an amino acid indispensable in growth and may be conditionally essential in post-traumatic situations. It is a hormone activator and precursor of polyamines (important in cell growth and in the differentiation of immune and gut cells). Arginine can also be metabolised to nitric oxide, which is implicated in a wide range of metabolic activities. At doses of 20 to 30g per day, arginine improves nitrogen balance, wound healing and immune function in healthy volunteers and surgical patients.17
**Nucleotides** These are precursors of DNA and RNA, carriers of genetic information which participate in a number of metabolic activities fundamental to cellular activity. It appears that rapidly dividing cells such as T-lymphocytes and intestinal epithelial cells lack the ability to synthesise nucleotides under conditions of stress. Supplementation has been shown to benefit T-cell and macrophage response to infection.\(^\text{18}\)

**Polyunsaturated fatty acids (PUFA)** These include the omega-3 and omega-6 PUFAs. These are essential components of cell membranes and dietary lipids influence the fluidity of these membranes. Any alterations in the fluidity of cell membranes could change the readiness with which cytokines bind to receptors, thereby influencing their activity.

**Omega-3 fatty acids** Derivatives of these PUFAs can decrease inflammatory responses, platelet activation and thromboxane production, while the omega-6 derivatives are pro-inflammatory. It is suggested that the ratio of omega-3 to omega-6 fatty acids in feeds can alter the types of eicosanoids produced by cells, thereby influencing the immune response.\(^\text{19}\) The evidence for the use of immune enhancing formulae is still debatable. In a large multi-centre trial of 326 intensive care unit patients, Bower et al failed to demonstrate any overall benefit from supplementation with RNA, omega-3 fatty acids or arginine. Within a smaller septic population he was able to demonstrate a decreased length of stay and a reduction in infections.\(^\text{20}\) Galban,\(^\text{21}\) in a later study, was able to demonstrate reduced mortality and infections using the same formula in septic patients. It is still unclear whether a combination of nutrients is more beneficial than one specific nutrient, and therefore these formulae should be used judiciously.

**Antioxidants** During stress or major trauma, it is believed that an overproduction of free radicals occurs as part of the inflammatory response. These free radicals are involved in bacterial killing but can also harm normal tissue. There could potentially be a benefit in providing antioxidants such as vitamins E, C, beta-carotene and selenium to counteract these effects. However, dosages and efficacy are still to be determined.

**Adult PN**

Parenteral nutrition (PN) is only indicated when there is intestinal failure. For the patient with a short bowel, the combined use of PN, intravenous fluid support, and enteral nutrition (EN) is a life-saving therapy. Patients with a jejunostomy or less than 100cm of jejunum and those with an intact colon but less than 50cm of jejunum or ileum usually require PN for life.\(^\text{22,23}\) Options for nutritional support in clinical practice have recently been
Meta-analysis of prospective randomised controlled trials (PRCTs) suggest that in surgical patients, post-operative PN increases the absolute complication rate by 10 per cent, while preoperative PN reduces the absolute complication rate by 10 per cent, but at the expense of longer hospital stay.\(^{25}\)

A review of 26 trials of 2,211 patients comparing the use of PN versus standard care in critically ill patients failed to demonstrate that PN reduced the rates of complications or diminished overall mortality.\(^{26}\)

One of the largest studies, carried out by the Veterans Affairs total parenteral nutrition (TPN) co-operative study group,\(^{27}\) was able to demonstrate a significant reduction in post-operative non-infectious complications, from 42.9 to 5.3 per cent, in a small subgroup of severely malnourished patients given perioperative PN.

It is very easy to find flaws in most PRCTs.\(^{25}\) Klein pointed out that "the quantity and type of substrates given in past studies were not optimal by current standards; for example, calories were often given in amounts substantially greater than metabolic needs. Therefore it is possible that outcomes in many of these trials would be different if the trials were repeated using our present day understanding of calorific needs and other metabolic requirements in specific patient groups." In a recent editorial, Wilmore\(^{28}\) concluded that, in general, nutritional support only benefited a small group of malnourished hospital patients such as those with a recent weight loss greater than, or equal to, 13 to 15 per cent; and that conventional nutritional support did little for the stressed, normally nourished, or only moderately malnourished patient in the short term.

Since new, large PRCTs are likely to be very rare, it is important to adopt a sensible and pragmatic approach to the use of PN in nutritional support. The extent of starvation that can be tolerated without increased morbidity is unknown but it seems reasonable to initiate PN in patients unable to tolerate enteral feeding, and who are not expected to resume oral feeding for 7-10 days.\(^{24}\) The use of intradialytic PN in haemodialysis patients is now accepted practice, and seems to be associated with decreased mortality, but the data supporting its use is weak.\(^{29,30}\)

**The nutrition team** The role of the nutrition team in the delivery of nutrition support is well accepted. The safe and effective delivery of PN depends on the following:

- Insertion and care of IV lines by experienced and trained staff
- Proper evaluation and review of nutrient requirements
- Fluid management
- Proper compounding of the PN feed under aseptic conditions
- Knowledge of current drug therapy
- Knowledge of EN support
- Management of the home PN patient in the community
An effective team will be able to reduce the use of inappropriate PN. Most teams comprise a pharmacist, dietitian and nutrition nurse, with occasional support from a clinician and chemical pathologist. Practice varies from centre to centre: some teams will review all requests for PN; others will advise on difficult cases upon request. Specialist pharmacists or dietitians may take the lead within clinical directorates and liaise with pharmacists and pharmacy technicians in the aseptic compounding unit. Nutrition committees may be formed to review policy and evaluate audits. It is important that PN patients are reviewed regularly and the PN service is audited from time to time. At least one member of the nutrition team should visit the patient on a daily basis.

**PN administration** PN feeds can be given by peripheral or central line infusion. While it is possible to infuse feeds of high tonicity through central lines, the tonicity of typical peripheral PN would be less than 1000mosmol per kg of feed to avoid thrombophlebitis. Some centres have been able to infuse feeds of high tonicity through a peripheral line by adopting the following measures:

- Adding heparin 500iu per litre and hydrocortisone 10mg per litre to the PN feed
- Rotating sites of access
- Using the basilic rather than the cephalic vein
- Using a fine-bore cannula

The use of a 5mg GTN patch distal to the entry site is common practice to reduce thromphlebitis in peripheral PN. A recent ultrasonic study failed to demonstrate venodilation following the application of GTN ointment, thus challenging the commonly held view that GTN improves blood flow by dilating the vein. Fine-bore polyurethane cannulae are considered first choice in peripheral PN since they last longer and have a reduced tendency to occlude, compared with silicone. A trial comparing fine-bore catheter length 5cm versus 15cm showed no difference in risk of thrombophlebitis or extravasation. The practice at UCLH is to use a fine bore polyurethane catheter (Nutriline) of 30cm length and gauge 3Fr, for peripheral PN. Using a PN feed with an osmolality of approximately 900mOsmol/kg and GTN patches, such lines can last for up to five weeks.

Tunnelled Hickman lines continue to be used for the administration of PN through a central line. Such lines can remain in place for several years. Both polyurethane and silicone lines are acceptable for long term PN. More recently, peripherally inserted central lines (PIC lines) have been used for PN administration. While PIC lines are not associated with increased line sepsis or risk of thrombosis, one study demonstrated an increased incidence of local complications such as leaking catheters, phlebitis, and malposition.

PN requirements The provision of "sensible" amounts of nutrients to
support the patient until sufficient oral or enteral feeding can be established could be described as the mission statement for PN therapy. The word "sensible" captures the well accepted view that overfeeding, particularly in the critically ill or stressed patient, can do more harm than good. A commentary from the USA predicts a move towards hypocaloric and hyperproteic feeding in the critically ill patient. Glucose loads have tended to be higher in the USA whereas, in Europe, patients routinely receive non-protein energy as both fat and glucose, thereby lowering the glucose load. Baseline amounts are presented in Table 2. (NB: The amounts of electrolytes and final volume of PN will vary depending on concurrent fluid and drug therapy, allowance for oral and enteral intakes, and the requirement to replace body fluid losses.)

Table 2: Baseline adult PN requirements

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>PN amount (per kg body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen</td>
<td>0.2g</td>
</tr>
<tr>
<td>Non-protein energy as glucose* and fat</td>
<td>30kcal**</td>
</tr>
<tr>
<td>Sodium</td>
<td>1.5mmol</td>
</tr>
<tr>
<td>Potassium</td>
<td>1mmol</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.1mmol</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.1mmol</td>
</tr>
<tr>
<td>Phosphate (including lipid)</td>
<td>0.5mmol</td>
</tr>
<tr>
<td>Chloride</td>
<td>sufficient quantity</td>
</tr>
<tr>
<td>Acetate</td>
<td>sufficient quantity</td>
</tr>
<tr>
<td>Zinc</td>
<td>1micromol</td>
</tr>
<tr>
<td>Trace elements</td>
<td>standard amounts</td>
</tr>
<tr>
<td>Vitamins</td>
<td>standard amounts</td>
</tr>
</tbody>
</table>

* Keep the glucose infusion rate below 3mg/kg/min for septic patients
** This is rather high for critically ill, septic patients on intensive care. For these patients the total energy (including that from protein) should be 25-30kcal/kg

Lipid emulsions containing long chain triglycerides (LCT emulsions) continue to be the most widely used source of fat in PN. While most hospital patients on PN receive lipid every day, this is not necessarily the case for patients on home parenteral nutrition (HPN). The infusion of 500ml of 20 per cent lipid emulsion once a week is sufficient to prevent essential fatty acid deficiency in HPN patients. It is known that the current 10 per cent lipid emulsions are cleared more slowly from the plasma compared with the 20 and 30 per cent formulations, leading to higher concentrations of triglycerides, phospholipids and free cholesterol. Whether this is of clinical significance is not known but it suggests a preference for the use of 20 and 30 per cent LCT emulsions. Emulsions containing a mixture of LCT and MCT (medium chain triglycerides) are used in PN. Potentially, the LCT/MCT emulsions offer the
advantage of faster plasma clearance, a non-carnitine dependent transport of MCT into the mitochondria with higher oxidation rate, and a decreased tendency to accumulate in the reticuloendothelial system.43 Designer, structured lipids are currently being developed and emulsions of these structured lipids are cleared from the circulation as quickly as, or even faster than, LCT/MCT emulsions.44 The extent to which these new emulsions improve clinical outcome remains to be determined and therefore LCT and MCT/LCT emulsions will continue to be used for some time to come.

The place of glutamine in PN still remains undecided, despite its theoretical potential, illustrating how difficult it is to design clinical trials of sufficient size and robustness to justify the introduction of new nutrients. Not only must trials demonstrate clinical benefit but also balance this benefit against monetary cost. Recent studies, although small, are promising and suggest that glutamine will eventually find a limited place in PN.45,46

Stability of PN

Over the past 15 years, a lot has been learnt about the stability of 3-in-1 (fat, glucose and amino acids in one bag) PN feeds. Much of this knowledge has been the result of studies carried out in the UK and for which British pharmacists can be justifiably proud. Guidelines for assessing the physical and physicochemical stability of PN feeds have been published by the British Pharmaceutical Nutrition Group (BPNG, formerly the National TPN Group, NTPNG).47 The major concerns include: the stability of the lipid emulsion, the potential for calcium phosphate precipitation, the stability of vitamins and trace elements, and the stability implications of adding drugs to PN or giving drugs concurrently via the same cannula as the PN.

Lipid emulsions The stability of lipid emulsions in 3-in-1 PN feeds is well documented.48,49 One study has shown that LCT/MCT emulsions are more stable than LCT in 3-in-1 PN feeds.50 It is now possible to compound a range of 3-in-1 feeds to suit most clinical requirements provided that formulation and compounding guidelines supplied by the manufacturer are adhered to. Prompt refrigeration of compounded PN after preparation, and correct storage on the ward are important.

Concerns about the peroxidation of lipids to form reactive lipid hydroperoxides have been raised.51,52,53,54 Several recent studies have investigated factors affecting lipid peroxidation and have (a) emphasised the importance of light protection for 3-in-1 PN and infusion lines,55 (b) demonstrated that at high concentration vitamin E can act as a pro-oxidant, making matters worse56 and (c) recommended that trace elements are added just before administration.57 The clinical significance of
Infusing lipid peroxides is not known but it would seem prudent to protect all 3-in-1 PN feeds from light. Light protection of infusion lines should be considered for paediatric PN, particularly for preterm infant feeds. Manufacturers will need to supply covers for light protection and ensure that the materials have been adequately assessed. The consequences of covering bags on wards and the implications for visual checks will need to be addressed.

**Calcium phosphate precipitation** Calcium phosphate precipitation in a PN feed led to the death of a patient in the USA and prompted an FDA safety alert. The death resulted from concentrated solutions of inorganic calcium and phosphate salts being added to a PN solution consecutively, without mixing between additions. The infusion of calcium phosphate particles led to fatal pulmonary emboli.

Provided that compounding guidelines are adhered to, the amounts of calcium and phosphate in adult PN should pose little risk of precipitation. The higher amounts of these ions added to paediatric PN means that there is a more serious risk. This risk is increased if the pH of the feed is raised (eg, by using amino acid products with a high pH), or if the temperature of the feed is increased (eg, from room temperature, 25°C to catheter temperature, 37°C).

The risk of precipitation can be reduced by using calcium gluconate rather than calcium chloride, and by using the more acidic monobasic rather than dibasic phosphate salts. The free ion concentration of phosphate, and hence the risk of precipitation, can be reduced by using an organic phosphate. Disodium glycerophosphate has been used successfully at UCLH for the past five years, as the sole phosphate source in neonatal PN. This approach should be adopted.

Since the PN feed will reach temperatures of 37°C during administration, testing of new formulae should be undertaken at elevated temperatures.

**Vitamins and trace elements** Much is known about the stability of vitamins in PN feeds. Vitamin C oxidises rapidly by reaction with dissolved oxygen, a process catalysed by copper ions. The amount of degradation depends on the amount of dissolved oxygen in the PN, which in turn depends on the compounding method and oxygen permeability of the PN bag. The use of multilayer bags and the removal of the air space before sealing filled bags will reduce losses. Vitamin C eventually degrades to oxalate. There is concern that oxalate may form highly insoluble calcium oxalate which has been implicated in the aetiology of nephrocalcinosis in preterm infants. Since this process is catalysed by trace elements, there is good reason to keep vitamins and trace elements apart in the administration of PN to preterm infants.

Vitamin A is rapidly degraded by ultra-violet light or daylight. It was assumed that the fat emulsion would offer light protection but this is only
partial, reinforcing the need to cover 3-in-1 feeds with light-proof materials.62 What goes into the bag is not necessarily what comes out! Different salts of vitamin A bind differently to plastic. Vitamin A acetate in the USA multivitamin preparation MVI binds more strongly than vitamin A palmitate in the European emulsion system Vitlipid. It is not known therefore whether the two formulations are bioequivalent. New higher doses of Vitlipid Infant, used for paediatric PN, are based on the USA recommendations. The amount of vitamin A that leaves the catheter tip needs to be determined by simulated infusions before firm dosage recommendations can be made. Similarly, vitamin E is known to be degraded by photo-oxidation.

Heparin is able rapidly to destabilise lipid emulsions in 3-in-1 PN feeds.65 66 67 The addition of heparin to PN feeds at a dose of 0.5 to 1 unit per ml has been common practice in paediatric 2-in-1 (amino acid and glucose in one bag) PN, adult 3-in-1 and 2-in-1 feeds for home PN, and is added to PN for peripheral infusion by some hospitals. Aggregation of the lipid droplets takes place in the presence of calcium, and is irreversible. The lipid aggregates are most likely removed from the circulation by the reticuloendothelial system, thus posing a strain on the immune system. The clinical implications are unknown. The addition, or otherwise, of heparin to PN feeds may have affected the outcome of past clinical trials. Low molecular weight heparins are now commercially available. These heparins do not destabilise lipid emulsions and should therefore be used when heparin is prescribed with PN.

In paediatric PN, it is usual practice to infuse the lipid emulsion separately to the 2-in-1 solution. The lipid emulsion and 2-in-1 solution come together at a Y set and move through a single infusion line towards the catheter. It has been observed that the lipid and 2-in-1 solution do not mix at the Y point but continue to move through the line as separate layers. At the interface, aggregation of the lipid emulsion can be seen with a rise in the numbers of oil droplets greater than 5micron in diameter.68 The clinical significance is unknown. The addition of extension lines between the Y point and catheter increases the contact time between the lipid emulsion and 2-in-1 solution. This can lead to line blockage as lipid aggregates build up.69 70

Interactions between PN components and trace elements are known.71 An interaction between copper and hydrogen sulphide (from the breakdown of cysteine during manufacture of amino acid solutions) leads to the formation of insoluble complexes which can be observed on the in-line filters used in paediatric PN.72 73

**Drugs and PN** As a rule of thumb, no drugs should be added to 3-in-1 PN feeds. However, the stability of some drugs, for example, cimetidine, under given storage conditions, is known.74 Ranitidine is less stable and depends on the amino acid source, the amount of oxygen incorporated in the PN
mixture during compounding, and the oxygen permeability of the PN bag material.\textsuperscript{75} This highlights the need for PN admixtures to be tested individually. More important for clinical practice is information on the compatibility of intravenous drugs given concurrently with PN feeds via a Y site. A recent study, using visual examination, has assessed the physical compatibility of 103 drugs with 3-in-1 PN feeds.\textsuperscript{76} A microscopic method for assessing Y site compatibility has been developed at Cardiff university.\textsuperscript{69,70}

The second article of the special feature will look at drug incompatibilities with enteral and parenteral nutrition.

Risks of PN

The success or otherwise of PN administration depends on a team of healthcare specialists. Insertion and subsequent care of feeding lines by dedicated and experienced clinicians and nutrition nurses have done much to reduce the problems of misplaced lines (eg, pneumothorax) and line sepsis. A rare but serious problem is inadvertent contamination of the PN feed with micro-organisms. The death of a child given PN contaminated with Enterobacter cloacae led to an audit of all unlicensed hospital pharmacy aseptic units in the UK.\textsuperscript{77} Guidelines for aseptic dispensing\textsuperscript{78} and quality assurance\textsuperscript{79} have been published. Proper design, validation and control of facilities and equipment, control of workload (capacity planning), adequate training and supervision of staff are recognised to be of paramount importance.

An important role for the pharmacist is the provision of advice on the PN prescription. In an increasingly technological world it is all too easy for the PN pharmacist or dietitian to read off clinical chemistry results from a computer at some remote location, and fail to take note of important clinical changes at ward level, such as a patient who has just stopped amphotericin which has an effect on potassium requirement. Since the PN feed will provide a substantial part of the daily fluid intake, it is not surprising that complications of over- (more common) and under-hydration are possible. An awareness of concurrent fluid and drug therapy is important as is an appreciation of the special requirements of the severely malnourished,\textsuperscript{80} the tiny and the very large patient. It is important to know when a standard "off the shelf" PN feed is appropriate and when it is not. As stated previously, it is also good practice for one member of the nutrition team to visit and review the PN patient on a daily basis.

Contamination of the PN feed with trace metals may lead, particularly in the patient on long term home parenteral nutrition (HPN), to the development of clinical toxicity. Manganese toxicity, which used to be an issue in paediatric PN\textsuperscript{81} has now been resolved with the introduction of paediatric trace element solutions of lower manganese content. Since manganese is largely excreted in bile,
there are concerns about dose requirements in patients with chronic liver
disease. The problems of interpreting whole blood and plasma manganese
levels have recently been described. 82 Contamination of the PN feed with aluminium, leading to bone deposition, reduced developmental attainment, and neurotoxicity, is of concern in the neonate and long term HPN patient. 83,84 Recommendations in 1990 by the Food and Drug Administration (FDA) to set an upper limit of 25mcg per litre in large volume parenteral infusions has yet to be implemented. 85 High aluminium contamination has been noted in calcium additives. One unpublised study at Great Ormond Street Children's hospital found high amounts of aluminium in trace element solutions; the low pH of the solutions caused leaching of aluminium from the glass container. The range of aluminium levels in PN feeds for paediatric and HPN patients in the UK needs to be determined and reviewed. Packaging of trace element and calcium additives into plastic containers may be helpful. A calcium additive with a guaranteed low aluminium content is urgently required in the UK. Trace element contamination of PN feeds has been recently studied. 86,87 Omission of micronutrients from the PN feed can lead to deficiency states. Manufacturing problems in the USA have led to a rationing of vitamin additives, affecting MVI Adult and MVI Paediatric. There have been reports of thiamine deficiency. 88,89 American guidelines recommend that copper intake be reduced in cases of biliary obstruction. Complete omission of copper from a PN feed, and failure to adequately review levels, led to pancytopenia in one patient. 90 The importance of baseline micronutrient levels at the start of PN, and regular review, is recognised in adult and paediatric home patients. Are lipid emulsions contra-indicated in patients with liver disease or sepsis? Nutritional support in hepatic encephalopathy was recently reviewed. 91 It is generally agreed that patients with liver disease are able to adequately clear parenteral lipid emulsions. 92 A dose level of not more than 1g per kg per day has been recommended, with regular monitoring of plasma triacylglycerol, which should be less than 3.95 mmol per litre. 91 There is no clear evidence that lipid emulsions should not be used in the septic patient. A recent study showed no increased incidence of bacterial or fungal infection in PN patients undergoing bone marrow transplant. 93 Polymorphonuclear leucocyte function was not affected by lipid doses of 0.5 to 3g per kg per day for up to 21 days in the neonate. 94 However, a study in paediatric patients suggests that neutrophil function was reduced in patients on long term PN. 95 Further studies are warranted, particularly in paediatric PN.
Contamination of PN feeds with particulates has been demonstrated by several studies. 96,97,98 As yet there are no UK guidelines recommending in-line filtration of PN feeds. Guidelines exist in the USA 99 where 1.2
micron filters would be required for 3-in-1 feeds and 0.2 micron filters are routinely used for 2-in-1 feeds in paediatric PN. The filtration of lipid emulsions through 1.2 micron filters in paediatric PN is fairly routine practice in some European countries, but not yet in the UK. Occlusion of PN lines can occur, particularly in long term HPN patients. The occluding material appears to be fatty, with evidence of calcium, silicone, heparin, and cellular material.\textsuperscript{100}

Anecdotal reports at UCLH suggest that line patency in fine-bore peripheral catheters was much improved following the decision to lock lines with normal saline rather than a heparinised saline. Strategies to reduce line blockage in HPN patients have included reducing fat infusion to once or twice a week. The addition of heparin to PN feeds is likely to make matters worse.

**Home PN**

The care of patients on HPN requires specialist knowledge. In the UK, there are several specialist centres, including St Mark’s hospital, London and Hope hospital, Salford. It is common practice for home care companies to be involved in HPN support.

Patient interest groups such as Patients on Intravenous and Nasogastric Nutrition Therapy (PINNT) and half PINNT (a paediatric interest group) have been formed. A report from the British Association for Parenteral and Enteral Nutrition (BAPEN) made the following recommendations:\textsuperscript{101}

1. There should be a national system of organisation to cater for the wide range of patients requiring HPN and enteral tube feeding
2. An integrated system of registers and audits should be set up to regulate the procedure
3. The guidelines establishing approved methods and standards of care should be published and made widely available.

Liver complications remain a long term problem for HPN patients. One recent study links this problem to lipid input.\textsuperscript{102} There have been several reviews of HPN.\textsuperscript{103,104,105}

**Future trends**

Although there is plenty of science in nutritional support, there is also a good deal of art. Encouraging the sick patient to eat is a skill and requires an appreciation that eating is very much a social activity. There is considerable interest in practice-based research. Simple ward studies that measure the amount of wasted food (and hence calories lost on the side of the plate), strategies for providing energy dense menus for at-risk patients, and quality of life studies in long-term nutrition support, raise many questions and do much to improve standards of care. Recording
baseline data on admission to hospital and at the start of nutritional support is very important for the assessment of nutritional intervention and outcome. In many hospitals it is now accepted practice for nurses to carry out simple nutrition screening on admission. By using a scoring system, "at-risk" patients are identified and nutrition intervention initiated. Policies will need to be implemented that make the recording of diet history, and simple measurements such as height and weight, routine on admission. Strategies for providing nutritional advice and support before the patient is admitted to hospital for elective operations might well be considered. Implementing such measures effectively is surprisingly difficult and poses the greatest challenge for all those involved in catering and nutritional support.

Moving the catabolic, critically ill patient into anabolism is the focus of much research. The use of growth hormones and steroids shows promise. There is likely to be less emphasis on calories per se but greater interest in the pharmacological effects of specific nutrients, particularly amino acids and antioxidants (vitamins A, C, E, zinc and selenium). The nutrition team will continue to play a vital role in nutritional assessment, ensuring that nutritional support is sensible, appropriate and timely. The importance of proper fluid management and the emerging use of specific nutrients for their pharmacological effect suggest two areas where the role of the pharmacist could be extended.

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**References**


60. Reedy JS, Kuhlman JE, Voytovich M. Microvascular pulmonary emboli secondary to precipitated


77. Department of Health. EL(96)95. Department of Health; 1996.


87. Pluhator-Murton MM, Fedorak RN, Audette RJ, Marriage BJ, Yatscoff RW, Gramlich LM. Trace


