Approach to Oral and Enteral Nutrition in Adults

Topic 8

Module 8.4

Formulae for Enteral Nutrition

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Learning Objectives

- To know about the different types of nutritional products available for specific medical purposes;
- To understand which formulae should be used in which conditions;
- To understand the potential metabolic effects of specific nutrients added to some formulae;

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    - 1.1 Nutritionally complete/incomplete formulae
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Key Messages

- Formulae for enteral nutrition, the so-called "dietary foods for special medical purposes", are legally defined in the European Commission Directive: 1999/21/EC of 25 March 1999;
- Standard enteral formulae have a composition which reflects the ideal values for macro- and micronutrients for a healthy population;
- Fibre-containing formulae are now considered the default; reduced fibre products exist for specific indications;
- The components of enteral formulae are mainly high quality staples of natural origin (e.g. milk, soy, plant oils, corn);
- In most patients standard formulae (including those of high energy and/or high protein) will provide all that is needed;
- Disease-specific enteral formulae are modified with the intention of better addressing characteristic metabolic demands of individual disease states;
- The addition of nutrients (e.g. glutamine, arginine, omega-3 fatty acids) to some formulae to reach levels not regularly encountered in normal food, adds potential value as "functional foods";
- The evidence supporting use of modified formulae is robust in only in a small number of specific indications, and only rarely is there a useful effect on mortality or serious morbidity.

1. General Characteristics of Enteral Formulae

Commercially available formulae for EN include those intended for tube feeding and the oral nutritional supplements (ONS) which can also be administered by tube if necessary. They are regulated by the European Commission Directive 1999/21/EC (1), in which they are officially designated as "dietary foods for special medical purposes".
The EC Directive regulates composition and labelling requirements. For a product to be considered nutritionally complete it is mandatory that it must have not only a balanced macronutrient composition but also sufficient micronutrients. The micronutrient content is defined in relation to energy provision, and it is required that the amount of feed that yields 1500 kcal must contain 100% of the recommended daily allowance (RDA) for all of the other (non-energy) nutrients.
Standard formulae are sufficient for the majority of patients, but situations of prior deficit, continuing increased requirements, or increased losses of specific nutrients must be taken into account and additional supplementation instituted. It is helpful to recall that the content of a standard formula is based on a maintenance diet for a healthy subject.

1.1 Nutritionally Complete/Incomplete Formulae

Nutritionally complete formulae can be used safely as the sole source of nourishment for prolonged periods. However their composition is generally based on a compilation of nutritional RDAs and thus corresponds to recommendations for food intake in the healthy population, and not necessarily to the needs of patients. Clinical heterogeneity has to date rendered it impracticable to estimate the pertinent values in individual patients, and therefore prescription of customised feeds is rarely possible. However, for some broad disease groupings it has been possible to devise modifications that promise benefits.
In general, formulae intended for tube feeding are nutritionally complete, whereas some ONS are not. European regulations require a statement as to whether or not the product is suitable for use as the sole source of nourishment (1).

Nutritionally incomplete formulae are not suitable as the sole source of nourishment, but can nonetheless be useful as supplements. Most simply contain an incomplete array of nutrients (for example those providing only carbohydrate or lipid), but some contain large amounts of metabolically active ingredients (such as antioxidants), which could render them harmful as well as ineffective if used in large quantities or as the sole source of nutrition.

1.2 Low, Normal/Standard and High Energy Formulae

"Normal" or "standard" energy formulae are defined from their content of 0.9-1.2 kcal/ml; high energy formulae have anything above this, low energy formulae anything below (2). A typical distribution of macronutrients in standard feeds is summarised in **Table 1**.

Table 1
General characteristics of standard formulae

Standard Formulae

- 15-20% of energy from whole protein
- ~30% of energy from lipid - predominantly as long-chain triglycerides
- 50-55% of energy from carbohydrates – predominantly of low glycaemic index
- 10-20mg/ml fibre (fibre-free options are also available)
- Full complement of vitamins and trace elements
- Gluten-free and with minimal lactose
- ~85% water
- ~1kcal/ml (normal energy density)

1.3 Whole Protein, Polymeric Formulae

Whole protein formulae contain intact proteins, and usually include lipids, in the form of long chain triglycerides (LCTs), and carbohydrates, generally as a mixture including maltodextrins and different fibres. They may also be described simply as polymeric feeds, or high molecular weight or nutrient-defined formulae.
They require relatively normal gastrointestinal function for digestion and absorption, but can be used successfully in up to 95% of patients on artificial enteral nutrition. Since the nutrients included are not hydrolysed, polymeric formulae have an osmolality reasonably close to physiological levels (eg in the circulation) of 200 to 350 mosmol/kg). All standard feeds and most of the disease-specific formulae belong to this general category. Standard formulae, including their high energy and high protein variants, can be used for a broad array of disease states. The indications for standard formulae - including high energy and high protein variants - are given in the ESPEN Guidelines on Enteral Nutrition (3) and also in the newer guidelines for specific conditions (see https://www.espen.org/guidelines-home/espen-guidelines). The simple and general message is that if artificial nutrition is required, then in the great majority of circumstances a polymeric formula will be indicated. The strength of evidence varies according to the condition under consideration but is positive in almost all cases. Clinical scenarios where alternative actions should be taken will be outlined below. In broad terms, modified formulae can be justified when a standard feed has not been tolerated and there is not an indication for parenteral nutrition, and in a small number of specific diseases where trials have shown clear advantage to an alternative.

1.3.1 Standard Formulae

Standard formulae are enteral formulae with a composition that reflects the RDA values for macro- and micronutrients of a healthy population (**Table 2**). The RDA provision for micronutrients will be satisfied so long as sufficient feed is provided to supply 1500kcal of total energy. It is now convention that the description "standard" implies the inclusion of fibre.

1.3.2. High Energy Formulae

High energy formulae (also called energy dense diets, and high lipid formulae) are modifications of standard formulae which contain more than 1.2 kcal/ml. Usually this is achieved by removing water from a standard formula, accompanied by a small increase in the lipid fraction. An energy density of up to ~1.5 kcal/ml can be attained. To achieve an energy density of more than 1.5 kcal/ml the lipid fraction has to be increased considerably (to up to 50%), which is why these formulae are also called high lipid.
High energy formulae have a lower water content than standard formulae (70-75% vs. 85%) and extra care should be taken to ensure adequate fluid intake when they are used. Equally, high energy formulae can be especially valuable in patients subject to fluid restriction, as in cardiac and renal disease, and sometimes also in those with electrolyte imbalances. However, they are most widely used as oral "sip" feeds to decrease the nutritional volume load, which helps to increase compliance and reduce the time needed for their consumption. Their greater osmolality will sometimes lead to intolerance, and can provoke frank osmotic diarrhoea in some patients.

Table 2
The characteristics (per 100ml) of some typical standard fibre-containing formulae designed for administration by tube, demonstrating the similarity of the products of different manufacturers

Product	Jevity 1.0 Cal	Nutricomp Standard Fibre	Fresubin Original Fibre	Isosource Standard Fibre	Nutrison Multifibre 1.0
Manufacturer	Abbott	B Braun	Fresenius	Nestlé	Nutricia
Energy/kcal	105	104	100	103	103
Carbohydrate/g	15.0	13.8	13.8	13.5	12.3
Protein/g	4.0	3.8	3.8	3.9	5.5
Fat/g	3.5	3.3	3.4	3.4	3.9
Fibre/g	1.76	1.5	1.5	1.5	1.5
Protein:fat: carbohydrate ratio	16:30:54	15:29:56	15:35:50	18:31:51	16:35:49
Sodium/mg/mmol	93/4.0	100/4.3	75/3.3	80/3.5	100/4.3
Osmolarity/ mosmol/l	300	260	300	266	210

1.3.3. High Protein Formulae

High protein formulae are also modifications of standard formulae, amended so that they contain 20% or more of their total energy in protein form. Increasingly, guideline groups in ESPEN and other international bodies are identifying patients who need more than the background daily provision of around 1g protein per kilogram body weight. These new recommendations are typically for 1.2 to 1.5 g/kg/day, and in a few conditions higher still. As this recognition of greater need for protein supplementation is established these feeds are becoming more widely used. In general terms high protein formulae are valuable in the support of markedly catabolic patients and those with severe malnutrition.

1.4 Peptide-based, Oligomeric Formulae

Peptide-based formulae are also called oligomeric, low molecular weight, and chemically defined formulae. They are partially "pre-digested" and, at least in theory, are more easily absorbed than whole protein formulae. They contain nitrogen predominantly in peptide form (chains of 2-50 amino acids). Lipids are provided at least in part as medium chain triglycerides (MCTs), since these also are more readily absorbed, being dependent neither on digestion nor micellar handling via the lymphatics. The carbohydrate content too will be less expansively polymeric, and fibre will be omitted.

Few patients need a peptide-based formula. It is now some years since the guidance on their use from the experts of the Austrian Society of Clinical Nutrition, but newer data do not greatly contradict their general conclusions, which are summarised here in modified form (**Table 3**) (4). The ESPEN guidelines also refer to the occasional need for peptide-based formulae in patients with acute pancreatitis who have not tolerated standard formulae (5).

Where newer data exist the strong trend is away from pre-planned use of oligomeric formulae, limiting their use to patients in whom enteral feeding is strongly indicated (or parenteral nutrition relatively contraindicated) and in whom use of a standard feed has not been tolerated. Many units will now routinely commence jejunal feeding with cautious use of a polymeric formula, as this strategy is so often well tolerated and nutritionally effective. There are insufficient trial data for this to be mandated but it is generally safe and is increasingly recommended (6).

In essence the justification for oligomeric feeding is when enteral feeding with a standard formula has proved especially challenging and when there is no other indication for parenteral nutrition.

Table 3
Indications for peptide-based formulae (adapted from the recommendations of the Austrian Society of Clinical Nutrition (4))

Indications for Peptide-Based Oligomeric Formulae
• When whole protein formulae are not tolerated but enteral nutrition is still indicated
• When capacity for absorption is severely impaired
• In the initial phase after prolonged starvation
• When administration is to the jejunum (in critical care and in severe acute pancreatitis)
• In selected patients with short bowel syndrome
• In selected patients with enterocutaneous fistulae

1.5 Free Amino Acid-based, Elemental Formulae

Free amino acid formulae – also called elemental, monomeric, low molecular weight, and chemically defined formulae – provide nitrogen in the form of single amino acids. On theoretical grounds there should be very few indications for their use, since oligopeptides are generally better absorbed than free amino acids, and combine this property with lower osmolality. However clinical trial data support the use of amino acid-based feeds in certain circumstances including some forms of congenital metabolic disease, and in those with particularly severe allergy to dietary protein.

Free amino acid formulae are generally best avoided in short bowel syndrome, even if other formulae are not tolerated, as they provoke a secretory response which can have counter-productive effects on fluid and nutritional balance (see ESPEN Life Long Learning Module 12.2).

Trials of primary nutritional therapy in Crohn's disease have compared elemental with polymeric and oligomeric formulae with no marked differences in outcomes. Standard polymeric feeds are therefore preferred in the first instance (7).

1.6 Ingredients of Enteral Formulae

Nitrogen sources in the whole protein formulae are mostly milk proteins such as casein, often together with soy proteins. In peptide-based formulae hydrolysates of soy, lactalbumin, gelatine and/or whey are used. In each case the overall provision is sufficient to provide all of the essential amino acids and a balanced portfolio of non-essential amino acids. By contrast, the elemental formulae contain free amino acids, and accordingly do not contain glutamine, because this amino acid is not stable in its free state. This is obviously of potential concern in sick patients in whom glutamine may be conditionally essential.

Fat sources in standard polymeric formulae have traditionally been mixtures of oils high in polyunsaturated ω-6 fatty acids, such as sunflower, soy, safflower and corn oils. More recently, with increasing awareness of the potentially positive effects of the ω-3 fatty acids, canola, rapeseed and/or fish oils are widely included. Olive oil (ω-9 monounsaturated) is also included in some preparations given its immunologically neutral status.

Medium chain triglycerides (MCT) derived from coconut oil form part of several formulae. Peptide-based and elemental preparations often contain dominant amounts of MCTs, on the basis that they do not require bile salts or pancreatic lipase prior to absorption, and that they bypass the lymphatic system with direct uptake into the portal circulation. Self-evidently the MCTs do not contain any essential fatty acids, and polyunsaturated fatty acids (at least 5% of lipid calories) are added to any such mixture in order to ensure that the formula is nutritionally complete.

Carbohydrate sources in traditional low fibre feeds were predominantly partial enzymatic hydrolysates of corn starch (generally maltodextrins with at least 10 glucose molecules). With the uniform adoption of fibre into standard formulae it is now common to find carbohydrate also in the form of fructose oligosaccharides, guar gum and a mixture of cereal fibres, which will usually include soya. These feeds can sometimes therefore also be considered to be a source of prebiotics.

Some formulae, especially those intended for oral use, may contain small amounts of sucrose as this increases palatability. Some whole protein formulae may also contain starch. In elemental feeds simple sugars typically account for around half of the total carbohydrate content.

Minerals, vitamins and trace elements are included in all complete feeds, and given the statutory requirements, meet 100% of each RDA in the volume of the formula required to yield 1500 kcal.

Omitted substances. Enteral formulae generally do not contain lactose, cholesterol, purines, or gluten in biologically relevant amounts. This is achieved by careful choice of the base materials rather than through technical elimination processes. Cholesterol, for example, is avoided by the selection of plant oils as the predominant lipid sources. Purines are absent from the principal macro-ingredients (such as milk and soy). Gluten content is minimised by the choice of corn-derived carbohydrates. The protein component of most enteral products is added in highly concentrated powder form, usually with a protein fraction of about 85%; this helps to ensure that only negligible amounts of lactose remain despite the use of milk. Enteral formulae are therefore safe for patients with primary or secondary lactose intolerance and coeliac disease, and are appropriate for use in those with gout or hypercholesterolaemia. Strict vegetarians can accept most enteral feeds but the presence of gelatine in some preparations necessitates product-by-product checking. Commercially prepared feeds are often not suitable for strict vegans given the widespread use of milk as a starting material.

Despite their use of manipulated products, enteral formulae are still based on natural components mainly using common high quality staples. Emphasising their artificiality is no more logical than in respect of regular supermarket foods (such as milk desserts), and may be counterproductive when encouraging their use by patients. Nonetheless some children may be stimulated by the idea of astronaut food!

2. Disease-specific Formulae

Disease-specific formulae include those with their macro- and micronutrient composition adapted to the predicted needs of a specific disease, digestive or metabolic disorder (2).

2.1 Diabetes Formulae

Two broad types of diabetes formulae are available:

a: The "classical" diabetes formulae

Classical diabetes formulae are very similar to standard formulae. This is the direct consequence of the concordance between current guidelines for diabetic diets and the RDAs on which standard formulae are based. Classical diabetes formulae may have some sucrose replaced by fructose, and may contain a higher proportion of polysaccharides, but the differences are minor. These plausible but subtle biological benefits will not normally justify their higher price. Standard formulae are usually adequate and appropriate in uncomplicated diabetes mellitus.

b: High MUFA diabetes formulae:

A newer generation of diabetes formulae has been developed in which polymeric formulae have been adapted to contain up to 35% of energy in the form of mono-unsaturated fatty acids (MUFA), a higher total amount of fat, and less carbohydrate (**Fig. 1**). In a systematic review and meta-analysis in 2005 (8) high MUFA diabetes formulae were shown to reduce the postprandial rise in blood glucose, the peak blood glucose, and the area under the curve (AUC) for glucose concentrations, when compared to standard formulae. The results were clearly statistically significant, but they were all short-term studies (most of them based on a single exposure of the test product taken for breakfast). Evidence for clinical benefits from long-term use remained inconclusive. Several studies reported lower mean, fasting and/or postprandial glucose levels, but decreased HbA1c, fructosamine, and insulin

requirements appeared only as non-significant trends favouring high MUFA formulae in comparison to classical diabetes formulae. A pragmatic approach was therefore suggested in which these formulae were reserved for those in whom adequate glycaemic control proved difficult to achieve with the combination of standard formulae and appropriate pharmacological control of the diabetes.
A subsequent meta-analysis of 9 trials led to a stronger recommendation favouring this approach more generally (9). ESPEN has to date avoided a mandatory recommendation, and its main foci of nutritional management are on the control of obesity and long-term optimisation of glycaemic control (see ESPEN Life Long Learning Modules 21). However, several more recent publications based on patients in critical care settings lend additional support to the use of these high fat preparations. High MUFA feeds should now be considered to be standard when tube feeding is required in the sick and hyperglycaemic patient.

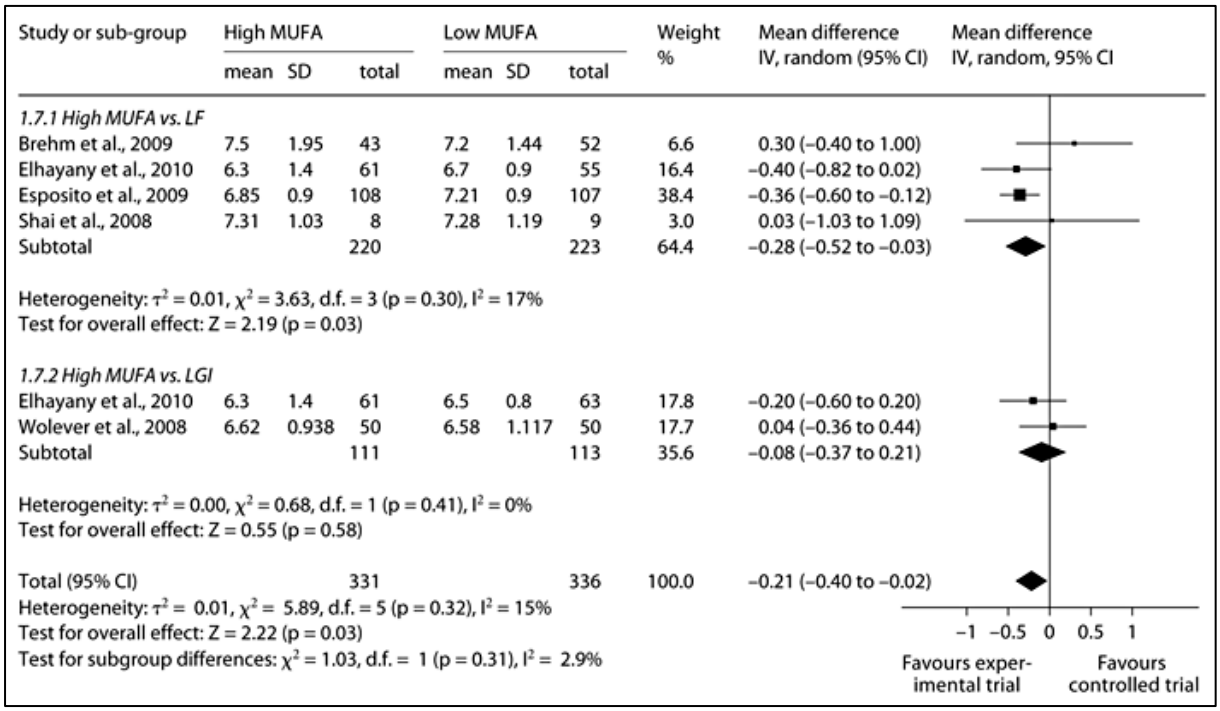

Fig. 1 High MUFA diabetic formulae versus standard formulae – results of a systematic review and meta-analysis (9)

2.2 Formulae for Patients with Liver Disease

In liver failure there is an altered amino acid profile, both in the blood and in the brain. Although the severity of encephalopathy correlates most closely with ammonia concentrations, the imbalance of amino acids is thought to contribute to the clinical features of the condition and to the persistence of encephalopathy. Disturbed synthetic liver function generally leads to high concentrations of amino acids, especially the aromatic amino acids (such as tyrosine), but with relatively normal levels of the branched-chain amino acids valine, leucine, and isoleucine. Disease specific formulae for patients with liver disease have therefore been devised on theoretical grounds. They have been modified to contain higher proportions of branched-chain amino acids and lower levels of aromatic amino acids than standard formulae in an attempt to rectify the abnormalities seen (**Table 4**). Liver-specific formulae are low in sodium but energy dense, usually with a high lipid content, as these patients are often both catabolic and in need of fluid restriction.

Furthermore, the lipid component is rich in MCTs given the likelihood of impaired fat absorption in cholestatic liver disease.

There are insufficient data to make specific recommendations in patients with acute hepatic failure. In the most severely affected patients the initial stance will be to defer nutrition until hyper-ammonaemia is controlled. When enteral nutrition is then required ESPEN's position is that the default prescription should be a standard polymeric feed (10).

When patients with non-alcoholic steatohepatitis require artificial feeding the emphasis lies with metabolic control; while diabetes formulae may be indicated, there are no data supporting the use of liver-specific preparations. Target daily energy provision of 25 kcal/kg and protein provision of 2.0-2.5 g/kg are suggested (10).

In patients with chronic liver disease there are better data. Liver-specific formulae have been assessed in the prevention and/or treatment of hepatic encephalopathy, but the results from these studies are not uniform. It is however clear that energy delivery should be maintained at a high level and that protein delivery should not normally be restricted.

Most patients with chronic liver disease, including those with severe alcoholic steatohepatitis and those with cirrhosis, who need enteral nutrition will be well served by standard high energy (≥1.5 kcal/ml) formulae with normal or high protein content. ESPEN's general recommendation for patients with cirrhosis is a daily intake of 30-35 kcal/kg and 1.2-1.5g protein/kg. The higher doses are for those with evidence of malnutrition or sarcopenia. There are currently insufficient data to support the use of supplementary antioxidants or omega-3 fatty acids (10).

In cirrhotic patients who are intolerant of dietary protein ESPEN recommends the use of supplementary branched-chain amino acids (BCAA) 0.25g/kg/day. There is also evidence to support the same dose of BCAA (or 30g/day) to improve event-free survival in the long-term management of cirrhotic patients (10). Data from different trials are not entirely concordant but BCAA-rich feeds appear to improve the prognosis in severely malnourished patients with alcoholic hepatitis and those with cirrhosis. Meta-analysis is needed to support the conclusion that BCAA-rich feeds can also improve encephalopathy in cirrhotic patients.

There is only a small body of evidence in support of supplementation with BCAA in the pre-transplant phase, but the data are a little more persuasive in children with cholestasis. Encephalopathy occurring after transplantation appears responsive to the use of BCAA-supplemented feeds, but there is no clear evidence to support their more general use in nutrition after transplant surgery.

Table 4
Characteristics of typical liver formulae in comparison with standard feeds from the same manufacturers. Liver formulae are of high energy and have more branched chain amino-acids (BCAA) and medium chain triglycerides (MCT) than standard formulae. Their osmolarity is accordingly increased, to a degree reflecting the amounts of MCT and free amino acids.

Product	Nutricomp Hepa	Nutricomp Standard Fibre	Fresubin Hepa	Fresubin Original Fibre	Nutrihep	Isosource Standard Fibre
Manufacturer	B Braun	B Braun	Fresenius	Fresenius	Nestlé	Nestlé
Energy/kcal	130	104	130	103	150	103
Protein/g	4.0	3.8	4.0	3.9	4.0	3.9
BCAA/%	40	18	48	18	39	18
Fat/g	5.0	3.3	4.7	3.4	2.1	3.9
MCT/%	50	9	36	5	70	20
Fibre/g	1.0	1.5	1.0	1.5	0	1.5
Sodium/ mg/mmol	23/1.0	100/4.3	19/0.8	75/3.3	16/0.7	80/3.5
Osmolarity/ mosmol/l	395	260	360	300	790	266

Content in 100ml in each case

2.3 Formulae for Patients with Renal Failure

Nutritional support of patients with renal impairment is one of the more complex areas in clinical nutrition. The nutritional imperatives of preventing and treating malnutrition must be balanced with efforts to minimize blood urea nitrogen and to reduce the accumulation of toxic products, while maintaining fluid and electrolyte balance. This set of challenges is then partially reversed when the patient goes onto dialysis; then there may still be a catabolic state but almost always one where nitrogen losses are exaggerated and in which a high protein intake is needed (11).

It is understandable that a range of renal formulae have been developed. Renal formulae are high energy (often 2 kcal/ml) with a low content of potassium, phosphate and sodium, the electrolytes that most tend to accumulate in renal failure. The formulae may also have other specific modifications, such as a reduced amount of vitamin A.

Many patients with acute renal failure or acute kidney injury (AKI) have a short-term, reversible problem with little need for artificial nutrition. In those with more severe disease the illness is often characterised by a markedly catabolic state. In those who need enteral tube feeding it will usually be possible to use standard high energy feeds (12). Even when 1500-2000 kcal are required the electrolyte content of regular formulae is generally sufficiently modest that this will not pose additional problems. Various forms of dialysis and haemoperfusion may be needed in AKI, but not because of complications of enteral feeding. Critical care patients may however need modified enteral regimens once dialysis has commenced given the losses of many key nutrients in the dialysate. There is a little evidence that additional enteral glutamine may be helpful (see below).

Modification of the nutritional regimen is much more important in chronic renal failure, and here it is crucial to make the distinction between the patient who has established renal failure but who is still independent of renal replacement therapy/dialysis, and the patient with end-stage renal failure who is being treated with peritoneal or haemodialysis.

In the patient with chronic renal failure who is still independent of dialysis the objectives include all efforts to maintain residual renal function and avoid the early need for dialysis. There are strong and reliable data to indicate that moderate protein restriction will assist in this endeavour (13). Specific formulae have been devised to help (**Table 5**). These so-called predialytic formulae are low in protein content and overall nitrogen content, but with some enrichments intended to optimise their biological value. They are also rich in energy to cater for the chronic catabolism of these patients. There are theoretical advantages to the inclusion of boosted levels of essential amino acids and the inclusion of ketoanalogues when the total protein/protein equivalent provision is restricted. Although this strategy appears logical there are still no robust controlled data to support their use from a clinical point of view.

Once a patient progresses to need chronic dialysis the situation changes radically, as the dialysed patient has an increased requirement for protein (>1.7g/kg/d) because of the substantial protein losses during both haemodialysis and peritoneal dialysis; there may still be an increased energy demand. Dialytic formulae are accordingly designed with a deliberately high protein content (**Table 5**). Since such patients still have problems with hyperphosphataemia the electrolyte composition of these formulae is adjusted relative to more standard high protein feeds.

Table 5
Characteristics of typical renal formulae. They have low concentrations of electrolytes and are of relatively high energy, and have either a restricted and modified nitrogen content or a high protein content depending on their intended use in patients in the predialytic phase or those on dialysis

	Pre-dialytic formulae		**Dialytic formulae**	
Product	Fresubin renal	Renilon 4.0	Novasource Renal	Nepro HP
Manufacturer	Fresenius	Nutricia	Nestle	Abbott
Energy/kcal	200	200	200	180
Protein/g	3.0	3.9	9.1	8.1
Carbohydrate/g	26.4	23.5	18.5	14.7
Fat/g	8.9	10.0	10.0	9.8
Sodium/mg/mmol	68/2.9	37/1.6	94/4.0	69/3.0
Potassium/mg/mmol	100/2.6	22/0.6	82/2.1	.105/2.7
Phosphorus/mg/mmol	55/1.7	4/0.13	70/2.3	72/2.4
Osmolarity/ mosmol/l	500	500	534	538

Content in 100 ml in each case

2.4 Formulae for Patients with Pulmonary Disease

Most patients with nutritional problems associated with acute or chronic respiratory disease can be managed with completely conventional approaches and standard formula feeds. Occasionally it becomes necessary to devise special strategies.

In type 2 respiratory failure there is carbon dioxide retention, which poses several problems. In addition to the consequences of respiratory acidosis there may be particular difficulty in weaning from artificial ventilation commenced in association with an infective crisis (eg pneumonia) or an intercurrent surgical intervention. The formulae devised for use in this context therefore contain a higher percentage of total energy from fat to adjust the respiratory quotient (RQ) away from 1.0 (for pure carbohydrate utilisation) towards the 0.7 of pure lipid oxidation, thus contributing to a decreased formation of carbon dioxide.

Acute respiratory distress and critical care

Although there are theoretical advantages to pulmonary formulae, in the absence of any robust supportive data the current ESPEN guidance on Critical Care Nutrition does not advocate the general use of any special formula (14).

The situation may be somewhat different in patients with acute respiratory distress associated with carbon dioxide retention. In these patients, immune modifying formulae may offer some advantage (see below), but any efficacy does not seem likely to be as a result of a lower RQ.

Chronic obstructive pulmonary disease

Although it has been suggested that special pulmonary formulae should be used in stable patients with chronic obstructive pulmonary disease (COPD) (in amounts of 300-600 kcal/d in addition to normal food) this is not logical as there is then little impact on the RQ and because standard feeds or normal food could have a proportionally greater effect. The ESPEN guidelines have not been updated for some time, but there is no apparent reason to amend their conclusion that there is no additional advantage of a disease specific low carbohydrate, high fat pulmonary formulae compared to standard, high protein or high energy feeds in patients with stable chronic obstructive pulmonary disease (15).

2.5 Formulae for Patients with Neurological Disease

Most patients with neurological problems can be managed nutritionally along standard lines for disease-related malnutrition. However the unusual energy demands of those with acute head injury will often necessitate generous provision, which may need to be in excess of 40kcal/kg per day (16).

As in other areas it is possible to demonstrate patterns of nutritional need that differentiate these patients, and accordingly the nutrition industry has devised a number of disease-specific formulae, some of which have been assessed in clinical trials. It is considered logical to increase the fat to carbohydrate ratio (in its extreme forms in the ketogenic diet advocated for refractory epilepsy), and to provide additional amounts of vitamin E, carnitine and taurine. Supportive data from robust clinical trials are however lacking.

The most frequently encountered neurological conditions receive specific attention in the ESPEN guidelines (17). The guidelines consider the ethical issues around when to commence or discontinue artificial feeding as well as the content and quantity of that feed.

Amyotrophic lateral sclerosis, Parkinson's disease and multiple sclerosis

In motor neurone disease/amyotrophic lateral sclerosis (ALS), the focus is on prompt identification of nutritional need and its safe and effective administration rather than on specific nutrients. Similar concerns are emphasised in Parkinson's disease, although there

is evidence in support of vitamin supplementation, especially of vitamins B9, B12 and D, which may not be adequately addressed by the amounts in standard commercial formulae. There is also evidence in support of the use of fermented milk to reduce the frequency of constipation (17).

There has been a lot of interest in diet in the possible aetiology of multiple sclerosis that has spilled over into potential therapeutic approaches. Accordingly there are studies of supplementary vitamin D and regimens rich in omega-3 fatty acids, but the results do not support their general use. Attention to nutritional need and safe delivery are much as for ALS and Parkinson's.

Stroke

Nutritional problems after stroke are a major problem in all healthcare systems and there is good evidence for improved outcomes when intensive rehabilitation including full supportive nutrition commences at the earliest possible point. ESPEN provides guidance on when and how to administer enteral nutrition. When artificial formulae are needed for the safe and effective delivery of nutrition the use of high energy, high protein preparations is supported by the literature (17). There is however insufficient evidence to support the use of any disease-specific formula.

Traumatic brain injury

In traumatic brain injury systematic review indicates advantages from early feeding, the use of immune-enhancing formulae (see below), and protection from pneumonia if a jejunal feeding tube is employed (16).

Inborn errors of metabolism

The specific requirements of patients with inborn errors of metabolism such as maple syrup urine disease are beyond the scope of this manuscript but may be critical in the avoidance of irreversible neurological manifestations. Specifically modified formulae are available, tailored to these (mostly rare) conditions.

2.6 Immune-modulating Formulae

Immune-modulating formulae (immunonutrition, immune-enhancing diets) contain substrates included with the express intention of modulating (enhancing or attenuating) immune functions. Immune-modulating nutrients are accordingly given in supra-physiological amounts aiming to achieve what is therefore a pharmacological or nutriceutical effect on the response of the body to surgery, trauma or infection. Many nutrients have potentially immune-modulating properties, but to date attention has focused mainly on omega-3 fatty acids, nucleotides, arginine, and glutamine. The effects of individual potential nutriceuticals is considered in the next section (Section 3) but the most persuasive arguments in favour of the use of immune modulating feeds comes from studies in which combinations have been used in formulae designed for this purpose (**Table 6**). Conclusions and recommendations are therefore especially difficult to generalise - whether from one product to another or from one condition to another.

Cancer

For cancer patients ESPEN has provided a recent synthesis of the available data (18). In general there should be an active plan to ensure adequate nutrition, with a daily protein intake in excess of 1.0g/kg and a fat rich energy dense diet for those losing weight. Studies have explored supplementation of standard formulae with extra leucine or of a more general increase in essential amino acids aiming to improve muscle protein synthesis, and of supplementary fish oil to boost omega-3 fatty acid levels aiming to improve appetite and lean body mass and to ameliorate active inflammation. Supplementary arginine and nucleotides are also being assessed as potential aids to

enhance an appropriate immune response. Studies of individual nutrients are not sufficiently persuasive to change practice (see also below) but specific combinations within nominally immune-enhancing feeds have been shown to offer statistically and clinically significant benefits in patients having cancer surgery. Mortality is not clearly reduced but there are fewer post-operative infections. These combination feeds have also been shown to improve immune responsiveness in patients undergoing radiotherapy.

Meta-analysis of randomised controlled trials permits a confident conclusion that immune-enhanced formulae offer worthwhile advantages in patients undergoing major cancer surgery, with those having upper gastrointestinal procedures showing the greatest benefit. There are lower rates of infectious complications, and hospital stay is shorter than when patients are treated with standard isocaloric, isonitrogenous feeds.

Surgery and Critical Care

There is some evidence supporting the use of immune-enhancing feeds in the perioperative period, but the most convincing results are for malnourished patients with cancer. For the generality of abdominal surgery there is much less concordance of results. The ESPEN surgical guidelines accordingly continue to recommend standard feeds other than in the cancer context (19).

There are increasingly convincing data from critical care studies which advocate the use of specific and potentially immune-modulatory ingredients (14). These have been studied individually more than as immune-enhanced commercial mixtures and these results are considered below.

Table 6
Characteristics of some examples of immune-modifying formulae. They are all enhanced with omega-3 fatty acids and all are promoted as having antioxidant properties although these are generally presented as vitamins and not always in concentrations widely different from those in more standard formulae.

	Immune-enhanced formulae			
Product	Ensure Surgery	Impact	Forticare	Supportan
Manufacturer	Abbott	Nestle	Nutricia	Fresenius
Energy/kcal	140	100	160	150
Protein/g	7.5	5.6	8.8	10.0
Carbohydrate/g	18	13.4	19.1	12.4
Fat/g	3.8	2.8	5.3	6.7
Fibre/g	0.8	1.0	2.1	1.5
Special features				
Antioxidants	S	Y	Y	S
Arginine	Y	Y	N	N
EPA and DHA	0.46	Y	0.6/0.3	0.4/0.2
Nucleotides	N	Y	N	N

Content in 100 ml in each case
N: not included; S: present at relatively standard concentrations; Y: specifically supplemented

3. The Individual Effects of Single Special Nutrients

3.1 ω-3 Fatty Acids

It is clear that lipids have major effects on immune function and this is no less true when they form part of enteral formulae. Oils traditionally used in enteral formulae, like soybean, sunflower and safflower oils, are rich in ω-6-fatty acids. They were selected for reasons of availability, stability, low cost, and with the expectation that they would have neutral or beneficial effects on serum cholesterol levels. The ω-6-fatty acids are however precursors of the eicosanoid series 2 prostanoids, series 2 thromboxanes, and series 4 leukotrienes, all of which have strong pro-inflammatory profiles. In contrast, α-linoleic acid, an ω-3-fatty acid, is the parent of eicosapentaenoic acid (EPA). EPA in turn is the precursor of the eicosanoid series 3 prostanoids, series 3 thromboxanes and series 5 leukotrienes. Although it is often claimed that these have anti-inflammatory properties it would be more true to state that they have a much less pro-inflammatory profile and that they exhibit potentially immune-enhancing properties. Furthermore, thromboxane A2 produced in platelets from the ω-6 pathway is a potent platelet aggregator and vaso-constrictor, whereas thromboxane A3 (derived from ω-3 fatty acids) is a moderate vaso-constrictor and does not aggregate platelets. The ω-3 products have also been shown to inhibit the formation of the ω-6 products. The optimal ratio of ω-6 to ω-3 fatty acids is considered to be 5:1, although this has not been confirmed by any clinical studies, and ignores any effect of the ω-9 mono-unsaturated fatty acids. Although some primitive diets approach the idealised 5:1 ratio many do not, and the typical modern Western diet is certainly not compliant. It is however possible to modify enteral feeds to this effect by replacing a proportion of the conventional oils with so-called fish oils, in order to provoke an immunomodulatory effect and to promote a less thrombotic environment, with increased fluidity of cell membranes (20).

All of the leading manufacturers now produce enteral feeds and oral nutritional supplements with enhanced levels of ω-3 fats generally marketed as containing "fish oil". As in parenteral nutrition, there is a move towards all standard feeds having a meaningful ω-3 fat content, but at present clinicians wishing to deliver these lipids need to prescribe specifically.

There is moderately good evidence in favour of ω-3 rich feeds in cancer, in critical care and in perioperative patients, but in the latter group the evidence is very largely circumferential through their encouraging performance when given as part of immune-modulating mixtures (18).

The ESPEN cancer guidelines review their relevance to oncological practice. In advanced colorectal cancer a randomized study of 2 g fish oil daily during the first 9 weeks of chemotherapy showed that this significantly delayed tumour progression, and in two studies in lung cancer supplementation with eicosapentaenoic acid (EPA) yielded improvements in physical performance and quality of life (18).

In critical care there is not overwhelming support for routine use of ω-3 rich enteral feeds but the ESPEN guidelines recognise some advantages and note the recommendations of other bodies that the normal diet should contain a daily intake of 500 mg of EPA and docosahexaenoic acid (DHA) (14). It is logical therefore that formula feeds should aim to replicate this. Enriched enteral formulae have shown improvements in duration of ventilation, length of stay and in control of sepsis in a range of conditions including ARDS and acute lung injury. The ESPEN group's meta-analysis was weakly positive but unable

to give a firm recommendation, not least because so many of the studies included other interventions alongside the lipid modification (14). There is a curious observation that the nature of administration appears to make a difference with all the advantaged attributable to continuous infusion being lost when the ω-3 rich feed is given as boluses, and a persisting caution that high levels of ω-3 fats may be harmful in some non-surgical patients in critical care.
Given the supportive data from combined immune enhanced feeds (see above) the use of enteral formulae with lipid profiles rich in ω-3 rich fats now looks increasingly logical but cannot yet be considered firmly established.

3.2 Arginine

Although not an essential amino acid, the requirements for arginine increase in a variety of stress situations, including burns, trauma, and rapid growth; in these situations metabolic demands may outstrip the body's ability to provide enough, thus rendering it conditionally essential. At a biochemical level, arginine is key not only to protein synthesis, but also to the synthesis of other amino acids and to the ultimate handling of nitrogen moieties in the urea cycle. Immunologically, arginine stimulates lymphocyte function and appears to improve wound healing. Arginine also has multiple and potent secretagogue activities, including stimulation of growth hormone release, and increased release of insulin, glucagon and somatostatin.
Arginine performs a number of its roles through its function as a precursor for nitric oxide. In general this is likely to be beneficial (for example from vasodilatation) but the potential for harm also exists, and there is some weak evidence - mainly from animal work - that uncontrolled production and/or exogenous delivery are associated with increased mortality in septic shock. At present the evidence base is insufficient to warrant the addition of arginine to enteral formulae; equally there is no direct evidence of harm when it is given enterally either alone or as a component of a multi-agent immune-enhancing feed (21).
ESPEN guidelines are accordingly uniformly cautious about its administration.

3.3 Glutamine

Glutamine is the most abundant amino acid in dietary proteins and in the proteins of the human body. It was once considered non-essential, but it is now clear that the body is unable to synthesise it in sufficient quantity in stress and severe starvation. It is thus conditionally essential (21) and low circulating levels may be seen in the acutely ill. Glutamine is important for rapidly dividing immune cells, for maintaining gut barrier function (being also an important energy source for the small intestinal epithelium), and for synthesis of the endogenous antioxidant, glutathione. Given that there are large amounts in all protein sources there would not seem to be a problem in anyone fed enterally, but the positive experiences with glutamine supplementation given parenterally and the hope that a pharmacological effect might prevail have prompted many enteral studies also. These potential clinical benefits from enteral supplementation with glutamine have been systematically reviewed (22) and are mostly disappointing. There is however good evidence to warrant the addition of glutamine to the enteral nutrition given to severely burned patients (recommendation grade A) and probably also to those with major trauma (23).
The basal requirements of glutamine are readily satisfied with conventional whole protein formulae and there will normally be ample provision to accommodate the body's

inadequate synthetic response during stress. For a postulated pharmacological effect to address additional disease-associated requirements, up to 20g per day has been proposed; some immune-modulating formulae contain levels which can provide around this amount with a typical prescription (**Table 7**).

There is a disproportionately high concentration of glutamine in the exudates from burns, and in randomised trials of patients with major burns there has been clear benefit from supplementation with enteral glutamine. The benefits are predominantly from key reductions in rates of infection (especially with Gram negative organisms), but mortality is also consistently reduced. Meta-analysis supports these conclusions and the ESPEN critical care guidelines (14) and those specific to burns management (23) strongly recommend glutamine therapy for those with burns affecting more than 20% of the body surface area. Daily additions of 0.3-0.5 g/kg should be administered for 10-15 days alongside enteral nutrition.

Recommendations in severe trauma are based on a much smaller evidence base and mainly from a single study. It appears that wound closer is faster and is associated with the magnitude of the positive effect on circulating glutamine levels. This has been sufficient to lead the ESPEN critical care group to recommend the supplementation of enteral nutrition with glutamine at 0.2-0.3g/kg for 5 to 15 days (20g a day for 14 days in the trial) (14).

Manufacturers have also made glutamine available in supplementary forms that can be taken alongside conventional balanced formulae: these are clearly not suitable for use as sole nutritional provision and their use is not recommended other than in the critical care management of burns and severe trauma. The most dramatic example of the effects of pharmacological administration of glutamine comes from the REDOXS study where high doses of glutamine - given both enterally and parenterally and in doses well out of proportion to the protein provision - led to substantially worse outcomes, most dramatically so in those with hepatic or renal impairment (24).

In critical care patients undergoing dialysis or haemofiltration the substantial losses of glutamine in the dialysate suggest that its addition to feeds might be valuable, but this is yet to be confirmed. Some malnourished patients with head and neck cancer may also benefit. However, despite the passage of more than a decade since the preliminary studies there are still no data which support routine enteral glutamine supplementation in any other patient groups. It is not warranted as a stand-alone addition in general surgical patients, in critical care practice, nor routinely in cancer management.

Table 7
Glutamine content in commercial formulae

Glutamine in nutritional formulae

Glutamine content of typical commercial formulae

Standard whole protein formulae	2-3g/l
High protein formulae	3-4g/l
Peptide-based formulae	1-1.5g/l
Amino-acid-based formulae	

Glutamine supplemented complete formulae (from manufacturers' websites)

Impact Glutamine (Nestle)	15g/l	(1.3kcal/ml)
Nutricomp Immun (B Braun)	20g/l	(1.5kcal/ml)
Reconvan (Fresenius Kabi)	10g/l	(1.0kcal/ml)

3.4 Other Agents

Many other nutrients and potential nutriceuticals or functional foods have been advocated for nutritional practice. Some of these are included in combination with other modifications, most typically so in the immune-enhanced feeds where they sit alongside ω-3 fatty acids or arginine.

The most widely used are various combinations of antioxidants. It is difficult to provide a unifying commentary on antioxidant supplementation of enteral formulae as they have been used in so many different combinations and at so many different concentrations. As there is potential for harm at high doses and because no consensus can be drawn from the literature ESPEN guidelines currently advise against their use in all circumstances other than their inclusion in immune-enhancing combinations that have been specifically studied and found to be beneficial.

Nucleotides are also included in immune-enhancing formulae. Evidence that they are helpful is even less apparent and they cannot be recommended.

Amino acids other than glutamine and arginine have their protagonists including leucine, taurine and citrulline, but at present there is insufficient data to support their widespread use.

Supplementation with probiotics clearly falls outside the present brief, but the revision of standard feeds to include fibre has made an important step towards the utilisation of prebiotics since several manufacturers use fibre sources that have specific effects on identifiable components of the intestinal microbiome (such as fructose-oligosaccharides and the bifidobacteria). At present the benefits can be explained only in the broadest sense from the inclusion of non-specified fibre but it can be expected that the future choice of specific fibres will be better defined.

In many countries commercially prepared enteral feeds are poorly available and barely used, the provision of tube feeding relying very successfully on blenderised preparations of normal or modified foods. There is probably much to be learnt from analysis of their contents beyond their basic description in terms of energy and protein content, valuable though that is.

4. Summary

Formulae for enteral nutrition offer a variety of opportunities to prevent and treat malnutrition during the course of a disease. Most patients in need of enteral support will respond well to standard polymeric feeds based on whole proteins, complex carbohydrates and long chain triglycerides. Additional formulae have been devised incorporating (often hypothetical) adaptations to suit a specific disease area, or including novel components postulated to add a functional element to the pure delivery of nutrients. In only a very few specific contexts are there adequate data to support the use of these modified feeds.

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