Home Parenteral Nutrition

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Edited by

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A catalogue record for this book is available from the British Library, London, UK.

A catalogue record for this book is available from the Library of Congress, Washington DC, USA.

ISBN-10: 1-84593-156-4
ISBN-13: 978-1-84593-156-9

Produced and Typeset in 10pt Baskerville by Columns Design Ltd, Reading
Printed and bound in the UK by Biddles Ltd, Kings Lynn

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Preface

This Book has been designed to cover all the aspects of Home Parenteral Nutrition (HPN) on basis of the evidence-based medicine but also on the experience of worldwide experts in this field. We are deeply grateful to all the contributors – physicians, surgeons, nurses, dieticians, pharmacists – who contributed to the realization of this Book.

HPN was initiated by some pioneers in the early seventies in North America and in Europe and was initially conceived to provide nutrition to patients who were suffering of life threatening chronic intestinal failure. Progressively, the HPN use was extended to patients with advanced cancer who were enable to eat. HPN being at the edge of medical, ethical, psychological issues, a multidisciplinary approach is mandatory for taking care of these patients.

For these reasons, we felt useful to collect all the knowledge in this field – covering all these aspects of such treatment – in a book. The main objective of this Book on HPN is to share the knowledge and the expertise of clinical researchers in this field with all the teams following patients on HPN.

The first part provides an overview on the history of HPN in the world and the epidemiology in different areas around the world, raising some differences in the use of HPN throughout various countries.

The second part is dealing with the most frequent clinical conditions in which HPN can be initiated, from the short bowel syndrome to the cancer patient.

Part III is devoted to HPN complications but mainly conceived to provide recommendations for preventing these complications.

In the part IV, the authors detailed practical issues – requirements, teaching, monitoring, etc – of HPN including the contribution of pharmacists, dieticians, nurses and physicians.

A special section (V) has been reserved to HPN in children. Indeed, the use of HPN in pediatrics – infants or adolescents – has its specific

concerns ; exchange of knowledge between pediatricians and physicians for adults is obviously a wonderful source for improving our daily practice.

Finally in the part VI, some miscellaneous issues of HPN has been debated. A special interest has been given to intestinal transplantation that is considered in some patients who are on HPN; progress in this field could change our strategy in the next future.

This Book is also dedicated to our HPN patients who – in some way – also participated for improving the practice of HPN in sharing their experience and feelings with the nutritional teams.

We also underline the role of the ESPEN-Home Artificial Nutrition working group that supported the project of this Book, but also provided the opportunity to create a network on HPN in Europe.

Finally we wish to thank CABI Publishing for the joined effort to produce a moderne and updated Book that – we hope – will be of interest for each people being involved in a HPN programme.

Federico Bozzetti Michael Staun André Van Gossum

Part I

Parenteral Nutrition: an Overview

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1 History of Parenteral Nutrition

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Introduction

Although the modern era of home parenteral nutrition (HPN), using central venous catheters to treat patients with disease, began almost four decades ago, its origins are almost four centuries old. A number of authors, including several pioneers in the field, have reviewed various aspects of parenteral nutrition (PN): some focused on nutrients and nutritional requirements (Levenson *et al.*, 1984; Shils, 1984; Winters *et al.*, 1984), others on pharmaceutical developments (Hardy, 1995), fluid administration (Barsoum and Kleeman, 2002), access routes, paediatric PN (Winters *et al.*, 1984) or on combination of these (Meng, 1976; Dudrick, 1977; Macht, 1980; Rhoads *et al.*, 1981; Hartmann, 1985; Wretlind and Szczygiel, 1998; Vinnars and Wilmore, 2003). Here, a very brief overview is provided, with a focus on HPN.

Terminology

PN involves the administration of nutrients using routes other that the gut. This could include infusion of nutrients into veins, arteriovenous shunts, subcutaneous tissue, muscle or bone. Although all of these access routes have been tried at one time or another, PN usually involves the intravenous route, and for patients on HPN it almost invariably involves central venous catheters. The term hyperalimentation, introduced by Jonathan Rhoads in the USA, implies that patients can be given nutrients in excess of their normal requirements, even if they are sick or unconscious. The term 'artificial gut' was used by Scribner *et al.* in 1970 (Scribner *et al.*, 1970) to describe the use of PN to treat patients with intestinal failure (analogous to renal failure or cardiac failure).

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Early Historical Developments

Since venous access is of key importance to the practice of PN, its history can be justifiably said to begin with the discovery, in 1628, of the circulatory system (Harvey, 1628) by William Harvey. By 1658 Sir Christopher Wren and colleagues had reported on the effects of infusing ale, wine, opium and oil to dogs, using hollowed-out goose quills, which acted as needles/catheters, and a pig's bladder which acted as a reservoir. For example, Sir Christopher Wren wrote: 'I injected wine and ale into the mass of blood of a living dog by vein in good quantities, till I made it drunk'.

Some key historical events leading to the successful introduction of PN, first in hospital, and then in the community, are summarized in Box 1.1. It lists the developments under different headings ('General', 'Venous access', 'Macronutrients' (fats, carbohydrates and proteins/amino acids) and 'Other nutrients'), although the developments overlapped in time and were interdependent. Developments in PN, and ultimately in HPN, were facilitated by a better understanding of the metabolic response to trauma, sepsis and other diseases, as well as a better understanding of the nutritional fluid and electrolyte needs of these conditions and their effects on acid-base regulation. Understanding the chemical structure, stability and biological effects of a variety of nutrients that were discovered in the latter part of the 19th century and first half of the 20th century was also very important. However, before PN could become widespread and used to treat patients at home, it was essential that the nutrients could be delivered in a safe and predictable way.

Patients and Indications

The first case of home PN took place in 1969, and was managed by Shils and colleagues in New York, USA (Shils *et al.*, 1970). It involved a 37-year-old woman with a short bowel syndrome, who was given PN for a period of 7 months. She was readmitted for small bowel transplantation, but she died from post-operative complications (see Chapter 3, this volume). This patient was infused through an arteriovenous shunt, which became infected and blocked. Most of the subsequent cases of HPN in the USA and other countries involved central venous catheters.

The first patient to receive HPN in Canada started treatment in 1970, following an almost complete bowel resection due to mesenteric vessel thrombosis (Langer *et al.*, 1973). The patient survived for another 20 years. Another patient, who started HPN in Canada in 1972, probably holds the record for being on HPN the longest (over 32 years; see Chapter 4, this volume).

Following these landmark events, HPN began to be practised in the 1970s more widely in North America and, for the first time, in several European and other countries, such as Australia. With the exception of

Box 1.1. Some key chronological developments leading to PN and HPN

General

1628: discovery of the circulatory system reported by William Harvey.
1658: intravenous infusion of alcohol, lipid and opium into animals reported (experiments began in 1656).
1831: successful intravenous administration of a solution (essentially saline solution) for treating excessive fluid losses due to cholera (Latta, 1831).
1923: Seibert's work on pyrogens (Seibert, 1923, 1963), led to the subsequent description of principles and methods for providing pyrogen-free intravenous fluids.
1904: subcutaneous PN (fat, glucose electrolytes and peptones) in humans (Freidreich, 1904).
1955–1965: peripheral and sometimes central PN was used by clinicians for limited periods (5 or 10% glucose, protein hydrolysates and intravenous fat) (Levenson *et al.*, 1984).
1967: successful intravenous nutrition over prolonged periods, allowing normal growth in beagle puppies (Dudrick *et al.*, 1967).
1967: successful prolonged central venous PN with 20–25% dextrose and 4–5% amino acid solution.
1969: home PN in USA (Shils *et al.*, 1970).
1970: home PN in Canada (Langer *et al.*, 1973).
1970s: home PN in several European and other countries (see text).
1972: introduction of the 'all-in-one' bag for long-term use, which is now routinely used in HPN (Romieu *et al.*, 1972).
1970 to present: evolution of HPN in different ways in various countries (Elia and Baldwin, 1999; Moreno *et al.*, 2001) (see text).
2003: International Organization for Standardization (ISO) produced a document (ISO 14698-1) outlining a strategy for implementing ISO 14644 (limits to particles and bacteria in the environment). This development arose from an outbreak of bacterial contamination in PN bags.

Venous access

1658: hollowed-out goose quills used as needles for intravenous infusions.
1940s: variable success at administrating 15–20% dextrose solutions to humans (Dennis, 1944; Dennis *et al.*, 1948); phlebitis was a problem.
1949: hypertonic dextrose and protein solutions given successfully through central venous catheters in dogs (Meng and Early, 1949; Rhode *et al.*, 1949).
1952: description of central (subclavian) vein cannulation (Aubaniac, 1952), although catheters threaded centrally had been reported as early as 1944 (Levenson *et al.*, 1984).
1967: use of a technique for placement of central venous catheters for hypertonic PN in humans (Dudrick *et al.*, 1968, 1969).
1969: arteriovenous shunt used for venous access in the first patients on home PN in the USA (Shils *et al.*, 1970).

Macronutrients

Carbohydrate

1843: Claude Bernard showed that sugar solutions could be safely given parenterally to animals (Foster, 1899) (later, he injected glucose into one of his own veins).

Box 1.1. *Continued*

1887: Landner proposed that glucose could be used as part of a regimen for 'artificial nutrition'.
1896: successful intravenous infusion of glucose in man (Biedl and Kraus, 1896).
1915: Woodyatt *et al.* reported that up to ~0.85 g glucose/kg/h could be supplied intravenously to humans without resultant glycosurea (Woodyatt *et al.*, 1915).
1967: Long-term hypertonic glucose infusions in humans (Dudrick *et al.*, 1968).

Protein/amino acids

1870–1900: infusions of milk into man, but severe systemic reactions could occur.
1913: successful infusion of non-allergenic protein hydrolysate to nourish a goat for 16 days (Henreiques and Anderson, 1913).
1937: similar and more extensive successes with protein hydrolysates in animals (Elman and Weiner, 1939).
1939: a solution of 2% casein hydrolysate and 8% dextrose was infused into a patient without reaction (Elman, 1937).
1940: synthetic crystalline amino acids infused into infants reported (Schohl and Blackfan, 1940).
1964: crystalline amino acid solution introduced in Germany (Bansi *et al.*, 1964).
1970s: crystalline amino acids replaced commercial protein hydrolysates.
1980s: dipeptides, such as glycyl-glutamine or alanyl-tyrosine, were developed to stabilize unstable amino acids (e.g. glutamine) and solubilize amino acids with poor solubility (e.g. tyrosine). These are used in some commercial preparations today.

Fat

1678: intravenous administration of lipid in animals reported by Christopher Wren.
1869: subcutaneous injection of fat in dogs without adverse effects (Menzel and Perco, 1869).
1869: subcutaneous injection of fat into man suffering from malnutrition and Pott's disease.
1915: first fat emulsion given intravenously to animals (Murlin and Riche, 1915).
1920: first fat emulsions given intravenously to paediatric patients in the USA (Rhoads, 1975).
1961: safe and effective intravenous lipid emulsion (Intralipid) developed by Wretlind in Sweden (Schuberth and Wretlind, 1961). This was approved in most European countries by 1963, but not in North America until 1977.
1964: Food and Drug Administration in the USA banned fat emulsions derived from castor oil and cotton seed oil due to adverse reactions.
1980 to present: new types of lipid emulsions developed, including those containing medium-chain triglycerides, fish oils and structured lipids, but these have not been widely used.

Alcohol

1658: alcohol infused in animals.
1970s: alcohol was included in some commercial PN preparations, and used widely in some centres.
1980 to present: intravenous nutritional products containing alcohol were withdrawn at a time when the practice of HPN was growing in many countries.

Other nutrients

See text.

Solassol *et al.* in France, who by 1973 had already reported the use of long-term intravenous feeding in 75 patients (Solassol *et al.*, 1974), HPN in Europe was generally slow to develop. For example, in Britain, the first reports of HPN appeared in the late 1970s.

The commonest indication for HPN in different countries, which mainly involved adults, was the short bowel syndrome due to surgical resections, in patients with Crohn's disease, and mesenteric vascular disease. Over time, the age distribution of patients increased to encompass more (often younger) children and older adults – trends that are continuing in several countries today. At the same time, the indications for HPN widened. HPN began to be used for an increasing number of paediatric conditions, such as autoimmune enteropathy, necrotizing enterocolitis and congenital malformations. In some countries, such as the USA, it was also used for a growing number of patients with HIV, and in both the USA and many other countries it began to be used increasingly to support patients with malignant conditions. However, international differences in the indications for HPN became apparent. For example, although the proportion of patients given HPN because of malignant disease has steadily increased in the UK, the proportion has been relatively small (< 5% among those who started HPN in the period 1996–2000, and < 5% among those who received it at a given point in time during the same period) (Elia and Baldwin, 1999). In contrast, in other European countries the figures were several-fold greater (Van Gossum *et al.*, 1999).

It has also became apparent that the prevalence of HPN (per million of population) varied considerably between countries (Elia, 1995; Elia and Baldwin, 1999; Elia *et al*, (2001)) and was related to economic factors: lowest in low-income countries, such as several African countries and in India, intermediate in Western European countries and highest in the USA.

The success of PN in human patients led to its use in animal patients (veterinary medicine), such as dogs and horses, although this practice has not become widely used.

Developments in Preparation, Setting up and Infusing PN

In the 1970s the administration of PN, including HPN, often involved multiple bottles (dextrose, amino acids, saline, fat emulsion). This was tedious, time consuming and increased the risk of errors and complications, such as catheter-related infections. In addition, the composition of vials containing vitamins and micronutrients was not optimal for long-term intravenous use. For example, the first patient on HPN (Shils *et al.*, 1970) was reported to have received four different commercial vials of vitamins, which were believed to be necessary, as well as eight other types of solutions (a fat emulsion was not included in the initial formulation). Infusion schedules were also frequently complex.

Commercial companies took up the challenge of producing new formulations that simplified the administration. Such developments which

have taken place since the 1970s were also made possible by pharmaceutical developments and appreciation of specific patient needs:

1. Large plastic bags ('all-in-one' bags), which allowed nutrients to be mixed together and delivered all nutrients together over a prescribed period of time. Although the use of 'all-in-one' bags in the community was first reported in 1972 (Romieu *et al.*, 1972), their use did not become widespread until the 1980s. The compatibility of nutrients had to be carefully assessed to avoid, for example, precipitation of calcium phosphate, or destabilization of lipid emulsions by divalent cations. This field of investigation led to the development of pre-nutrients, such as organophosphates, which were stable and soluble and did not cause precipitation. Once within the body, the organophosphates, such as glucose phosphate, or glycerol phosphate, were hydrolysed to yield free phosphate and either glucose or glycerol.
2. Multilayered bags, which were studied in the 1990s, were found to limit the diffusion of oxygen that was responsible for degradation of the following: (i) some amino acids, such as cysteine; (ii) some vitamins, such as vitamin C, especially in the presence of the catalytic effect of copper; and (iii) some drugs, such as ranitidine. Such bags are now routinely used for HPN in many countries.
3. Backpacks and plastic 'vests', which allowed the infusate to be carried in plastic vests or backpacks while the patient remained mobile, e.g. able to work outside their home. The infusate is delivered into a central vein via a lightweight portable infusion pump, which is also carried in the backpack.
4. Infusion pumps. Many of the initial infusion pumps, which were designed for use on hospital wards, were bulky, noisy and not ideal for home use. Therefore, new pumps were designed that were smaller, lighter and more user-friendly for home use.
5. Administration stands. Some of the stands were found to be unsuitable for use over certain surfaces in the home. For example they were bulky, had small wheels and could not easily be moved up or down different floors, or across surfaces covered with certain types of carpets. In the UK a patient organization, 'PINNT' (Patients on Intravenous and Nasogastric Nutrition Therapy), identified these problems and designed their own stand and pump system. Now, many patients use their tailor-made portable, lightweight and practical system.

Delivery of feeds and accessories

The feed and administration sets were initially delivered to the patient's home from hospital, although in many countries this practice has been largely taken over by commercial companies, whose role varies from delivery of feeds and accessories to total care, including clinical/nursing care. To allow international travel, some companies have established a network of care, so that patients can travel abroad to work or have holidays. Feeds and accessories are delivered according to individual patient specifications.

Nutrients

Key developments in the use of macronutrients (amino acids, carbohydrate, fat and alcohol) in HPN are summarized in Box 1.1. The trends in the 1970s were to replace protein hydrolysates with mixtures of synthetic L-amino acids, which could more easily be standardized to meet quality control criteria, and to replace alternative carbohydrates such as fructose (and to a much more limited extent other carbohydrates such as sorbitol) with glucose, which was always the most widely used carbohydrate. In the USA, the adverse effects of administering castor and cotton seed oils (fever, coagulation problems, back pain, jaundice) led to their ban in 1964. This also led to a slower introduction and use of smaller quantities of lipid emulsions compared to many European countries, when a safe lipid preparation emerged from Sweden in 1961 (Schuberth and Wretlind, 1961). Later, alcohol was introduced but withdrawn from commercial intravenous preparations, mainly in the 1970s, because of concern about potential adverse effects on the liver and brain.

A historical review of other nutrients in HPN is beyond the scope of this brief article, but three points are summarized below:

1. The quantity of some nutrients delivered to patients on PN (including HPN) was sometimes less than the amount prescribed. This was due to degradation (e.g. oxidation of vitamin C) or adsorption of nutrients onto the bags. It was found that photo-degradation of certain vitamins, notably vitamin A, could be reduced by administering the infusion overnight, covering the bag with a light, impermeable material and by using an all-in-one bag containing lipid emulsions, which limited the transmission of light.
2. The profile of trace elements and minerals for PN use was different from that for oral nutrition due to their variable absorption, which in healthy subjects ranges from less than 10% (e.g. chromium, manganese) to almost 100% (e.g. sodium, potassium fluoride). A range of nutrient deficiencies and some toxicities, due to inadequate or excess provision of the nutrients, was described within a few years of the introduction of PN in hospital and at home.
3. The term 'total parenteral nutrition' (TPN) is still used today, but it has now largely been replaced by the term 'parenteral nutrition' (PN), since it was recognized that several nutrients were not (and are still not) included in routine PN, e.g. carotenoids, choline, taurine, glutamine, fructose and certain fish oils.

Finally, in some patients, the 'artificial gut' (PN) has been replaced by a transplanted gut (Langnas, 2004). A study in Pittsburgh, USA, involving 169 patients, reported 75% survival at 1 year, 54% at 5 years and 42% at 10 years. There is still some way to go with intestinal transplantation, but in the future it may become a much more common and realistic option for patients on long-term HPN.

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2 Home Parenteral Nutrition in Europe

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History and Epidemiology

The use of parenteral nutrition started in the early 1960s. It is commonly cited that Shils *et al.* were the first in North America to report their experience of maintaining a patient at home on parenteral nutrition (Shils *et al.*, 1970). However, we should remember that Solassol and Joyeux were, at the same period, the pioneers of home parenteral nutrition (HPN) in Europe (Montpellier, France) (Solassol and Joyeux, 1976).

Although Shils' first patient survived only a few months, several teams in North America and in Europe initiated a programme of HPN during the 1970s. Subsequently, HPN programmes were progressively launched in several Western European countries.

After a few years of practice, several European teams reported their experience in HPN, describing a low incidence of complications and good survival rate (Jarnum and Ladefoged, 1981; Mughal and Irving, 1986; Messing *et al.*, 1988).

Since 1990, several people originating from different European countries who were interested in the field of HPN have collaborated in creating the Home Artificial Nutrition (HAN) working group, which was further officially recognized as an ESPEN working group in 1997. The main goals of the ESPEN-HAN group were to perform epidemiological surveys throughout Europe, to harmonize the use of HPN and to formulate recommendations for good practice.

Multicentre surveys were performed by the ESPEN-HAN working group in 1993, 1997 and 2003, respectively (Van Gossum *et al.*, 1997; Van Gossum *et al.*, 1999; Staun *et al.*, 2004). Between January 1 and December 31 1997, a total of 494 patients were registered as having started HPN in 73 centres from nine European countries (Van Gossum *et al.*, 1999). On 1 January 1998, there were 756 patients receiving HPN from these

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centres. Incidence and prevalence could be estimated in seven out of the nine countries. At this time, the incidence was estimated to be $3/10^6$/year in France; $1.2/10^6$/year in the UK and $0.7/10^6$/year in Spain. The highest prevalence was described in Denmark ($13/10^6$/year), while it reached about $4/10^6$/year in the UK and in France. So, it was clearly apparent that the prevalence of HPN patients was the highest in countries having the longest duration of HPN experience (Denmark, France and the UK). A similar survey was performed by the ESPEN-HAN group in 2003, but reliable estimation of the incidence was not possible (Staun *et al.*, 2004).

Since 1997, data concerning HPN incidence have been available in only a few European countries. In the UK, a national register was started by BANS in 1996 (Glencorse *et al.*, 2003), and the number of registered adult HPN patients has grown progressively since then. An increase in the number of centres reporting was seen in 2002 but, despite this, it is felt that HPN is under-reported. A total of 103 new adult patients were registered in 2002, bringing the total number of registered patients receiving HPN at the end of 2002 to 465. It is noteworthy that there are significant national – but also regional – variations in the reporting of HPN. In Scotland, all patients receiving HPN have been identified with the development of the Managed Clinical Network (MCN), and data from 2001 found the point prevalence to be 12 patients per million of the population (Baxter and McKee, 2003). This figure exceeds the overall UK rate for that year of approximatively eight patients per million of the population. Within the UK, further regional variations have also been identified.

In Spain, data are collected annually throughout a designed questionnaire (Planas *et al.*, 2004). In 1997, the registration rate of HPN in Spain was about 0.7 patients/10^6 inhabitants/year. In 2000, 14 hospitals participated and 67 patients – adults and children – were newly enrolled. The registration of patients that was expected to reflect the incidence was $1.9/10^6$ inhabitants/year. In 2001, 17 hospitals participated, enrolling 66 patients (1.65 patients/10^6 inhabitants/year).

In France, a national HPN registry was open in 2001 (Joly *et al.*, 2004). Between June 2001 and June 2004, 413 adults were included in the registry; the estimated incidence being three newly enrolled patients/10^6 inhabitants/year.

There are very few data about the incidence of HPN in children in Europe. A survey on HPN in children was performed in Europe in 1997 (Van Gossum *et al.*, 1998). The incidence and prevalence of child HPN were calculated according to the estimated population – from 0 to 16 years – for the countries in which more than 80% of HPN patients were registered. At this time, a total of 100 patients were registered from 19 centres that belonged to six European countries. Estimated incidences (patients/million inhabitants below age 16 years) were as follows:

- France, 4.9;
- Denmark, 3.7;
- Belgium, 2.5;

- UK, 1.7;
- Poland, 0.7; and
- Spain, 0.23.

Estimated prevalences at 1 January, 1998 were as follows:

- France, 8.9;
- Belgium, 3.5;
- Denmark, 3.5;
- UK, 3.3;
- Poland, 1.3; and
- Spain, 0.34.

According to the recent French registry, the estimated incidence for HPN children in France was stable in 2004 at $5/10^6$/year (Joly *et al.*, 2004). In the UK, there has been little variation in the number of children registered with BANS over the last 4 years (new registrations: (i) 1999, 11 cases; (ii) 2000, 14 cases; (iii) 2001, 13 cases; and (iv) 2002, 11 cases) (Glencorse *et al.*, 2003). Since 1999, the point prevalence of HPN in children has remained stable (68 in 2002).

Indications

The survey that was performed in Europe in 1997 showed that, overall, the distribution of underlying diseases requiring HPN was quite similar in Europe and in the USA (Van Gossum *et al.*, 1999; Howard and Ashley, 2003). At this point in time, cancer had already become the largest single worldwide indication for HPN (40%). Crohn's disease, mesenteric vascular diseases, radiation enteritis and disorders of intestinal motility remain the most frequent benign conditions requiring long-term HPN. HPN is also used in AIDS patients with intractable diarrhoea. However, the number of AIDS patients receiving HPN has recently decreased since the introduction of more efficacious triple therapy. We have to emphasize that 25% of HPN patients suffer from 'miscellaneous' diseases, including chronic pancreatitis, intestinal mucosal atrophy, anorexia nervosa, cachexia, etc.

However, the distribution of underlying diseases in HPN patients varies markedly between the different European countries (Van Gossum *et al.*, 1999; Table 2.1). For example, in 1997 Crohn's disease accounted for 44% of indications in UK but for only 13% in The Netherlands; in contrast, cancer represented 60% of indications in The Netherlands but only 5% in the UK. An earlier (1993) survey showed that cancer was the main indication for HPN in Italy (67%) (Van Gossum *et al.*, 1997). If we consider the benign diseases, the most common indications were small bowel resection, digestive fistulae and motility disorders. For cancer patients the main indication is intestinal obstruction, which is common in the case of peritoneal carcinomatosis.

Table 2.1. Indications for HPN in seven different European countries (1997) where reporting was assumed to be more than 80% of patients (from ESPEN-HAN, 1999).

	Patients (*n*)	Crohn's disease (%)	Vascular (%)	Cancer (%)	Radiation (%)	AIDS (%)	Others (%)
France	173	16	23	27	15	0.5	18.5
United Kingdom	72	44	14	5	2	–	35
Belgium	26	12	15	23	15	35	–
Denmark	15	20	13	8	26	–	33
The Netherlands	45	13	11	60	–	–	16
Spain	31	16	13	39	–	6	25
Poland	14	14	50	–	14	–	22

Another survey was performed by the ESPEN-HAN group between December 1998 and March 1999 (Van Gossum *et al.*, 2001). Nine centres in five European countries participated in this study, including only patients with benign diseases who had been receiving HPN for at least 2 years. This survey included 228 adult patients, including 141 females and 87 males, with a median age of 49 years (19–92). The underlying conditions were:

- Crohn's disease (33%);
- mesenteric vascular diseases (25%);
- post-surgical (19%);
- intestinal pseudo-obstruction (8%);
- radiation enteritis (4%);
- abdominal trauma (2%); and
- miscellaneous (8%).

Intestinal anatomy was defined in 222 patients. The remaining small bowel length was less than 50 cm in 84 patients, less than 100 cm in 67 patients, less than 200 cm in 44 patients and less than 300 cm in six. Twenty-one patients had undergone no small bowel resection (12%). In patients with a short bowel, the intestinal surgery had been terminal jejunostomy (I) in 41%, jejunocolic anastomosis (II) in 46% and jejuno-ileocolic anastomosis (III) in 13%. As also expected, 80% of the patients had a short bowel. The fact that 65% of these patients had less than 1 m of remaining small bowel and that 88% had a type I or II anastomosis confirms previous observations that showed the importance of both the length of the residual small bowel and the type of intestinal anastomosis for predicting HPN dependency (Messing *et al.*, 1999).

In the UK, according to the most recently available data, Crohn's disease was still the most common underlying condition, representing 25% of new registrations in 2002 (Glencorse *et al.*, 2003). However, the point prevalence data for Crohn's disease have decreased from 44% of HPN patient registrations in 1996 to 32% in 2002. In 2002, cancer represented 14% of new registration as opposed to 5% in 1997. In Scotland, the distribution of underlying diseases was very similar to that of the rest of the

UK, with 39% of patients with Crohn's disease and 10% with cancer (Baxter and McKee, 2003; Glencorse *et al.*, 2003).

In the Spanish Registry, the percentage of cancer patients was 16.4% in 2000 and 22.7% in 2001, respectively (Planas *et al.*, 2004).

It has been known for at least 10 years that cancer is the main indication for HPN in Italy (Van Gossum *et al.*, 1997). In 2001, the SINPE Registry had recorded 1604 patients, of which 1103 (68.8%) had cancer pathology (Balzola, 2001). These cancer patients were divided between 33 centres, with one to 263 patients per centre (average 33). The gender distribution was 56% male and 44% female. When grouped by age, 28% were aged 18–44 years, 54% were 46–65 years and 29% were over 65 years old. The distribution of tumours was as follows:

- gastric and oesophageal (32%);
- intestinal (22%);
- head and neck (19%);
- other cancers (17%);
- pancreatic (6%); and
- ovarian (4%);

The main indications for HPN in these cancer patients were:

- insufficient oral intake (36%);
- motility disorders (34%);
- short bowel syndrome (7%); and
- presence of intestinal fistulae (3%).

According to the last data available from France, the percentage of cancer patients has now reached 30% (Joly *et al.*, 2004).

Recently, a retrospective survey on HPN in Europe from January to December 2003 was performed by the ESPEN-HAN group (Staun *et al.*, 2004). Forty-one centres in nine countries completed the questionnaire. Of these centres, 18 had participated to the previous survey in 1997. The experience of the centres ranged between 3 and 32 years (mean, 16 years). Centres ranged in size from three to 135 patients (mean, 35/centre), representing a total of 1117 patients on HPN. The distribution of underlying disease in the total cohort of the ongoing patients was:

- Crohn's disease (22%);
- mesenteric vascular disease (21%);
- surgical circulatory complications (16%);
- cancer (15%);
- radiation enteritis (7%); and
- miscellaneous (17%).

In the case of child HPN, the 1997 European survey provided the following distribution:

- intestinal atresia (19%);
- intractable diarrhoea (13%);

- necrotizing enterocolitis (12%);
- intestinal congenital malformation (6%);
- autoimmune enteropathy (3%);
- gastroschisis (3%);
- microvillus inclusion criteria (3%);
- volvulus (1%);
- other diseases, including Crohn's disease and Hirshprung's (40%) (Van Gossum *et al.*, 1998).

Practical Aspects

Perfusion regimen

In the 1997 survey, in the majority of the cases (69%), administration of nutritional solutions was performed through a subcutaneous tunnelized catheter positioned in the vena cava via the internal jugular vein or subclavian vein, preferably on the right side (Van Gossum *et al.*, 1999). Based on the reports of the North American Registry on HPN and the European surveys, the use of subcutaneous reservoirs (port-a-cath) is growing (Van Gossum *et al.*, 1999; Howard and Ashley, 2003). This trend is due, on the one hand, to its wide use in cancer patients receiving chemotherapy and, on the other, to the preference of some patients for implantable catheters for functional and aesthetic reasons – for instance, for practising aquatic sports or for taking a shower. In the 2003 survey, 26% of 1117 HPN patients had received an implanted port (Staun *et al.*, 2004).

The number of perfusions administered per week may vary with intestinal adaptation capacities. The European survey has shown that the numbers of bags used per week were as follows: 7 (67%), 6 (9%), 5 (12%), 4 (8%) and 3 or less (4%) (Van Gossum *et al.*, 1999).

Oral feeding is not only allowed but also encouraged in patients without bowel obstruction or in need of bowel rest. It has been shown that patients with short bowel are in fact hyperphagic. In the 1997 European survey, 50% of patients had free oral intake, 27% had limited oral intake, while 23% ingested nothing (Van Gossum *et al.*, 1999).

In the ESPEN-HAN survey, which included only long-term HPN patients, the median duration of HPN was 7 years (range 2–24) (Van Gossum *et al.*, 2001). At the time of evaluation, the mean number of nutritional bags used per week was 5.6 (range 1–7), with a mean of 1.6 lipid-based bags per week. The regimen of perfusion was cyclical nocturnal in 224 patients, cyclical diurnal in 2 and over 24 hours in 2. Intravenous (IV) catheter care was performed by patients (94%), community nurses (4%) or by relatives (2%). Oral food intake was unlimited in 81%, restricted in 17% and nil in 2%.

In this population, the composition of the nutritional support was conventional, with a mean number of 5.6 bags supplied weekly, with a predominance of the cyclical nocturnal regimen and autonomous

manipulation. The provision of bags containing lipid emulsions was, however, quite low (1.6 bags per week); this could be explained by the fact that low caloric supplementation is needed in some patients with a short gut because of the capability of energy absorption by the colon, as well as by the hyperphagic behaviour of these patients who nearly all – in this series – had unlimited oral intake. It is also probable that some teams limited the administration of lipid emulsion because they were concerned about hepatic changes.

Training

In the 73 centres that reported their training technique in 1997, 75% had a nutrition support team and 76% had an HPN training programme (Van Gossum *et al.*, 1999). Seventy per cent of the patients received in-hospital training. After training, 48% of patients had become self-caring; for the others, the necessary care was provided by relatives (10%) or by community nurses (35%).

In a more recent survey – also performed by the ESPEN-HAN group – in 51 centres in seven European countries, one or more criteria were used by 62% of the centres to exclude patients from their HPN programme:

- intellect (33%);
- social situation (25%);
- physical disability (24%);
- underlying disease (18%); and
- age (16%) (Wegner *et al.*, 2003).

Generally, hospital nurses/clinical nursing specialists (84%) and/or doctors (39%) trained two or more people in an in-patient setting over 1–2 weeks.

Prognosis

Several studies have shown that survival (prognosis) is linked to the underlying disease. In the 1997 European survey, the mortality rates after a 6–12-month follow-up period were as follows:

- cancer, 74%;
- AIDS, 34%;
- radiation enteritis, 21%;
- miscellaneous, 16%;
- vascular disease, 13%; and
- Crohn's disease, 4% (Van Gossum *et al.*, 1999).

The North American HPN Registry reported similar results (Howard and Ashley, 2003). The 2003 survey, performed by the ESPEN-HAN group, included 1117 newly enrolled patients in 41 centres; this showed that the

mortality rate was slightly better than that found in the 1997 study for patients with benign disease (Staun *et al.*, 2004). Indeed, the mortality was 0.8% in Crohn's disease patients and 5.1% in patients with vascular disease. In cancer patients, the mortality rate was still very high (85%). Messing *et al.* performed a study on 217 HPN patients with benign diseases enrolled in an HPN programme between 1980 and 1989 in Belgian/French specialized centres (Messing *et al.*, 1995). Seventy-three patients died during the follow-up period, with a mortality rate due to HPN of 11%. This work showed a survival probability at 1, 3 and 5 years of 91%, 70% and 62%, respectively. Multifactorial analysis of prognostic factors showed that independent factors associated with a good survival rate were:

- aged below 40 years at the start of HPN;
- initiation of HPN after 1987 – a reflection of the experience of the centre; and
- the absence of chronic intestinal obstruction.

HPN-related complications

The ESPEN-HAN group also focused on HPN-related complications in the 2001 survey (Van Gossum *et al.*, 2001). Within the 12-month period prior to evaluation, the mean number of hospitalizations was 2.7 (0–12), corresponding to a mean period of 23 days (range 0–270 days). Reasons for hospitalization were related either to the underlying diseases in 27% of those admitted to hospital, to HPN complications in 48% or to other medical reasons in 25%. Of the HPN complications, catheter-related sepsis accounted for 61%, metabolic disorders for 27% and venous access thrombosis for 12%. One of the main goals of HPN is, by definition, to avoid prolonged or recurrent hospitalization.

When we consider the 12-month period before the evaluation, the mean time of hospitalization corresponds to 8% of the year. This seems acceptable for patients with life-threatening intestinal failure. However, we have to accept that a few patients stayed much longer in hospital (up to 270 days). The mean number of central venous catheters used during the total HPN period was three (range 1–17), with a mean survival time per catheter of 34 months (range 4–245 months). During the 12-month period before evaluation, an episode of catheter-related sepsis occurred in 31% of the patients. Central venous thrombosis was reported in 9% and vascular access problems in 13% of the patients.

Rehabilitation status

When comparing the rehabilitation score before HPN with that at the time of evaluation, it appears that the percentage of HPN patients who are capable of coping with employment is about 65% (Van Gossum *et al.*, 2001).

Nevertheless, there is a sharp decrease in this percentage in favour of part-time work when on HPN. This can easily be explained by the limitations caused by the time spent on taking parenteral nutrition. On the other hand, it is clear that the percentage of grade IV (bedridden at home) patients significantly decreased, meaning that HPN may improve the status of patients who had a very low rehabilitation score before starting HPN. This study also confirms a 30% prevalence of analgesic and opiate dependence that has previously been reported as predicting a poor outcome for HPN patients. Interestingly, depression was noted in 17% of the patients. Eight per cent of HPN patients claimed a willingness to undergo intestinal transplantation, while it was considered by the medical team for 10% of the patients.

Legislation and funding

The ESPEN-HAN working group has also performed a survey on the different legislation and modes of funding home parenteral nutrition throughout Europe (Moreno *et al.*, 2001). These aspects are discussed in greater detail in Chapter 32, this volume. There is, at present, no legislation covering HPN in many Western European countries. However, in Italy, where there is regional administration, the rules apply nationwide. There are different levels of regulation of HPN, with restrictions either to certain hospitals or to use in patients with specific conditions.

The funding for HPN is provided by a national health service in all those countries with regulations. Hospital pharmacies, private pharmacists and home care companies are all involved to different degrees in providing and distributing solutions and disposables.

Conclusions and Perspectives

The use of HPN started about 35 years ago in a few European centres – as in North America – on the impulse of some enthusiastic physicians, pharmacists and nurses who were dealing with patients suffering from life-threatening intestinal insufficiency. Since then, the central IV line is considered to be an 'artificial gut'.

In most Western European countries, HPN was initiated in specialized centres that developed increasing expertise down the years. In the meantime, the number of HPN centres has increased, with a highly variable number of patients between centres. A recent survey in Europe has shown that 50% of 41 centres followed less than ten HPN patients (Pironi *et al.*, 2005). There is, however, a potential risk of loss of expertise. Indeed, it has been observed that the percentage of HPN complications and the need for intestinal transplantation (due to HPN complications) was inversely related to the experience of the HPN centres. The use of pre-filled nutrition bags (3-chamber) may certainly contribute to the more

widespread use of HPN. That may be beneficial in extending the use of HPN for some patients, but should not hide the need for specific application of parenteral support that should be adapted for each individual by specialized nutrition teams.

Initially, HPN was exclusively reserved for patients with intestinal insufficiency related to benign diseases such as Crohn's disease or mesenteric vascular disorders, short bowel syndrome being the main indication. Since the 1990s, home parenteral nutrition has been more and more used for patients with intestinal insufficiency related to an advanced cancer – mainly carcinomatosis. Cancer has become the largest indication for HPN in many European countries, as well as in North America. However, the use of HPN for cancer patients is highly variable from one European country to another, with a north–south gradient. This is probably due to medical, cultural, religious and economic factors. The global approach for cancer patients who need to be parenterally fed for a short-term period requires specific considerations that are – in some ways – different from those for long-term HPN patients with benign disorders.

Legislation and funding for HPN have been progressively adopted by several Western European countries, but the use of HPN is still problematic in many Eastern European countries. There is still a need for the expansion of expertise, the support of legislation and funding in some of these countries.

Acknowledgments

I wish to thank all the people who directly or indirectly participated in these studies, the working group that performed the ESPEN-HAN survey and, especially, the following: H. Bakker, F. Bozzetti, A. De Francesco, A. Forbes, X. Hebuterne, K. Ladefoged, M. Leon-Sanz, B. Messing, J. Moreno, A. Micklewright, T. Naber, L. Pironi, M. Pertkiewicz, J. Shaffer, M. Staun, P. Thul, A. Wegner and S. Woods. Thanks are also due to the centres that provided data.

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3 Home Parenteral Nutrition in the USA

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The Early History of HPN in the USA

Parenteral nutrition in hospitalized patients had been established for two decades before transfer of this technology to patients at home was first tried. The first attempt was made by Shils and his colleagues in 1967 (Shils, 1983). Their patient, with short bowel syndrome, was stable at home for several months but the medical consensus was that long-term survival at home was unlikely, so she was readmitted for an attempt at small bowel transplantation; she subsequently died from surgical complications. Although this first patient was receiving HPN at home only briefly, physicians were encouraged to try again, and 10 years later several centres published reports of sustained survival on HPN with high-quality rehabilitation (Jeejeebhoy *et al.*, 1973, 1976; Broviac and Scribner, 1974; Bozian and Macgee, 1976; Fleming *et al.*, 1977; Heizer and Orrigner, 1977; Steiger and Srp, 1983). Most of these early HPN patients had short bowel syndrome due to surgical resection for either Crohn's disease or mesenteric infarction.

In these early years HPN financial coverage was negotiated with the patient's medical insurance company on a case-by-case basis. Because the direct costs of home management were about 50% of the costs of in-hospital management, payers warmed to the concept of home care. In 1976 Medicare established an HPN reimbursement mechanism under their Part B prosthetic device benefit. Traditionally, this benefit had paid for artificial limbs. In this context HPN was an artificial bowel. Medicare beneficiaries were eligible if they could not be sustained by special oral or tube enteral feeding and needed parenteral support for life – or at least for an extended period of time (> 90 days).

Quite rapidly, other insurance carriers followed Medicare's lead and found a way to pay for HPN, adopting by and large the Medicare clinical guidelines (Health Care Financing Administration, 1984).

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With a reimbursement mechanism in place, the use of HPN expanded rapidly. Figure 3.1 documents the Medicare growth of HPN between 1989 and 1992. In those 4 years both the number of HPN beneficiaries and dollars spent doubled.

As clinical experience with HPN grew, two things happened: first, the age spectrum of patients widened (Table 3.1) and, secondly, the diagnostic indications broadened (Table 3.2). Oncologists began using HPN in bowel-

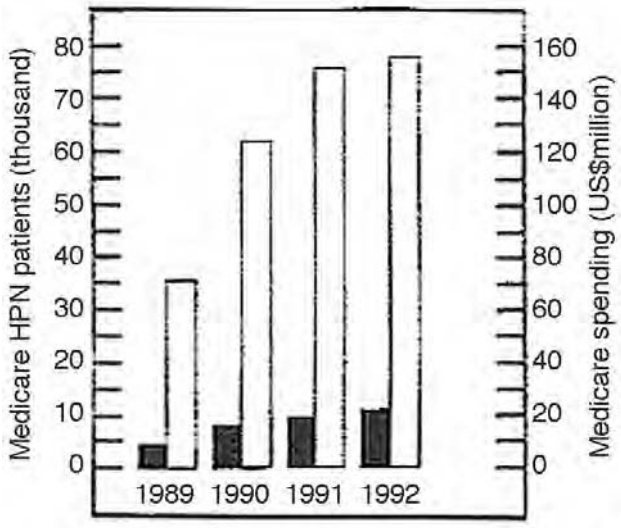

Fig. 3.1. An estimate of the number of Medicare patients receiving HPN in thousands ■ and the dollars paid in millions □ between 1989 and 1992. These estimates were derived from Medicare part B PEN workload statistics compiled by Blue Cross/Blue Shield of South Carolina (David Denny, personal communication, February 1993). This carrier processed approximately 75% of all Medicare PEN claims. Their workload statistics have been increased to provide an estimate of national Medicare activity.

Table 3.1. Change in age distribution of patients on HPN.

Age range	1980[a] (%)	1992[b] (%)
0–10	5.8	12.9
65+	8.9	15.2

[a] New York Academy Registry; [b] North American HPEN Registry.

Table 3.2. Changes in underlying conditions, 1978–1992.

Condition	1978 (%)[a]	1985–1992 (%)[b]
Crohn's and ischaemic bowel	63	17
Neoplasia	17	42

[a] New York Academy Registry; [b] North American HPEN Registry.

obstructed cancer patients (Howard, 1993): in the pre-protease inhibitor era of HIV disease, young people were wasting and dying from severe intestinal dysfunction. In many HIV programmes, HPN became the answer (Melchior *et al.*, 1998). HPN was used in congenital disorders such as extensive necrotizing enteritis, severe gastroschesis and long-segment Hirschsprungs, disorders that in prior years were considered fatal.

HPN Clinical Outcomes in the USA

Between 1984 and 1992, 217 nutrition support programmes, based in all areas of the USA and in several areas of Canada, pooled their HPN outcome data and formed the North American HPEN Registry (North American HPEN Registry, 1987–1994). Since there is no one source in North America to which all patients started on HPN have to be reported, the representativeness of the Registry sample is not known. None the less, the Registry provided a sample far bigger than any single programme experience. This large sample described the clinical outcome in 5357 HPN patients, entered in the Registry during their first year on therapy. Table 3.3 gives the percentage of patients with different diagnoses and compares this North American sample to a multinational European sample (Van Gossum *et al.*, 1999a). There are some differences, however, due to the fact that the North American sample included children. Although the proportion of cancer patients is similar, it is known that European HPN use in cancer patients is quite variable, being as low as 5% in some countries and as high as 60% in others. These points aside, the diagnostic indications for HPN appear quite similar on both sides of the Atlantic (Howard, 1999).

Figure 3.2 shows the age breakdown of HPN patients reported to the North American Registry. Clearly, HPN use extends from the very young to the very old (North American HPEN Registry, 1987–1994).

Table 3.4 summarizes 12 months of clinical outcome for 11 different underlying diagnoses. Outcome is assessed by survival on therapy, duration on therapy, rehabilitation on therapy and patient/year complication rates (this is identical to catheter/year complication rates used in other reports).

Table 3.3. Spectrum of underlying conditions in the USA and Europe.

Condition	USA[a] (%)	Europe[b] (%)
Cancer	2	39
Crohn's disease	11	19
Ischaemic bowel	6	15
Motility disorder	6	ND
AIDS	5	2
Congenital bowel	4	ND
Radiation enteritis	3	7
Other	23	18

[a] Data refer to all age groups; [b] data refer to adults only; ND, no data.

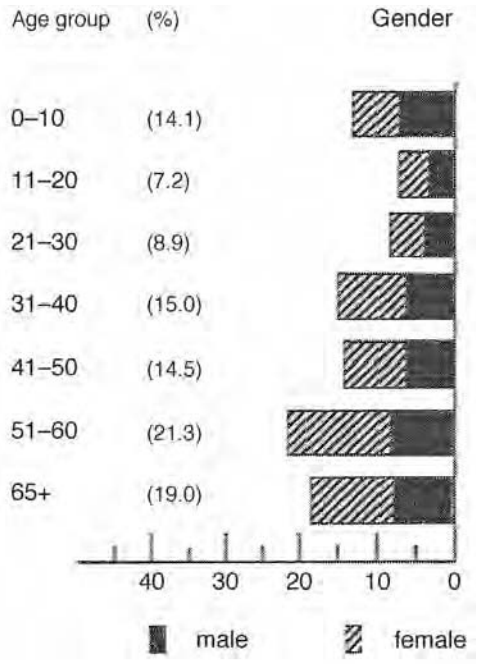

Fig. 3.2. Breakdown of US HPN patients by age and gender. Data from North American HPEN Registry, 1989.

The data show survival on therapy is largely dictated by the underlying diagnosis, and therefore it is important to report outcome in terms of a particular diagnosis and not lump several diagnoses together. While most HPN cancer patients have a short survival time, with 50% mortality in 4 months, most HPN Crohn's patients have a long survival time, with 96% surviving 1 year and 87% surviving 3 years. A number of short-bowel patients have now survived 30 years on HPN (Oley Foundation).

The Registry data show the duration on HPN as less than 1 year for most HPN patients. This finding surprises many clinicians who think short-term use is characteristic of cancer patients, but long-term use is characteristic of non-malignant, short-bowel patients such as those with Crohn's or mesenteric infarction. Table 3.4 shows the reasons why patients stop HPN, there being important differences between diagnostic groups; for example, the majority of cancer patients die but the majority of Crohn's patients eventually return to full oral nutrition.

These findings are consistent with studies in France, which showed that 75% of adults with non-malignant short bowel syndrome (< 150 cm of small intestine) achieved HPN independence, mostly in their first 2 years (Carbonnel *et al.*, 1996). After that point, 94% of adults still on HPN were indefinitely dependent. Children, on the other hand, often achieve full bowel adaption after much longer periods (5–10 years) of HPN dependency, presumably because their bowel continues to grow over many years (Vargus *et al.*, 1997). These facts about the duration of HPN explain

Table 3.4. Outcomes for various conditions of patients on HPN (from North American HPEN Patient Registry).

Condition	Average age (years)	Survival on therapy (observed/ expected deaths,%)[a]	Status at 1 year (%)[b]			Rehabilitation status in first year (%)[c]			Complications (per patient year)[d]	
			Full oral nutrition	Continuing on HPN therapy	Died	Complete	Partial	Minimal	HPN	Non-HPN
Crohn's disease	36	96	70	25	2	60	38	2	0.9	1.1
Ischaemic bowel disease	49	87	27	48	19	53	41	6	1.4	1.1
Motility disorder	45	87	31	44	21	49	39	12	1.3	1.1
Congenital bowel defect	5	94	42	47	9	63	27	11	2.1	1.0
Hyperemesis gravidarum	28	100	100	0	0	83	16	1	1.5	3.5
Chronic pancreatitis	42	90	82	10	5	60	38	2	1.2	2.5
Radation enteritis	58	87	28	49	22	42	49	9	0.8	1.1
Chronic adhesive obstructions	53	83	47	34	13	23	68	10	1.7	1.4
Cystic fibrosis	17	50	38	13	36	24	66	16	0.8	3.7
Cancer	44	20	26	8	63	29	57	14	1.1	3.3
AIDS	33	10	13	6	73	8	63	29	1.6	3.3

[a] Survival rates on therapy are values at 1 year calculated by the life table method. This will differ from the percentage listed as 'died under therapy' status because all patients with known end points are considered in this latter measure.
[b] Not shown are those patients who were readmitted to the hospital or who had changed to enteral therapy by 12 months.
[c] Rehabilitation is designated complete, partial, or minimal relative to the patient's ability to sustain normal age-related activity.
[d] Complications refer only to those complications that resulted in rehospitalization.

why long-term users of HPN comprise only 15–20% of those who commence HPN. Studies of long-term HPN survivors reveal a high percentage of short bowel Crohn's patients (70%) (Smith *et al.*, 2002).

Short-term users of HPN, if they die, almost always die from progression of their underlying disease process: only 1% die from an HPN complication. Long-term users of HPN, on the other hand, if they die have a 10–15% chance of dying from an HPN complication. This appears to be the case both in the USA (Howard and Michalek, 1984) and in Europe (North American HPEN Registry, 1987–1994; Van Gossum *et al.*, 1999a).

Table 3.4 confirms earlier reports about good rehabilitation on HPN, especially in non-malignant conditions. Ninety-eight per cent of Crohn's patients and 94% of ischaemic bowel patients experience complete or partial rehabilitation (Howard *et al.*, 1995); the majority of cancer patients experience partial rehabilitation. In the Registry, rehabilitation is assessed by the professionals supporting the patient and is therefore less valid than a patient's own evaluation of his or her quality of life (Howard, 2002).

The Registry shows that adults are readmitted to hospital with an HPN complication, on average, about once a year, and half of these readmissions are for line sepsis. This translates to one septic event every 2 years, a much lower frequency than that seen in hospital PN patients. However, the infecting organisms are similar; most common are the *Staphylococcus epidermidis* group (40%), then gram-negative bacilli (30%) *Staphylococcus aureus* (20%), and Candida species (6%). The low HPN infection frequency suggests that most HPN patients do a superior job with their life-line aseptic technique. HPN infection studies report even fewer septic events in very long-term users (Buchman *et al.*, 1994).

Registry data show that age influences HPN outcome. Figure 3.3 illustrates survival for children (0–18 years), middle aged (33–55 years) and elderly (> 65 years) subjects on HPN for Crohn's disease, ischaemic bowel or a motility disturbance. These disorders are seen in all three age groups. The survival of children is superior, even when the expected higher mortality of older patients is taken into account. Table 3.5 shows children also have better rehabilitation scores and a greater likelihood of graduating off HPN. The only negative factor for paediatric patients is their more frequent readmission for HPN complications, this occurring twice a year in children but only once a year in adults. Half of these HPN-related readmissions are for suspected or confirmed sepsis.

The North American experience discussed so far is similar to European experience (Messing *et al.*, 1995; Van Gossum *et al.*, 1999a,b). However, there is a major difference in the prevalence rate of HPN on the two sides of the Atlantic. Between 1989 and 2002 HPN prevalence in the USA reached 120 per million population. This was a *yearly prevalence*, calculated from the known number of Medicare HPN beneficiaries during those years and from the percentage of Medicare patients in the large Registry sample (Howard *et al.*, 1995). In European countries *point prevalence* is the method used. This calculates the number of HPN patients on one day of the year, usually January 1.

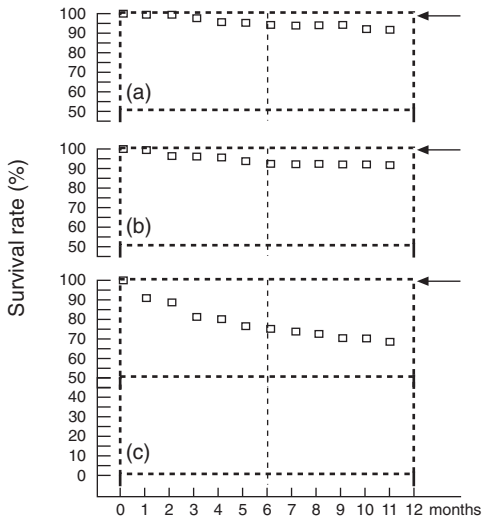

Fig. 3.3. Survival rates on HPN for (a) paediatric (age range 0–18 years), (b) middle-aged (age range 35–55 years) and (c) geriatric (age range 65 years and older) patients with Crohn's disease, ischaemic bowel and motility disorders showing the 95% confidence interval for patients surviving 12 months and indicating expected mortality rates (arrows) for the age and sex-matched individuals in the general US population. Data from Howard *et al.,* 1995.

Since a significant percentage of HPN patients use HPN for less than 1 year, *point prevalence* underestimates the *yearly prevalence*, perhaps missing two out of three patients. However, even if the US *yearly prevalence* is adjusted to resemble *point prevalence*, it would still be around 40 per million population, which is two or three times higher than the rate for any European country (Van Gossum *et al.*, 1999a). More current data about the US prevalence are unfortunately not available. However, since HPN continues to offer significant cost savings to hospitals and third-party payers, the use of HPN is unlikely to be lower, and may well be higher. In the USA, physicians may now need to block discharges on HPN when the patient is terminal or the home situation not appropriate (see Box 3.1).

Problems Facing HPN Therapy in the USA

The chief problem in the USA is not patient lack of access to HPN therapy, but a lack of qualified physicians willing to supervise HPN patients. While this problem may be systemic to how medical care is delivered in the USA, the issues involved could have relevance for Europe and for other medically advanced countries, if they move away from the model of HPN management by designated specialist centres.

To understand the US problem requires a brief description of how clinical nutrition developed on this side of the Atlantic. In the 1970s, when HPN first started, there were no trained clinical nutrition specialists – the

Table 3.5. Summary of outcome on HPN by age (from North American HPEN Patient Registry).

Age group	Average age (years)	Survival on therapy (observed/ expected deaths,%)[a]	Status at 1 year (%)[b]			Rehabilitation status in first year (%)[c]			Complications (per patient year)[d]	
			Full oral nutrition	Continuing on HPN therapy	Died	Complete	Partial	Minimal	HPN	Non-HPN
Paediatric	9	92	62	27	6	63	31	6	1.8	1.1
Middle-aged	45	90	48	42	8	62	34	3	0.9	0.9
Geriatric	72	67	34	31	29	38	47	15	0.9	0.7

Note: $\chi 2$ analysis showed a statistically significant effect ($P < 0.01$) of age on the four measures of clinical outcome. The following were formed to identify differences more specifically: survival, paediatric = middle-aged > geriatric; therapy status (resumption of full oral nutrition vs. continuing on HPN or died), paediatric > middle-aged > geriatric; rehabilitation (complete vs. partial or minimal), pediatric = middle aged > geriatric; and complications due to HPN, paediatric > middle-aged = geriatric.

[a] Survival rates on therapy are values at 1 year calculated by the life table method. This will differ from the percentage listed as 'died under therapy' status because all patients with known end points are considered in this latter measure. The ratio of observed vs. expected deaths is equivalent to a standard mortality ratio.

[b] Not shown are those patients who were readmitted to the hospital or who had changed type of therapy by 12 months.

[c] Rehabilitation is designated complete, partial, or minimal relative to the patient's ability to sustain normal, age-related activity.

[d] Complications refer only to those complications that resulted in rehospitalization.

Box 3.1. Home parenteral nutrition (HPN) is an appropriate therapy if the patient meets all of the following criteria.

1. The patient can not be maintained by oral feeding or by tubal enteral nutrition.
2. The patient has severe bowel dysfunction which is expected to persist for a long period of time.
3. The therapy will restore the patient to, or sustain them at, a normal nutritional status.
4. The therapy will restore the patient to, or sustain them at, a partial or complete level of rehabilitation.
5. The patient has sufficient home support and is medically stable enough to be managed on HPN therapy comfortably and without undue hazard.

individuals supervising hospital parenteral nutrition comprised: (i) gastroenterologists interested in absorption and the short bowel syndrome; (ii) surgeons interested in metabolism and the support of injured patients; and (iii) paediatricians interested in feeding children with failure to thrive or small premature babies.

In the mid-1970s clinical nutrition training programmes began to emerge (Howard *et al.*, 1986) and by the mid-1980s there were approximately 50 fellowship programmes graduating 20–30 trainees per year (Heymsfield *et al.*, 1985). These trainees needed subspeciality certification. The American Board of Medical Specialties (ABMS) traditionally supervises training programmes and the certification process of recognized medical specialities and subspecialities, but the ABMS had not yet recognized clinical nutrition as a subspeciality. The only certification mechanism available to these trainees was through the American Board of Nutrition (ABN) (American Board of Nutrition, 1997). The ABN was a free-standing board, developed in 1948 to qualify MDs and PhDs who wanted to participate in international surveys of human nutrition in different countries. The ABN accommodated the new genre of physician trainees by creating an MD clinical nutrition examination, alongside their PhD human nutrition tract.

Subsequently, the MD tract was subdivided into separate examinations for medical, surgical and paediatric subspecialists. Over the years attempts were made to obtain ABMS recognition for this subspeciality, but all applications were turned down on the grounds of small graduate numbers, too small to cover the ABMS fiscal responsibility for a new subspeciality. This resulted in a circular dilemma for this new field, too many uncertainties about professional recognition and too few candidates applying to be trained.

In 1997, in an effort to grow this subspeciality, several societies with an interest in nutrition formed the Intersociety of Professional Nutrition Education Consortium (IPNEC http://main.uab.edu/ipnec) and the ABN folded into this organization. Since 2001 IPNEC has offered a certifying examination under the aegis of their American Board of Physician Nutrition Specialists (American Board of Nutrition, 1997). In the past 4

years the number of physicians taking this examination has increased from 20 to 55 per year. The examination is offered in multiple locations and could, in the future, become an international certification process. If this field grows, recognition by the ABMS may be possible for US graduates in the future.

Traditionally, US physicians are reimbursed for hospital care, for clinic visits and for procedures, but they are not reimbursed for telephone management. In the supervision of HPN patients, telephone communication is central and extensive. If the patient develops a problem there are calls to the patient or the family, calls to the laboratory and radiology department to order tests and check results, calls to the home infusion service to change the nutrient formula, calls to the home nursing service to adjust infusion orders, etc. A study from the Cleveland Clinic, published in 1996, showed that this HPN off-site management cost almost $2000 per patient per year (Curtis *et al.*, 1996). These costs are rarely reimbursed, and as a consequence physicians became reluctant to accept HPN patients.

While physicians were, and are, inadequately reimbursed for their HPN patient care, home infusion pharmaceutical services were generously reimbursed and they had a strong desire to expand HPN services. The industry saw two barriers to expansion: first, the lack of physician reimbursement; and, secondly, the lack of physician knowledge about HPN. To solve these problems infusion companies offered physicians 'management fees' for documented care and provided technical assistance by hiring experienced HPN pharmacists, nurses and dieticians. These developments did indeed expand HPN use and many physicians, with no nutrition training, started prescribing HPN therapy. Simultaneously, many institutions and groups of physicians decided to capture these pharmacy revenues by starting their own home infusion services or contracting for shared ownership with national pharmacy vendors.

In 1986 the office of the Inspector General issued a fraud alert in regard to these joint venture arrangments (Kusserow, 1989). By then 'management fees' had escalated into a marketing device and were, in effect, payment for patient referrals. Physician ownership of pharmacies created self-referrals for HPN business. Both practices were illegal under newly passed Stark Legislation (Burrows and Fernandez, 1992). Several pharmaceutical vendors and physicians were prosecuted.

After the fraud alert was issued improper payment practices ceased, but legitimate HPN reimbursement for clinical nutrition physician specialists remained largely unaddressed. Medicare provided modest payment under two ICD 9 codes for 30 or 60 min of telephone care per month.

In recent years many aspects of health care in the USA have come under increasing fiscal restraint. The majority of teaching hospitals have suffered financial losses and drastic cuts have been made to all non-lucrative programmes. Clinical nutrition programmes are at best break-even programmes and many have been cut, while the number of training

programmes has now dwindled to 15 (personal communication from Douglas Seidner, MD Chairman, American Society of Clinical Nutrition Committee on Professional Nutrition Education). Clearly, there are many forces ranged against this young subspeciality of clinical nutrition. Meanwhile, HPN patients are finding it difficult to secure experienced physician care and industry pharmacists, nurses and dieticians are more and more picking up responsibility for this complex therapy. This begs the question: what is happening to HPN clinical outcome and patient quality of life in the USA? The answer is – we do not know.

The North American Registry was discontinued in 1994, partly for financial reasons and partly because it lacked a statistically representative sample, limiting what conclusions could be drawn. Today, it would be harder than ever to collect a representative sample with patients so widely dispersed. National pharmaceutical vendors of home infusion services claim less than 20% of HPN users are now managed by large medical institutions caring for 25 or more patients. The majority of HPN users are managed by single or small groups of physicians and the home infusion staff of their pharmacy vendors (Personal communication, 2004).

Potential Solutions to HPN Problems in the USA

Currently, third-party payers have little information beyond the diagnosis for assessment of the care their covered patients receive. Once electronic records become available, perhaps in the next 2 or 3 years, it will be possible to assess the suitability of care, and large payers can then identify programmes with superior outcome and may opt to channel patients towards those programmes. This is already happening in other highly technical and expensive medical areas.

Another positive influence could come from robust intestinal failure programmes, where HPN management, reconstructive bowel surgery and small bowel transplantation are all in concert, and patients and their families could receive a coordinated clinical approach. A patient might have to travel quite a distance to an intestinal failure centre, and thus only one or two visits a year might be feasible. The intestinal failure programmes could support the local physician and be available to help with management problems. With this arrangement, if the patient did eventually need transplantation, the mechanism for post-operative support would be more prepared.

Good intestinal failure care will happen only if all contributing clinicians are fairly reimbursed.

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4 Home Parenteral Nutrition in Canada

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Historical Perspective

The home programme was initiated at the Toronto General Hospital in 1970, when the first patient was discharged (Langer *et al.*, 1973). This patient, who had undergone an almost complete enterectomy for mesenteric vein thrombosis, with a gastroduodenal anastomosis and gastrostomy drainage, enjoyed a good quality of life for 7403 days (20 years) and died of infection around the gastrostomy stoma. The next three patients were entered in 1972, and one of them is still alive and on HPN (2005), a record duration of 11,833 days (32 years). Since that time the programme has entered over 400 patients (Jeejeebhoy *et al.*, 1973, 1976).

Since then, programmes of HPN were started in Calgary, Edmonton, Quebec City, Vancouver and Hamilton in the 1970s. Subsequently, programmes have been established in Halifax, London, Montreal, Regina, Saint John and Winnipeg.

Patients on HPN

The number of patients started on HPN over the past 30 years is estimated to be 4–5/million population/year. There were more females than male patients on HPN (Fig. 4.1).

Programme structure

The programme structure varies from province to province: in the Ontario and Alberta models there are nurse clinicians in each hospital who oversee

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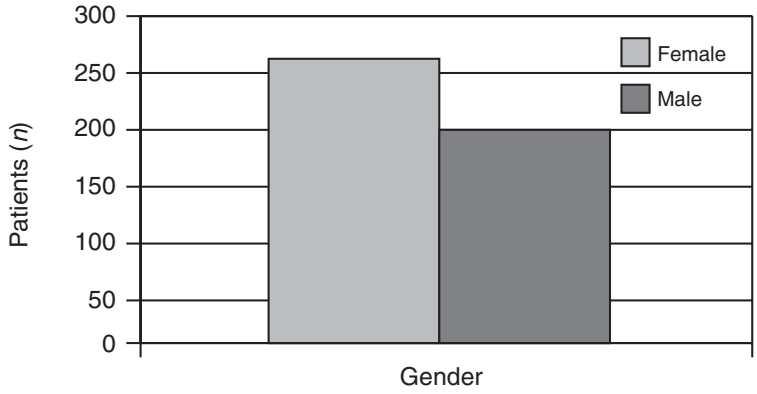

Fig. 4.1. Sex Distribution of Patients on HPN.

various aspects of TPN, including but not limited to: training, ordering (often with the help of a pharmacist), patient follow-up and research. Training is performed in-hospital before HPN patients are discharged. TPN clinics run once a week with a dietician, pharmacist, TPN nurse clinician and gastroenterologist present. Home care support for the outpatients includes (but is not limited to) community care nurses' involvement. The Ontario Health Insurance Plan covers all HPN costs for patients.

By contrast, in British Columbia there are nurses under the 'Home IV Infusion Program', who train each HPN patient before discharging them from the hospital. A nurse calls each HPN patient for a follow-up phone call. There are no HPN clinics, and community care is non-existent. HPN costs are maintained through the BC health plan, but some drug and supply costs are borne by the patients themselves.

In comparing the situation in Ontario with that in British Columbia, the following significant relationships were noted (Chang *et al.*, 2005).

- More patients rate their level of initial TPN training lower in Ontario than in BC ($P = 0.04$).
- More patients rate their level of follow-up TPN care lower in BC than in Ontario ($P = 0.002$).
- Ontario patients rely more on their family members to prepare *all* aspects of TPN (preparation, stopping and catheter dressing) ($P = 0.022$).
- Ontario patients rely more on their family members to prepare *some* aspects of TPN (preparation, stopping and catheter dressing) ($P = 0.0016$).
- Ontario patients have more external support (e.g. home care nurse) ($P = 0.011$).

Conditions of patients receiving HPN

The data have been grouped into the following categories: (i) short bowel syndrome (SBS); (ii) chronic bowel obstruction – including pseudo-

obstruction (Warner and Jeejeebhoy, 1985); and (iii) motility disorders such as scleroderma (PSEUDO), Crohn's disease (CROHNS), cancer (CA), radiation enteropathy (RAD), malabsorption syndromes (MAL) and fistulae (FIST). The most common indication is SBS; however, the number of CA patients has increased and now comprises about 16% of patients.

Complications

Catheter sepsis is one of the main complications of HPN, and in a recent study the incidence of catheter sepsis was analysed in detail for both the Ontario and British Colombia programmes (Chang *et al.*, 2005). The mean incidence of line sepsis was 2.2 ± 0.4 per 1000 patient days for Toronto and 3.2 ± 1.1 in Vancouver (Chang *et al.*, 2005). The following variables did not contribute to line sepsis: (i) community agency or Home Care nurse involvement; (ii) alcohol and smoking; (iii) level of education and of written and spoken English; (iv) employment status ($P = 0.12$) or work environment; (v) income status ($P = 0.15$); and (vi) whether or not patients know why they have line sepsis.

However, line sepsis was higher if medication and/or blood work done through the catheter ($P = 0.011$) or if patients had a higher number of dependents ($P = 0.0083$). Combining data from the two provinces, patients who had been on HPN for less than 5 years had an increased incidence of catheter sepsis ($P = 0.013$).

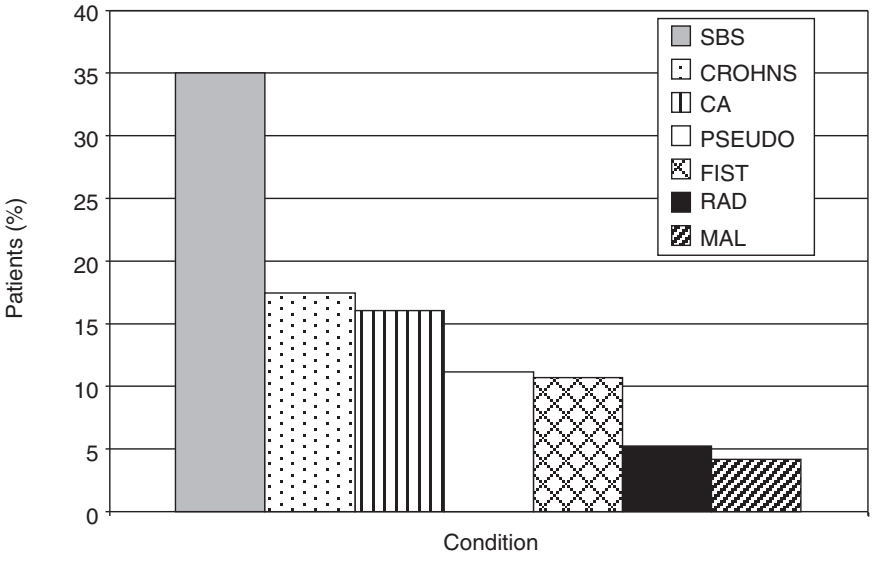

Fig. 4.2. Diagnosis of patients on HPN.

Duration and survival on HPN

Overall, 35% of patients died while on HPN, and of the remainder about equal numbers were either discontinued or continued on HPN (Fig. 4.3). The duration on HPN is dependent on two factors: (i) resumption of oral/enteral diet; or (ii) death. Figure 4.4 shows the duration on HPN irrespective of why the procedure was terminated. Figure 4.5 shows the attrition rate due to death alone. It is clear by comparing Figs 4.4 and 4.5 that in cancer patients (CA) the short duration on HPN is due to early death. In contrast, patients with Crohn's disease survive far longer, and the major reason in this case for stopping HPN is resumption of oral or enteral feeding. Patients with obstructive bowel disease (PSEUDO) and those with short bowel syndrome (SBS) exhibit around 50% mortality within the first 1000 days (3 years), and those who survive this period remain on HPN for a long time.

Quality of life and cost/utility

Detsky *et al.*, in a cohort of 73 patients, found the quality of life and survival depended on whether they had required HPN following an acute episode or after a period of chronic malnutrition (Detsky *et al.*, 1986a). The former were often patients with acute bowel infarctions, whereas the latter were patients with Crohn's disease. They found that acute patients had a shorter survival time, less quality of life and used more resources initially. Using three utility assessment techniques (category scaling, time-tradeoff and direct questioning of objectives), the quality of life of the patients interviewed was good (mean value 0.73, where 0 represents death and 1.0 represents perfect health); for those who had experienced a period of chronic malnutrition before HPN,

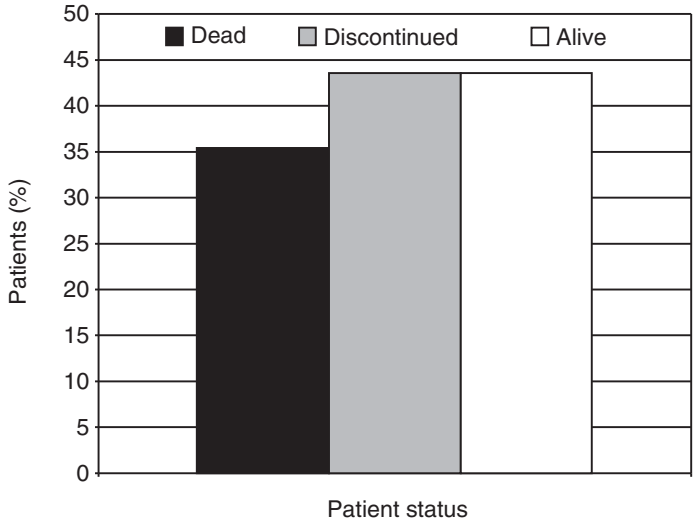

Fig. 4.3. Proportion of patients dead, HPN discontinued and those alive on HPN.

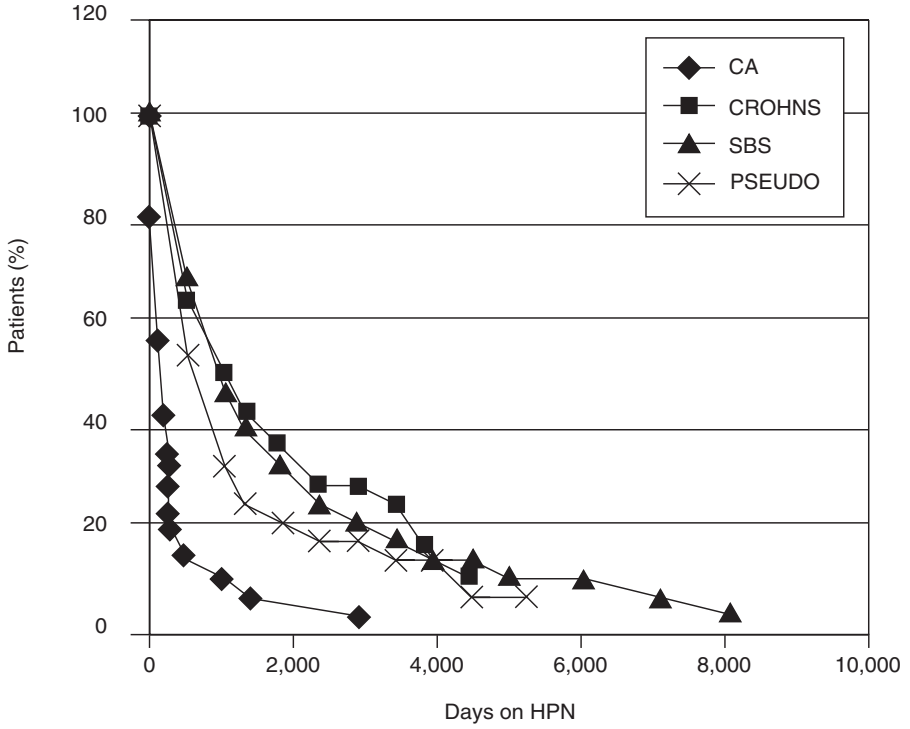

Fig. 4.4. Patients of each of the major categories remaining in HPN. The reduction in numbers were due to either being taken off HPN or having died.

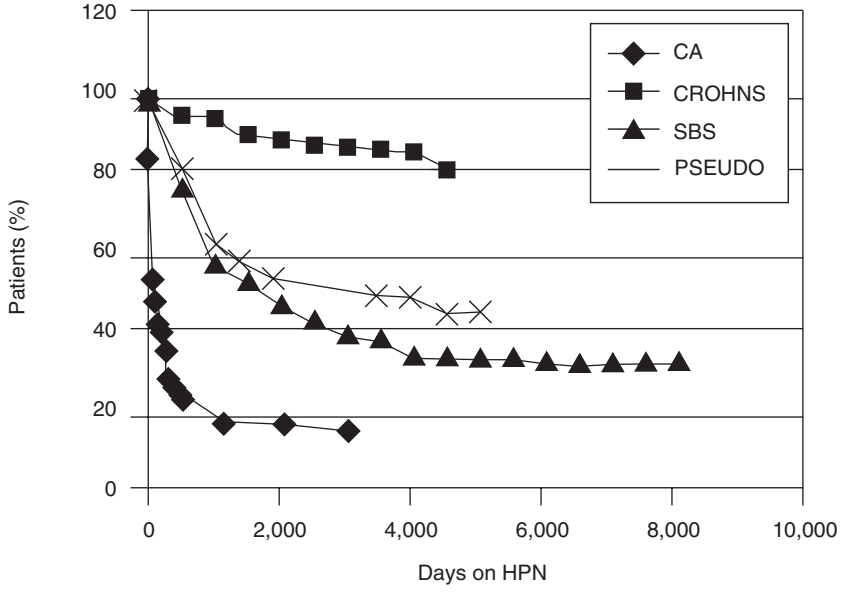

Fig. 4.5. Patients alive on HPN or discharged living while on HPN.

the quality of life had improved. For the entire cohort, the estimate of quality-adjusted survival was four times greater with HPN than with the alternative therapeutic strategies ($P < 0.001$). However, in this analysis there was only one patient with cancer in the cohort.

Cost/utility analysis

A cost/utility analysis was performed in a cohort of 73 patients in order to determine the cost per year of useful life saved by HPN (Detsky *et al.*, 1986b). It was estimated that HPN resulted in a net saving in health care cost of $19,232CA per patient and an increase in survival of quality-adjusted life of 3.3 years, compared with the alternative of treating these patients in hospital with intermittent nutritional support as required. When these assumptions were most unfavourable to the HPN programme, we estimated that HPN resulted in incremental costs of $14,600 per quality-adjusted life-year gained.

Conclusion

Canada was one of the first countries to start an HPN programme. It has now developed into a nationwide concern, and studies have shown that it is cost-effective, saves years of useful life and is most effective in diseases where the survival is limited only by lack of nourishment. The role of this modality of treatment in patients with cancer is controversial. However, the successful control of cancer by new forms of treatment will change the role of HPN for patients where cancer is controlled but nutrition is the limiting factor.

Patients with acute bowel infarction and those with motility disorders also have a higher initial mortality over the first 3 years, but the remaining patients have prolonged survival on HPN.

With the increased number of HPN programmes geographically dispersed throughout Canada, an HPN Website Registry was recently put in place to collect patient data. The objective of this project, supported by the Canadian Society for Clinical Nutrition, is to define better the Canadian HPN patient population and to assess their clinical outcomes so that future treatment strategies can be designed and standardized across the provinces.

Acknowledgements

We are grateful to Ms Olivia Saqui of Toronto General Hospital and Clare Meechan of St Michael's Hospital Toronto for their help in compiling information about their programmes. We would like to acknowledge the help of Linda Brickwood of the London Ontario programme, Siobhan Carney of the McGill programme and Marianne Siemens of the Calgary Programme for information about their programmes.

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5 Home Parenteral Nutrition in Australia and New Zealand

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Introduction

Australia and New Zealand have both had home parenteral nutrition (HPN) services operating since the mid-1980s (some Australian centres started as early as 1979). Neither country has an established, national system for obtaining HPN services, but any patient entitled to treatment for whom HPN is genuinely required should be able to access it under the provisions of the respective public health systems. The two countries share some major similarities in the issues they face in the provision of HPN services.

National Profiles

Australia and New Zealand have their own identities and cultures, but these draw heavily upon the predominantly Anglo-European roots of the majority populations, who greatly outnumber the indigenous populations. The legal and political systems, many of the actual laws and the health systems were originally modelled on their British equivalents. Both countries still owe allegiance to the British Crown.

According to the Australian Yearbook (Anon., 2005), one in three Australians were either born overseas or have at least one parent or grandparent who was. Although both countries have increasing numbers of people from other backgrounds and cultures, the dominant culture in both still clearly reflects European origins.

The health systems were fundamentally modelled on the British NHS, but over the years have been modified to suit each country's perceived needs and/or governmental aspirations. They appear to differ in that New Zealand is a single country whilst Australia is a Commonwealth of six States

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and two Territories, with each of the eight states responsible for their own hospital services. However, functionally, the differences arising from this are blurred somewhat because New Zealand has 21 District Health Boards, each with a considerable degree of autonomy in how they allocate funding in their particular area.

Further details of the public healthcare systems in Australia and New Zealand can be found at: http://www.medicare.gov.au (Australia) and http://www.moh.govt.nz/moh.nsf (New Zealand).

The training of most health professionals follows similar models to the UK, and many professions receive reciprocal registration and/or mutual recognition of qualifications. Each year there is a considerable interchange of health personnel as professionals from a wide range of disciplines seek their 'OE' (overseas experience). The majority of those travelling from Australia and New Zealand tend to work in the UK because all speak (approximately) the same language; however, many – particularly those who can speak another European language – also take the opportunity to tour and work or study elsewhere in Europe. This means that those involved in the provision of HPN services frequently have direct experience of working in healthcare in at least one other country.

What makes Australia and New Zealand fundamentally different is that compared to Western Europe both countries have a very low population compared to their land area, with large distances between centres of population. The Australian population is currently approximately 20 million (Anon., 2005) and New Zealand's about 4 million. Although New Zealand is much smaller than Australia, the topography is very different: sitting astride major geological fault lines, New Zealand has many high mountains and an extremely varied landscape, with few flat areas.

The geographical constraints, combined with too few taxpayers to fund massive infrastructure projects, means that the roads and railways mostly go around the mountains, not through them as in much of Europe. This frequently entails road and rail journey times from rural areas and small towns to the main population centres of 4–6 h duration, although some of Australia's most remote health service outposts are 12–14 h land journey from the nearest small town. Air transportation is available in both countries for emergencies, although problems can arise: in Australia the distances involved can be too great for the use of helicopters, although most small communities have some form of airstrip for at least small, fixed-wing aircraft. In rural New Zealand the mountainous terrain and the complex weather systems associated with them can prevent airborne access to some areas for several days at a time.

Climate

Both countries span considerable variations in climate, from tropical to temperate. In a country that is always hot, or always cold, people plan

accordingly, but in offering a nationwide service with such extremes, plans and policies from one area can come unstuck when applied elsewhere. This has issues for patients, with a number of centres reporting patients from the northern (hotter) areas requiring additional infusions of 0.9% sodium chloride, or modification of their formula during the summer months. At least one hospital in northern Australia reported having experienced problems with maintaining the cold-chain for delivery to a rural HPN patient, whilst another in southern New Zealand reported having a patient's HPN bags arrive part-frozen one winter morning.

HPN History

The history of home parenteral nutrition (HPN) in both countries is similar, and comparable with European experiences. Since both health systems are modelled upon and seek to maintain standards similar to those of Europe, in the development of parenteral nutrition (PN) and HPN, the drivers were very similar. Technical advances in medicine and surgery presented a similar number of patients with relatively long-term gastrointestinal dysfunction, necessitating PN to maintain viability or achieve recovery. Some notable centres, including Professor Graham Hill's unit at Auckland Hospital (NZ), became involved at a pioneering and research level early in the development of PN as a practical technique. In Australia the Australian (now Australasian) Society for Parenteral and Enteral Nutrition (AuSPEN) was the first of the PEN societies to be formed. These pioneering centres expanded into HPN as a logical development. Many other centres moved into PN largely as a matter of necessity: the technique existed and they had patients who needed it.

Despite having the foresight to form AuSPEN, collegiality has been impeded by the geography and populations of the countries, the distances between centres and limited communication between them compared to Europe. Also, the low population limits the number of specialist appointments and the degree of specialization they enjoy. As in Europe, there have been very few specialist positions in PN created; the majority of professionals involved in the technique have other responsibilities and interests. Therefore, when choosing conferences to attend, many would elect to go to a mainstream conference within their speciality rather than to one specializing in PN, particularly since their PN practice has frequently been small scale and peripheral to their main activity. A Medline and Embase search for articles on HPN in Australia and New Zealand returned only two (1991; Jones *et al.*, 1995), but it must be remembered that in both countries there are a number of local journals that are, or were, not always picked up by the major abstracting services.

Stokes and Hill (1991) reported the results of HPN from Auckland Hospital (New Zealand) up to 1991. In the previous $2\frac{1}{2}$ years, six patients had been sent home receiving HPN. Four were continuing after periods of 1–30 months. There had been one death and one patient who had

developed catheter sepsis. The paper reported that the quality of life on HPN had, in general, been very good. This paper was groundbreaking for its time in that the Department of Surgery at Auckland was pioneering methods in measuring body composition. Studies on these patients had shown that a normal body composition could be maintained while on HPN.

Jones *et al.* (1995) reviewed the outcomes in 14 patients treated with long-term HPN at the Royal Prince Alfred Hospital in Sydney between 1978 and 1994. The median time patients had been on HPN was 468 days (range 7–5352 days), and seven patients were continuing on HPN at the time of the review. They reported that the majority of patients had been able to resume a reasonable place in society for varying periods, and four of the patients had returned to work. They concluded that, in their experience, HPN was a cost-effective treatment in selected patients with chronic intestinal failure.

In this context, national standards have been slow to emerge. It is not that individual units have not evolved their own standards; most have, and the number of professionals gaining overseas experience, plus high-quality library facilities in both countries, means that centres have been well aware of practices elsewhere in the world. Most of the local procedures have been developed with knowledge of published standards and/or in consultation with overseas centres. However, with the growing international interest in evidence-based practice, defined standards, risk management and benchmarking, there are now active initiatives aimed at developing and promulgating national – and hopefully trans-Tasman – standards.

In each centre, both PN and HPN have evolved in relative isolation; with many hospitals managing only one or two HPN patients at a time. Dedicated teams have worked to overcome their own problems and find systems of working that suited them and kept their patients well. When discussing national standards, some have been understandably reluctant to change practices that have served them and their patients well. Nevertheless, AuSPEN and others are keen to harmonize standards.

HPN Today

Patient support groups

The isolation and distances involved have affected the patients also. In these individual centres, there has been little contact between the patients themselves; with only small numbers serviced by a particular hospital, many patients have never met another patient on HPN. Individual patients in both countries have made contact with overseas groups – such as the Oley Foundation in the USA and PINNT in the UK – and reported having found it most helpful but, to date, no local patient support groups have emerged in either country.

HPN patient demography

There are no national published statistics in either country, and this information has been assembled from personal communication with a number of centres.

As would be expected from the similarities in training and practice, the indications for HPN do not differ significantly from those of the UK and Europe. Uptake of HPN in both countries appears to have been stable, at around five to seven HPN patients per million of population for the last 10–20 years. Unsurprisingly, in Australia the number of HPN patients in each state appears broadly proportional to the general population distribution, with the majority in New South Wales followed by Victoria and Queensland, with only small numbers in the other states. Likewise, in New Zealand, where 1.5 million of the 4 million population live in the environs of the city of Auckland, the largest number of HPN patients are concentrated in that area. More details of the HPN populations from two sample centres are provided below

Structure and funding of HPN services

Neither Australia nor New Zealand have a nationally or, in the case of Australia, state-organized HPN service. Both countries have individual centres that have been recognized as centres of research and/or opinion leaders, but although it occurs on an *ad hoc* basis there is no formal routine referral of patients to specialist centres. When patients are referred to a specialist centre, the patient will usually receive support for their own travel costs, but not for a partner or support person. This does not facilitate consultation. Nevertheless, numerous individual examples of effective collaborative shared-care models exist.

To date, only the State of Victoria has allocated specific funding to HPN, although this was recently pooled into a general ambulatory care fund. There is no automatic method for public funding of HPN services elsewhere in either country, but any patient requiring HPN, who would normally be entitled to publicly funded health services, does not have to pay for HPN. In New Zealand, it is arranged through the 'Special Authority' mechanism for discretionary funding of treatments that are not universally funded. In Australia, the mechanism varies from state to state. Some of the private health insurance schemes will fund short-term HPN, but this is provider specific. The cost varies with individual patient requirements and transport costs, but in both Australia and New Zealand the average cost in the national currency is in the range of $60,000–70,000 per patient per year (A$1 = €0.60; NZ$1 = €0.56)

Standards

As stated above, no national standards exist for the provision of HPN services, and no HPN register, but hospitals have excellent internal standards and

record keeping, and have frequently consulted with colleagues in other centres. A degree of commonality and standard of service also arises through most centres using the same commercial homecare servicing companies. Although the companies have a commendable record of working with individual hospitals and their own preferred methods of doing things rather than forcing company practices to be adopted, an inevitable degree of standardization results. There are committees actively working on both recommended HPN standards and a trans-Tasman HPN register, and it is anticipated that both will be in place within the next 12–18 months.

Criteria for HPN

There are no national criteria in either country, but the principles applied in all the centres that responded are very similar, and correlate closely with those of BAPEN:

- Patients having severe gastrointestinal dysfunction, such that they are unable to maintain their nutritional status by the enteral route alone: HPN will restore or sustain normal nutritional status.
- An expectation of recovering or maintaining general health: HPN is not generally provided in palliative care or the last stages of terminal illness.
- Sufficient home support and facilities: the patient is competent in self-care and there is another person in the house.

Individual hospitals have reported dilemmas such as being confronted with patients who live alone, or who have a partner who is an invalid. An Australian hospital reported the successful treatment of a blind HPN patient and one New Zealand hospital reported having a candidate referred for HPN where it was found that although the patient lived not far from a major city, the farmhouse was without electricity or a telephone; the patient – whose family had farmed the land for nearly 100 years – had previously never perceived any need for either!

Compounding services

In Australia, at the time of writing (2005), only one commercial compounding service exists, but reports received suggest that a second company will be offering a service shortly. To date, no commercial service is currently available in the State of Western Australia, where patients have to be supplied from their referring hospital but, again, reports suggest this will change in the near future.

New Zealand has two companies offering a comprehensive HPN service. Both are based in Auckland at the top of the North Island, but both offer a service to all parts of the country. In addition to the supply of the PN solutions and associated equipment, these companies provide some training and support.

In reality there are remote regions in both countries where a home delivery service would be challenging, but these are areas of low population making it unlikely that HPN would regularly be required. However, increasing use of other home parenteral therapies such as cytotoxic agents, analgesia and antibiotics is already being applied sporadically even in these remote areas, and will provide valuable experience should the need for HPN arise.

Specific examples of HPN services

Two examples are provided, one from Australia, the other from New Zealand.

The St George Hospital, Kogarah, Sydney, New South Wales, Australia (http://www.sesahs.nsw.gov.au/sgh)

The motto of The St George Hospital is a quotation from Louis Pasteur: 'Tu souffre, cela suffit', which has been freely translated to 'you are sick, that is enough.' They began their HPN service in 1979.
The components of the philosophy underpinning their HPN service are:

- Every possible effort must be made to utilize the patient's own gastrointestinal system.
- HPN must be shown to have benefits for the patient.
- Expected survival ideally 12 months or more, *but*
- No patient is automatically excluded, each person is unique and requires individual assessment and conscientious and objective evaluation.

This hospital currently has four HPN patients, and over the period since the commencement of the scheme has serviced a total of 17 patients. Over the period 11 patients have died whilst receiving HPN, with a median duration of HPN of 5.4 years (range 1–15 years). A summary of the progress of 15 of these patients is shown in Table 5.1.

The hospital uses the services of a commercial homecare company. Of these patients, 15 were managed exclusively by the hospital, and two by shared care with a rural general practitioner. Excluding the patients who have died from their underlying malignancy, their long-term HPN patients have lived for 14, > 15 and 9 years to date, respectively.

Auckland Hospital, Auckland, New Zealand (http://www.adhb.govt.nz/ach.htm)

Auckland hospital sent their first patient home on HPN in 1987.

When the European HAN survey report published their HPN findings (Van Gossum *et al.*, 2001), the nutrition support team at Auckland Hospital took the opportunity to compare their experiences. These were presented at the 2002 AuSPEN Annual Scientific meeting (Ball *et al.*, 2002). The survey instrument used by the European group was obtained. Due to the relatively

Table 5.1. Progress of HPN in 15 selected patients in Australia.

Gender	Age	Diagnosis	Duration of HPN
Female	46	Intestinal pseudo-obstruction	14 years
Female	33	Gardner's Syndrome, polyposis, enterocutaneous fistula	15 years to date
Male	60	Pseudomyxoma peritonei	1 year
Male	64	Severe trauma, bowel resection, enterocutaneous fistula, blind	$2\frac{1}{2}$ months, then EN
Male	57	Recurrent enterocutaneous fistula, tubal, colonic cancer with ischaemia	9 months, then EN
Female	59	Scleroderma	5 years
Male	61	Adult Kwashiorkor following intestinal by-pass for obesity	3 months, then EN
Female	47	Radiation enteritis, bacterial overgrowth	6 months, then EN
Female	56	Short bowel syndrome, venous infarction following colectomy, anti-phospholipid syndrome	HPN suspended after 6 months – sepsis. Survived on EN
Female	67	Radiation enteritis (cervical cancer), extensive resection, short bowel syndrome	6 years
Female	19	Tumour invading superior mesenteric artery, resection, short bowel syndrome	1.75 years, then EN
Male	46	Widespread carcinoid tumour, fistula	2.25 years
Female	46	Coeliac disease	9 years to date
Male	58	Duodenal cancer, mesenteric infarctions, repeated resections, short bowel syndrome with high losses, IDDM	1.2 years to date
Female	67	Mesenteric infarction, short bowel syndrome	3 years to date

low overall numbers, in order to provide useful groups for comparison, all current ($n = 5$) and a retrospective cohort(s) of the most recent past patients ($n = 15$) were examined by retrospective analysis of their progress notes and other records maintained by the service. Information was extracted corresponding with that obtained for the European survey. The results of this work are shown in Tables 5.2, 5.3, 5.4, 5.5 and 5.6.

Overall the results were similar, suggesting that the HPN service provided through Auckland Hospital in association with Baxter Healthcare (NZ) Ltd was broadly in line with international standards, but there were clearly issues to address: the average duration of HPN therapy appeared shorter than that in Europe. This was mostly because the ESPEN-HAN survey aimed to target patients who were long-term HPN dependent and excluded all those receiving HPN for less than 2 years. To exclude these from the Auckland survey would have severely restricted numbers for comparison, so the survey included nine patients who, after a period of HPN, achieved full enteral intake. It should also be noted that the Auckland group was older, and included six patients who died whilst on HPN from causes unrelated to their HPN.

Table 5.2. Comparison of population characteristics of European[a] and Auckland (NZ)[b] HPN patients.

	European HAN Survey		Auckland Hospital	
	n	%	*n*	%
Female	141	61	17	85
Male	87	39	3	15
Median age in years (range)	49 (19–92)		61 (49–74)	
Median duration of HPN in months (range)	84 (24–288)		39 (12–204)	
Nutritional status				
Standard global assessment normal	180	79	18	80
Moderately malnourished	48	20	4	20
Severely malnourished	2	1	0	0
Regular smoker	82	27	5	25
Regular alcohol consumption	4	2	2	10
Mean bags/week	5.6		6.3	
Mean catheters used (range)	3 (1–17)		7 (1–15)	
Mean catheter survival in months (range)	34 (4–245)		6 (< 1–23)	
Septic episode in previous 12 months		31		82

[a] $n = 228$; [b] $n = 20$.

Table 5.3. Presenting conditions of European[a] and Auckland (NZ)[b] HPN patients.

	European HAN survey		Auckland Hospital	
	n	%	*n*	%
Crohn's disease	75	33	4	24
GI ischaemia	57	25	5	25
Radiation enteritis	9	4	2	20
Pseudo-obstruction	18	8	0	0
Post-surgical	43	19	5	25

[a] $n = 228$; [b] $n = 20$.

Table 5.4. Feeding patterns of European[a] and Auckland (NZ)[b] HPN patients.

	European HAN survey		Auckland Hospital	
	n	%	*n*	%
Mean bags/week	5.6		6.3	
Cyclical nocturnal	224	98	20	1
Cyclical diurnal	2	1	0	0
Continuous	2	1	0	0
Mean catheters used (range)	3 (1–17)		7 (1–15)	
Mean catheter survival in months (range)	34 (4–245)		6 (< 1–23)	
Septic episode in previous 12 months		31		82

[a] $n = 228$; [b] $n = 20$.

Table 5.5. Hospitalization patterns of European[a] and Auckland (NZ)[b] HPN patients.

	European HAN Survey	Auckland Hospital
Hospitalizations per year (mean)	2.7 (0–12)	5.5 (1–18)
Caused by underlying disease (%)	27	15
HPN complications (%)	48	85
Total catheters used (mean)	3 (1–17)	5 (3–8)
Septic episode in previous 12 months (%)	31	82

[a] $n = 228$; [b] $n = 20$.

Table 5.6. Concurrent medication of European[a] and Auckland (NZ)[b] HPN patients.

	European HAN Survey		Auckland Hospital	
	n	%	*n*	%
Antidiarrhoeals	153	67	11	55
Octreotide	12	5	3	15
Antidepressants	33	14	5	25
Anxiolytics	42	18	1	10
Analgesics	81	36	5	25
Opioids	17	7	4	20
Steroids	20	9	2	10
Immunosuppressants	11	5	2	10
Acid suppression	Not stated		6	30

[a] $n = 228$; [b] $n = 20$

The catheter problems/line sepsis data for Auckland Hospital were well below international standards, but in fact had been identified as a problem 4 years prior to the date of the survey. A nurse specialist had been appointed to the service in late 1998, and closer examination demonstrated that since this appointment had been made, catheter sepsis rates had improved considerably and were still steadily falling.

Another issue the team identified was that of record keeping. Each patient was found to have between six and ten volumes of clinical notes. It proved impossible to assemble all the volumes for any single patient in one place at one time. In addition, separate records were kept by the surgeons, the specialist nurse, the dieticians, the pharmacist and the homecare provider. As part of a larger project within the Auckland Hospitals to centralize and digitize clinical records, efforts will be made to share records and reduce duplication.

The team concluded that the HPN service provided by Auckland Hospital is serving a similar, if slightly older, patient population to that of the ESPEN-HAN survey, and that the outcomes were comparable. It was clear that management of central venous access has been sub-optimal in

the past but was now improving, but that information management needs further improvement.

Travel on HPN

A number of centres reported having supported their own HPN patients in undertaking travel and holidays including destinations in Europe, the USA, India and cruising. The assistance of centres in these countries in providing local contacts for emergencies was acknowledged. Also, the Australian and New Zealand homecare companies have gone to considerable lengths themselves – and through their networks of international sister companies and other contacts – to facilitate these trips.

Likewise, a number of centres and the homecare companies in both countries reported having helped to facilitate HPN patients from overseas visiting Australia and New Zealand.

Conclusion

HPN in Australia and New Zealand has evolved along very similar lines to that in the UK and Europe, with similar patient populations and similar techniques. The low population density and broad climate variation of both countries provide some unique challenges in providing nationwide services. Compared to Europe, the number of patients managed by individual hospitals has been small. Nevertheless, most patients requiring HPN enjoy long-term survival with good quality of life.

Acknowledgements

The author gratefully acknowledges the help and support of the following people in the preparation of this chapter: The Australasian Society for Parenteral and Enteral Nutrition; Dr Alan McKeag, The St George Hospital, Sydney, Australia; Lyn Gillanders, Kerry McIroy, Elana Brokenshire, Dr Lindsay Plank and Prof Bryan Parry, Nutrition Support Team, Auckland District Health Board, New Zealand; Sally Piggott, Westmead Hospital, Sydney, Australia; Martel Davison, Baxter Healthcare Australia Pty, Ltd; Bronwen Kerr, Baxter Healthcare, New Zealand Ltd; Alan Spencer, Gold Coast Hospital, Queensland, Australia; Dr Andrew Thompson, Canberra Hospital, Australian Capital Territory, Australia; Janet Hope, Monash Hospital, Melbourne, Australia; Katerina Angstmann, Royal North Shore Hospital, Sydney, Australia; Sam Saunders, John Hunter Hospital, Newcastle, New South Wales, Australia; and Kath Murrell, Princess Alexandra Hospital, Brisbane, Australia.

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Part II
Clinical Conditions

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6 Short Bowel Syndrome

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Key Points

- The incidence of short bowel syndrome (SBS), which results in the need for a home parenteral nutrition (HPN) due to either transient or permanent intestinal failure, affects two to four adult patients per million population per year.
- Short bowel syndrome is best defined by the length of the remaining post-duodenal small bowel rather than by the length of resection. From an anatomical point of view, patients have short bowel syndrome when the post-duodenal length of small bowel is <150–200 cm, i.e. less than half the median length of the adult small intestine.
- The presence of part or whole of the colon remaining in continuity results in a better prognosis and outcome, and patients will depend less on HPN.
- The natural history of short bowel syndrome is classically divided into three periods: (i) a post-operative period of 4–6 weeks; (ii) an adaptative period of around 2 years; and (iii) and a stabilization phase.
- Short bowel syndrome may affect both water/sodium and energy balance, so both should be evaluated to define the patient's requirements regarding nutritional support.
- Measurement of the plasma concentration of citrulline (an amino acid produced by the enterocyte) can be used as a biomarker of remaining functional enterocyte mass.
- Medical treatment of diarrhoea includes loperamide, proton pump inhibitors and anti-secretory drugs, including somatostatin analogues.
- Complications include: (i) peptic ulcer secondary to hypersecretion of gastric acid; (ii) cholelithiasis (gallstones); (iii) renal stone formation; and (iv) rarely, d-lactate acidosis.

 Home Parenteral Nutrition (eds F. Bozzetti, M. Staun and A. Van Gossum)

Introduction

Short bowel syndrome (SBS) is usually observed after resection of ≥ 2 m small bowel, or after extensive enterectomy; it occurs in 15% of small bowel resections, i.e. in 85% of cases small bowel resection is < 2 m (Koberle, 1881); in such cases it is the length of the distal part of the small bowel, i.e. the ileum, that determines the type of diarrhoea observed. Indeed, if a resection of 1–2 m of proximal bowel (jejunum) does not induce diarrhoea, the same length of ileal resection may result in diarrhoea with significant lipid malabsorption (steathorrhea > 20 g/day). A resection of the terminal ileum of 0.3–1.0 m results in diarrhoea with a little steatorrhea (7–19 g/day). The surgeon should consequently indicate the length of the resected small bowel, especially for the terminal ileum.

The incidence of SBS, which results in the need for a home parenteral nutrition (HPN) programme due to either transient or permanent intestinal failure (IF), affects two to four adult patients per million population per year (Messing *et al.*, 1995). The length of the normal small bowel is 4 (range 3–6) m, i.e. 2 m of jejunum and 2 m of ileum, depending on the measurements performed in the theatre, at autopsy or with a barium meal follow-through. SBS is best defined by the length of the post-duodenal remnant small bowel rather than by the length of resection (Jeejeebhoy, 1994). From an anatomical point of view, patients have SBS when the post-duodenal length of small bowel is <150–200 cm, i.e. less than half the median length of the adult small intestine. Therefore, SBS implies almost always a resection of the ileum, but if more than 1 m of the terminal ileum is left in place – clinically seldom seen – diarrhoea would not occur. In SBS, the length of the remaining post-duodenal small intestine is measured in centimetres on its anti-mesenteric border with an opisometer during a barium meal follow-through.

These results are closely related to the peri-operative measures of the remaining short gut (Nightingale *et al.*, 1991), especially when the remnant small bowel is < 200 cm. The length of the colon is determined by dividing it into seven equal parts, each part representing 14% of its total length. The remaining colon is expressed as a percentage of the whole (Cummings *et al.*, 1973). The SBS is best characterized not only by the length and site of the remnant small bowel but also by the presence of part or whole of the colon remaining in continuity. This is best characterized by the three main types of anastomosis subsequently performed.

Re-establishment of bowel continuity is accomplished by one of three surgical techniques: (i) terminal enterostomy (type I); (ii) jejuno-colic anastomosis (type II); or (iii) jejuno-ileocolic anastomosis (type III) (Carbonnel *et al.*, 1996). These three anatomical types of SBS help to clarify the length and situation of the remaining bowel: jejunum in types I and II or jejunum + ileum in type III, as well as all or part of the colon in continuity. In types II and III absorption of water, minerals and macronutrients (energy balance) is greater than in type I (Nordgaard *et al.*, 1994). Preserving all or part of the colon gives a better prognosis and outcome and, consequently, a lesser need for HPN (Nordgaard *et al.*, 1996).

Pathophysiology of SBS

Gastric changes

In SBS, hypersecretion of gastric acid is more important relative to both the length of time since the resection and to the extent of the resection (Nightingale, 1994). The suppression of the intestinal brakes – i.e. mainly ileal but also colono-rectal – accelerates gastric emptying more for liquids than for solids (Nightingale *et al.*, 1993, 1996). Therefore, in the post-operative period, gastric hypersecretion provokes a profuse diarrhoea with an increase in electrolyte losses (gastro-duodenal ulcer has been described in 5–10% of cases) (Nightingale, 2003).

Small intestinal changes

In SBS, acceleration of transit time worsens the malabsorption by 'lack of time' (Cosnes *et al.*, 1982; Remington *et al.*, 1983; Fich *et al.*, 1992; Schmidt *et al.*, 1996; Lin *et al.*, 1997; Cosnes, 2000). In the small intestine, the intake of fluids – whether hyper- or hypotonic – becomes isotonic to the plasma through the movements of plasma-luminal water. Water and Na losses are more important according to the extent and site of small bowel resection: reabsorption of fluids is nearly complete at the end of the ileum since around 1 l enters the colon every day. The efficiency of fluid and Na absorption is greater in the ileum than in the jejunum. Therefore, an ileal resection impairs the capacity for absorption of NaCl in the case of an existing gradient of concentration between luminal and plasma solutes. In addition, the tight junctions are weaker in the jejunum than in the ileum, increasing the water exchanges and losses in the case of ileal resection (Fordtran *et al.*, 1982; Arrambide *et al.*, 1989).

Malabsorption of macronutrients (proteins, carbohydrates, lipids) is usually greater for lipids than for proteins or carbohydrate: there exists a correlation between the net absorption of carbohydrates and proteins and the length of the remaining small bowel. This relationship is not true for the lipids in view of the specific role of the ileum in absorption of biliary acids (Hofmann and Poley, 1972).

Indeed, the ileum is the specific site for active absorption of B_{12} and biliary acids. Extensive ileal resection greater than 1 m (Lin *et al.*, 1996) leads to a reduction in micellar solubility of lipids through a decreased concentration of intra-luminal biliary salts, resulting in malabsorption of lipids with significant steatorrhea (> 20 g/day) and liposoluble A, D, E and K vitamins (Hofmann and Poley, 1972). If ileal resection is < 1 m, malabsorption of biliary salts is moderate and can be compensated by hepatic synthesis: micellar solubilization of lipids is moderately decreased and steatorrhea is also moderate (< 20 g/day). However, malabsorbed biliary salts, dehydroxylated by the colic flora, exert a laxative effect on the colon resulting in an electrolytic diarrhoea (500–1000 ml) – named

cholerrheic diarrhoea. If steatorrhea is significant, the long-chain triglycerides (LCT) exert laxative effects on the colon (Spiller *et al*., 1986). Malabsorption of vitamin B_{12} is constant in a distal ileal resection ≥ 60 cm in the terminal ileum; with 10–60 cm of remaining ileum, the Schilling test is decreased in 50% of cases (Behrend *et al*., 1995).

Small intestinal adaptation

Positive adaptive absorptive function of nutrients such as amino acids, glucose, Na, Ca, cholesterol and vitamin B_{12} have been described in both SBS and intestinal bypass (Dowling and Booth, 1966; Koivisto and Miettinen, 1986; Gouttebel *et al*., 1989). This adaptation develops over a period of 2–4 years (Messing *et al*., 1999). Along with hyperphagia, an increase in the protein absorption correlated to the length of the remaining small bowel can be seen independent of oral intake (Crenn *et al*., 2004).

Until the present time, morphological adaptation had not been clearly demonstrated in humans, in contrast to that in animal experiments (Williamson, 1978). Treatment with hormone or trophic intestinal factors could further increase this adaptative function of the intestines (Byrne *et al*., 1995; Scolapio *et al*., 1997; Seguy *et al*., 2003; Messing, 2004), and this has been demonstrated for recombinant human growth hormone (rh-GH) and for GLP2 (Jeppesen *et al*., 2001). With the latter, it is possible that the adaptative process may also occur at the morphological level, which will be a unique observation in the human. Their action can be enhanced by the use of specific nutritional factors such as glutamine for the small intestine and short-chain fatty acids (SCFA) for the colon (Harig *et al*., 1989; Beaugerie *et al*., 1991). This physiological or pharmacological adaptive process must not be impaired, either by the privation of intra-luminal nutrition or through protein malnutrition (Thissen *et al*., 1994).

Colonic adaptation

Maximal hydroelectrolyte colonic absorption, without intestinal resection, can reach 6 l/day (Debongnie and Phillips, 1978). In SBS, this capacity is reduced due to poor absorption of either biliary salts or LCT. Inversely, because malabsorbed glucids are fermented in SCFAs (butyrate, propionate, acetate) by the colonic flora, there is an increase in hydroelectrolyte absorption – mainly Na – with possibly increased losses of K. In addition, colonic hyperfermentation of carbohydrates also allows an important increase in energy absorption via acetate which can reach – depending on the length of the small bowel resection – 1000 Kcal/day (Nordgaard *et al*., 1994). Therefore, bacterial colonic hyperfermentation in SBS must be explained to the patient because this induces flatulence, painful distension and gas emission. Indeed antiseptic or wide-spectrum antibiotic therapy alters colonic flora and can induce further diarrhoea for a period of several weeks (Rao *et al*., 1988).

Clinical Outcomes of SBS

Clinically, SBS is described as diarrhoea with malabsorption, with clinical consequences of variable speed of appearance schematized into four types:

- dehydration – H_2O, Na, K, acute or chronic;
- mineral deficit (Mg > Ca > P) – acute or chronic;
- protein/energy malnutrition – acute, subacute or chronic; and
- deficit in micronutrients (vitamins K, D, E and B_{12}) and trace metals (Se, Zn, etc.), acute, subacute or chronic.

These four types of deficit further reduce the optimal absorption of the remaining bowel (Nightingale, 2003).

The clinical progression of SBS is classically divided into three phases (Cosnes, 2000): (i) a post-operative period of 4–6 weeks; (ii) an adaptative period of around 2 years; and (iii) stabilization, the so-called sequel phase, in which it is imperative that gastroenterological and nutritional treatments instigated in the second phase must be pursued (Jeejeebhoy, 1994; Cosnes, 2000; Buchman *et al*., 2003).

Evaluation

Clinical evaluation of SBS requires the method of digestive balances (in-out) (Cummings *et al*., 1973; Levy *et al*., 1988; Nightingale *et al*., 1990; Messing *et al*., 1991). Lack of oral autonomy, i.e. the dependence on PN, is expressed either by a negative fluid–electrolyte balance or by a negative protein–energy balance, with interplay in both (Nightingale *et al*., 1990). In SBS, a negative fluid–electrolyte balance is seen in 13% and 33%, respectively, of patients with or without a remaining colon (Nightingale *et al*., 1992).

Water–sodium (Na) balance, other electrolytes and minerals

Fluid-electrolyte losses (stoma and diarrhoea) can be very high, particularly in total enterectomy, when they can reach 10 l/day, with losses of 600 mmol/day of Na. The ionic concentration of digestive electrolyte losses in enterostomy is near to that of plasma (Newton *et al*., 1982; Arrambide *et al*., 1989). In the case of colostomy, the losses of Na and potassium (K) are correlated negatively and positively, respectively, to the percentage remaining of the resected colon (Cummings *et al*., 1973) (Table 6.1).

The risk of K depletion is increased in patients with a terminal enterostomy situated < 50 cm from the Treitz Angle (Nightingale *et al*., 1990). This K depletion is secondary to hyperaldosteronism due to Na depletion, and is accompanied by a metabolic alkalosis with an increase in urinary K losses. The net digestive H_2O–Na balance is negative when the length of the remaining bowel is < 1 m, and may become positive

Table 6.1. Daily fluid and electrolyte losses at different levels of surgical intervention (from Cummings *et al.*, 1973).

	Proximal jejunum	Middle small bowel	Distal ileum	Colon[a] 50%	Colon[a] 100%
Volume (l)	4.0–6.0	1.5–3.0	0.5–1.0	1.0–2.0	0.5–1.0
Na^+ (mOsm/l)	80–100	100–120	100–120	50–70	20–40
Cl^- (mOsm/l)	80–100	70–90	70–100	30–50	10–30
K^+ (mOsm/l)	5–10	5–10	5–10	30–70	70–90
HCO_3^- (mOsm/l)	10–20	20–40	20–40	30–60	50–90

[a] 50% or 100% remaining colon with a distal ileum resection ≥ 100 cm.

for an enterostomy situated > 1 m from the Treitz Angle if the fluid dietetic *ad hoc* measures and medical treatment are strictly followed (Nightingale *et al.*, 1990). If part of the colon is preserved, faecal K losses are combined with bicarbonate losses and a tendency towards metabolic acidosis that are counterbalanced by overproduction and hyperabsorption of acetate (when it reaches the plasma it generates an equimolar quantity of bicarbonate).

A true deficit of Mg is very frequent in cases of SBS, and it leads in a few weeks to a 25% depletion in the intracellular K pool (Shils, 1969). Hypomagnesaemia induces a hypocalcaemia resistant to Ca salts and vitamin D (cholecalciferol, or 25 OH-cholecalciferol). This is due to the fact that hypomagnesaemia induces a decreased secretion of parathyroid hormone and reduction in activity of the 1-α renal hydroxylation – both can be reversed by repletion of the Mg pool. The persistence of hypomagnesaemia calls for active metabolites of vitamin D (either 1-α or 1-25, diOH-cholecalciferol) to correct hypocalcaemia (Jeejeebhoy, 2002).

The water–Na balance is more difficult to achieve than energy balance in SBS: this is exemplified by the fact that 20% of patients with a jejunostomy require only IV supplementation of water + Na (and eventually Mg) (Nightingale, 1994).

Energy balance

The determination of energy balance requires bomb calorimetry to measure food energy intake and stool energy output (the direct measurements of protein, fat and carbohydrate being performed either directly by the respective method of Kjeldahl, Van De Kamer and English (Van de Kamer and Huihink, 1949) or indirectly by the same protein and fat measurement, the carbohydrate being measured by the difference between the total energy losses and the two other macronutrients) (Miller and Payne, 1959). In this case, the energy (in Kcal) of each macronutrient is given by the combustion factors 5.35 for protein, 9 for LCT and 3.8–4.2 for glucids (Southgate and Durnin, 1970). The metabolizable energy in the

normal individual is evaluated as 4, 9 and 4, respectively, for protein, fat and carbohydrate, but it will vary according to the percentage of absorption in each specific SBS case. Indeed, it will be determined by the combustion of: (ingested foods – (stools + variable types of nitrogen losses in urine)) (Messing *et al*., 1991; Jeppesen and Mortensen, 2000).

Examples of energy balance for the two main types of SBS are indicated in Table 6.2 (Nightingale *et al*., 1990; Messing *et al*., 1991). In the presence of the entire or part colon, the net absorption of glucids is significantly greater than that of lipids and proteins (Nordgaard *et al*., 1996); this means that colonic energy absorption of the malabsorbed carbohydrate occurs, being fermented by the colonic bacterial flora in SCFAs, which are then absorbed (Briet *et al*., 1995; Nordgaard *et al*., 1996). In addition, comparison of absorption with the two main types of SBS (Table 6.2) indicates a difference of 50% in the energy balance, expressed as a percentage of the resting energy expenditure (REE) (Nightingale *et al*., 1990; Messing *et al*., 1991).

SBS and intestinal failure

It is better after the onset of SBS to correct or avoid malnutrition with HPN until a complete oral autonomy is achieved, rather than setting this up after failure by only oral or enteral routes, this failure being invariably complicated by – at times severe – denutrition (Koberle, 1881). Chronic intestinal failure (CIF) is seen when there is either negative water–electrolyte balance and/or a negative energy balance, with the need to pursue either IV supplementation by water, Na, K and Mg and/or complete parenteral nutrition (Messing *et al*., 1991; Jeppesen and Mortensen, 2000; Nightingale, 2003). For SBS of types II and III, we have calculated that an absorption equivalent to ≥ 1.5 times the BEE of patients (see Table 6.2) makes oral autonomy possible and successful (Messing *et al*., 1991).

Table 6.2. Examples of net digestive balance in SBS patients (from Nightingale *et al*., 1990; Messing *et al*., 1991).

	Terminal enterostomy[a]	Jejuno-(ileo)colonic anastomosis[b]
Ingested (kcal/day)	2500 (range 900–4800)	3100 (range 1700–4500)
Digestive losses (kcal/day)	1400 (range 550–2700)	970 (range 340–1600)
Absorption (%)	44 (range 10–75)	67 (range 41–85)
Net absorption (kcal/day)	1100 (range −200–2800)	2130 (range 750–3500)
Net absorption (% of REE)	0.80 (range 0.20–2.00)	1.50 (range 0.55–3.30)

[a] Type I (n = 15) ; [b] types II and III (n = 10); data calculated respectively from references: [a], remnant small bowel length 90 (range 25–140) cm of jejunum; [b], remnant small bowel length 75 (range 0–200) cm of jejunum and 15 (range 10–30) cm of ileum (present in 4 and absent in 6 cases) with 67 (range 0–100)% of remaining colon.
REE, resting expenditure energy.

In type I, however, oral autonomy has been observed for an absorption equivalent ≥ 0.85 times the REE associated with a water balance ≥ 1.4 kg/day (Jeppesen and Mortensen, 2000). In the latter case, it has been speculated that such a low energy requirement for maintenance of oral autonomy was due to decreased REE associated with malnutrition (Jeppesen and Mortensen, 2000). However, there is no decreased REE if below-normal body weight is associated with chronic intestinal disease (Carbonnel *et al*., 1995).

In the weeks following the post-operative period, nasogastric enteral feeding (~ 2000–2500 kcal/day) anticipates future oral autonomy if the stool output is less than 3 kg/day. If there is more than 3 kg/day the authors call this an 'overwhelmed intestine' – which indicates the need for parenteral nutrition (Cosnes *et al*., 1988).

Weaning a patient off HPN is achieved in 95% of cases within a period of 24 months. This period differentiates patients with transient CIF (weaning off before the 24th month) from those with permanent CIF (Messing *et al*., 1999). Indeed, the probability of being weaned off NPAD, 2 years following re-establishment of bowel continuity or since the last digestive circuit modification, is less than 10% overall (Messing *et al*., 1999).

Indeed, SBS becomes complicated in 50% of cases with permanent CIF and requires long-term NPAD. In such cases dependency on HPN is > 2 years, the length of the remaining small bowel being < 100–120 cm in type I, 60–80 cm in type II and 35–50 cm in type III. In addition, where post-absorptive citrulline (an amino acid produced by the enterocyte, which is a biomarker of – and the functional remaining – enterocyte mass) (plasma concentration in adulthood is < 20 μmol/l (has, following the adaptative period, been associated with permanent NPAD dependency), Crenn *et al*., 2000).

It has been demonstrated that anatomical data (delineating transient from permanent CIF) are in agreement with the balance of energy and water-Na absorption (Cummings *et al*., 1973; Messing *et al*., 1991; Briet *et al*., 1995). If a discrepancy exists it should be looked for in a non-healthy remnant bowel, from errors in dietetic fluid intake or from insufficient oral intake, i.e. not atttaining a state of hyperphagia (Messing *et al*., 1991; Jeppesen and Mortensen, 2000; Crenn *et al*., 2004). In the case of discrepancy between length of anatomical remnant and oral autonomy, there is an indication for a biochemical functional remnant evaluation, with the determination of post-absorptive plasma citrulline concentration.

Indeed, in 57 patients suffering from SBS without renal insufficiency (creatinine clearance > 60 ml/min), a significantly lower level of the citrulline level was found than among 51 controls (20 versus 40 μmol/l)(Crenn *et al*., 2000). Multivariate analysis indicated that the plasma concentration of citrulline was related only to the length of the remaining bowel ($r^2 = 0.75$) measured either directly in the theatre or indirectly with an opisometer; the citrulline level was correlated with the lipid absorption

($P > 0.01$) but to neither the albuminaemia nor the BMI (Crenn *et al*., 2000). A plasma level of post-absorptive citrulline (< 20 μmol/l) shows up better than the anatomical remnant in HPN dependence and conveys the existence of 'irreversible' CIF (Crenn *et al*., 2000). Recently, a threshold of 19 μmol/l has been defined in children as defining HPN dependency (Rhoads *et al*., 2004).

The conjunction of the determination of the level of oral solid and fluid intakes, the appropriateness of dietetic education, the precise determination of the remaining length of intestine (cm for small bowel and percentage for colon) and the evaluation of the health of the remnant (imaging endoscopy with biopsy, with the help of the plasma determination of citrulline in the absence of renal insufficiency or dehydratation) will allow definion of the probability of permanent CIF. If this is the case, trophic factors (such has GH or GLP2), reconstructive surgery (type II) of the remaining bowel – or intestinal transplantation of the bowel in the case of serious complications of HPN – have to be considered (see Part III, this volume).

Medical treatment of diarrhoea

Increasing the time of intestinal transit

Loperamide or codeine can reduce the flow from enterostomy and diarrhoea by up to 30% (Rodrigues *et al*., 1989). If high doses of loperamide appear insufficient (16–32 mg/day), codeine should be tried at a level of up to 10 cg/day (Jeejeebhoy, 2002). These treatments are contraindicated either in the case of digestive stenosis or anti-peristaltic loop following reconstructive surgery.

Proton pump inhibitors (PPIs)

As soon as feeding is commenced these are recommended by the oral route to reduce gastric acid hypersecretion, with a dose of either 40 mg Omeprazole®, 60 mg Lanzoprazole® or 80 mg Pantoprazole® twice a day (Nightingale *et al*., 1991; Jeejeebhoy, 2002). This is indicated for a period of 2 months, then reduced to 50% dosage once in the morning; administration of. PPI or anti-H2 (such as ranitidine at 2 × 300 mg/day) reduces by 20% the outflow of a proximal enterostomy without significantly improving the macronutrient malabsorption (Jeppesen *et al*., 1998). The duration of this treatment is *a priori* long term (2 years) in SBS type I, and around 1 year in SBS types II and III, except for those patients under HPN where this treatment can be continued. Indeed, the cyclic nocturnal delivery of HPN stimulates gastric acid secretion through IV amino acids at a level equivalent to their intra-duodenal perfusion – i.e. at the rate of one-third of the maximum gastric acid secretion (Nightingale, 2003).

Chelating biliary salts

Cholestyramine is not indicated in SBS with significant steatorrhea (> 20 g/day), but is remarkably efficient in controlling diarrhoea in short ileal resection with steatorrhea (≤ 20 g/day). This medication is taken 2 h before meals and again before sleep, having found an efficient optimal lowest dosage level (Poley and Hofmann, 1976; Cosnes, 2000).

Biliary salts

Ursodeoxycholic acid, even when absorbed through facilitated diffusion at the jejunum level, is not indicated in the treatment of the biliary salt deficiency following an extensive ileal resection because it has weak lipid emulsifying powers. Bovine bile, if available, improves steatorrhea in SBS type I but its use is limited by its colonic laxative effects (Fordtran *et al*., 1982).

Cholysarcosine, a synthetic biliary salt, is unfortunately not commercially available. It is not laxative, and is resistant to bacterial dehydroxylation and deconjugation. Its efficiency in the case of enterostomy is equivalent to that of bovine bile, i.e. reducing massive steatorrhea and Ca losses by up to 50 and 15%, respectively, but with a 15% increase in stoma output (Gruy-Kapral *et al*., 1999). These results are less positive and mixed in SBS types II and III (Heydorn *et al*., 1999).

Calcium carbonate

In a series of 15 jejuno-ileal short circuit patients, Calcium carbonate – or chalk powder – at a dosage rate of 2.4–3.6 g/day, administered separate from mealtimes, reduces stool output and steatorrhea by up to 50% without increasing the losses of biliary salts. This treatment can be tried in ileal resections, but some patients do complain of nausea with chalk (Cosnes, 2000).

Pancreatic enzymes

There is no pancreatic deficiency secondary to SBS itself (Messing and Chaussade, unpublished personal observation of Lund test in 15 patients), even though a reduction has been seen in the postprandial peak concentration of blood cholecystokinine (Ling *et al*., 2001). However, a reduction by up to 40% of trypsin and bilirubin outputs is seen with high dosages of loperamide and codeine, a potential factor for reduction of lipid absorption (Remington *et al*., 1982).

Antibiotics

Antibiotics are not usually indicated in the treatment of SBS type I. In types II and III (Rao *et al*., 1988) they may modify the colonic flora and increase the diarrhoea (cf. above). In type II, if bacterial overgrowth is

demonstrated by breath test, 10 days' treatment directed against Gram-negative or anaerobic bacteria can be tried to reduce diarrhoea. In such cases the diarrhoea should be clinically reduced by at least 20% (Attar *et al*., 1999). In our experience, this sequential antibiotic treatment is efficient only when bacterial overgrowth is associated with a remaining pathological bowel with non-occlusive stenoses.

Somatostatin

In SBS type I, subcutaneous (SC), short-lived octreotide at an anti-secretory dosage of 200 μg/day reduces by 30% the enterostomy output without reducing malabsorption (Lemann *et al*., 1993). Its use is possible in the post-operative period or as pulse therapy – for example 1 or 2 days per week in order to omit one or two nocturnal IV PN infusions. In one series of 15 patients, intramuscular (IM) long-acting somatostatin did not decrease the stool output in comparison to controls. At our present state of knowledge, we do not recommend this treatment (either short- or long-term octreotide) on a permanent basis (Nehra *et al*., 2001), as it can entail, on the one hand, a therapeutic escape (Ladefoged *et al*., 1989), but on the other anti-trophic intestinal and pancreatic effects (O'Keefe *et al*., 1994).

Nutritional and Dietetic Treatment (HPN excluded)

Post-operative period

Hydroelectrolyte losses (Na, K, Mg) must be compensated. This entails precise monitoring, measuring weight, urinary and digestive balance and dosages of serum and urinary electrolytes. The hydroeletrolyte re-animation and the use of PN reduce the loss of lean body mass, avoid severe loss of weight and improve long-term survival (Messing *et al*., 1999). Resuming oral feeding increases the volume of basal digestive output by a factor of 2 or 3, digestive secretions being stimulated: thus, it is a critical period where IV supplementation must be adjusted twice daily in order to avoid the acute and sudden occurrence of dehydration, hypokalaemia or hypomagnesaemia (Fagan and Phelan, 2001). Perfusions are reduced *pro rata* to the net in-and-out digestive balance.

After stabilizing the hydroelectrolyte balance and restarting transit, the priority is to optimize a diet by the enteral-oral route while sustaining or correcting the nutritional status by the IV route. Drinking is one of the key elements of dietetic education (see below).

To obtain oral nutritional autonomy is a long and often difficult task in the case of remnant bowel shorter than 1.5 m (Carbonnel *et al*., 1996); in the latter case, enteral nutrition (EN) at a constant rate can be proposed; this follows results obtained in a series of 62 patients where early post-operative EN and oral nutrition (ON) were allowed, PN being stopped after a mean period of 87 days (Levy *et al*., 1988).

Adaptative period

Hyperphagia

The diet must not prevent hypercaloric, hyperproteic feeding, in order to try to compensate for the malabsorption (Messing *et al.*, 1991; Cosnes *et al.*, 1992). Comparison between normo- and hyperphagic diets (up to 2.5-fold REE) does not indicate a reduction of net absorption of macronutrients. Therefore, the more hypercaloric the diet the more positive is the net energy and protein digestive balance.

SBS type I: oral rehydration solutions (ORSs)

The method of balance has allowed the separation of enterostomy patients into two groups: (i) the 'secretors', dependent on HPN; and (ii) the 'absorbers', where there is a possibility of the patient being weaned off PN (Table 6.3). The secretors have intestinal losses greater than their oral intake, they tend to have a shorter intestine (< 100 cm), to absorb < 35% of their oral energy intake and to have a negative hydroelectrolyte balance – which can be > 400 mmol Na/day, and 4 l of water/day. Therefore, they need IV infusion of fluids to ensure their hydroelectrolyte homeostasis.

Among the absorbers group, the oral intake is greater than intestinal losses and the net hydroelectrolyte balance is positive, due to ORSs, though some of these patients may lose up to 300 mmol Na/day. The efficacy of ORSs (glucose

Table 6.3. Dietary advice[a] in SBS patients[b].

	Type I Enterostomy[c]	Type II Jejuno-colic	Type III Jejuno-ileocolic
Small, frequent meals	+	NS	NS
Drinks			
ORS[d]	+++	NS	NS
Saline	++	+	NS
Milk	X/⩽400 ml/day[e]	X/⩽ 400ml/day[e]	NS/−
Hypotonic drinks	X	⩽750 ml/day[e]	⩽1000 ml/day[e]
Meals rich in complex carbohydrates	+	+++	+/NS
Meals rich in LCT	++	−/NS	−/NS
Meals rich in MCT	−	+	+/NS
Hypercaloric solid diet[f]	+++	++	+

[a] +++, imperative; ++, recommended; +, useful; NS, not stated; -, negative effect; X, prohibited.
[b] post-duodenal remnant length = 150–200 cm.
[c] All enterostomy patients, whatever the remnant length, benefit from advice when stoma output ≥ 600 ml/day.
[d] oral rehydratation solutions given as OMS in g/l: NaCl, 3.5; $NaHCO_3$, 2.5; KCl, 2.5; glucose, 20 g; water, 1000 ml.
[e] with 1 g of NaCl per 200 ml of drinks.
[f] hyperphagia, which tends to compensate for malabsorption, should be stimulated.

or polymer glucose/electrolytes with 90 mmol Na/l) is essential for patients with SBS type I; they rely on the glucose-Na transporter, which reduces significantly (by 35%) enterostoma losses relative to those with all other types of replacement therapy – including salty ones or NaC1 tablets – of an equivalent Na concentration. ORSs, administered in small sips spread throughout the day at the level of 2–3 l/day, have a sweet, salty taste frequently judged unpalatable. It is important to indicate that the use of ORSs and other treatments that reduce the intestinal flow (PPI, octreotide, transit-slowing factors) does not allow the re-categorization of secretors into absorbers.

SBS type I: other drinks

Hypotonic drinks (e.g. mineral waters whose concentration deviates from plasma osmolarity) induce a secretory diarrhoea through the increase of plasma-intraluminal flux, aiming to re-establish intraluminal iso-osmolarity (Newton *et al*., 1985). Thus, hypotonic drinks (water, tea, coffee) increase the enterostomy flow and render negative the hydroelectrolyte balance. It has been shown that the post-duodenal segment had to be at least 1 m in order to achieve a concentration of around 90 mmol Na/l (Cosnes, 2000). Thus, hypotonic drinking must be reduced to 600 ml/day and be preceded by the taking of salt tablets (Table 6.3). Milk lactose (20 g/400 ml) is less well absorbed (up to 50%) than an equivalent amount taken in yogurt (up to 70%), with a moderate increase in stoma flow through osmotic effect. In spite of this, some authors do not recommend milk due to increase in outflow among hypolactasic patients (Christopher and Bayless, 1971; Jeejeebhoy, 2002; Nightingale, 2003).

SBS type I: types and regimes of feeding

Liquid feeding, of whatever type (semi-elemental with MCT or polymeric), does not induce better absorption than solid feeding (with a variable percentage of fibre and LCT) (Nightingale, 2003). Drinking during or outside of mealtimes does not seem to modify the stoma flow; thus the control of fluid supplements with adequate Na during mealtimes is not required in a stable, orally fed patient. Frequent – but not plentiful – meals seem better tolerated than large meals. Milky diets are advised for their Ca and protein content in a semi-liquid or solid form (Arrambide *et al*., 1989; Mahe *et al*., 1991; Marteau *et al*., 1997). There might be a need to pursue enteral nutrition at a constant rate (through nasogastric tube or gastrostomy) in the adaptative period of SBS, especially when spontaneous oral intake is insufficient; we have noted in SBS types I and II significant improvement (> 20%) in net absorption with nasogatric tube feeding compared with standard oral iso-caloric feeding (Cosnes *et al*., 1980; Cosnes *et al*., 1992).

Among those patients with a high-output jejunostomy, lipid intake (TCL) must not be limited. Lipids in food, whether animal or vegetable, provide a good energy source that increases neither the osmotic load nor

the stoma flow. The increase in lipid intake is accompanied by an identical absorption percentage, and this increases the degree of oral energy autonomy – and eventually the intake of essential fatty acids (Simko *et al.*, 1980). The loss of divalent ions following the increase of steatorrhoea is not conclusive (Ovesen *et al.*, 1983; Woolf *et al.*, 1983, 1987).

Theoretical interest in MCT has resulted in practical applications; these are absorbed independently of biliary salts, and their introduction into meals (TCM 30% + TCL 30%) is accompanied by a percentage of absorption 60% better than with LCT alone. However, this positive effect is counterbalanced by a negative effect, which is the increase in stoma flow due to the osmotic load linked to MCT (C8 to C12) and, subsequently, the net global absorption of macronutrients is equivalent to the increased losses in protein and glucids (Jeppesen and Mortensen, 1998).

SBS types II and III: types and regimes of feeding

When colonic continuity is preserved, lipids are less well tolerated, with more diarrhoea, loss of divalent cations and more oxalate absorption. Thus, nutrition rich in complex glucids and relatively poor in lipids can reduce the volume of stools and store up calories via the colonic absorption of SCFA (Nordgaard *et al.*, 1994). The benefit from this kind of diet has, however, been demonstrated with comparatively abnormal intakes of glucids and lipids (60 and 20%, respectively). Patients themselves restrict the intake of lipids when they notice an obvious increase in their diarrhoea. If there is a risk of negative energy balance through insufficient overall calorie intake, the oral introduction of MCT is justified as, on the one hand, they do not increase diarrhoea and, on the other, when they reach the colon, being hydrosoluble, they are absorbed through facilitated diffusion (Jeppesen and Mortensen, 1998).

In practice, hyperphagia is encouraged and, in this case (ingestion $\geq$ 2.5 times REE), we have observed that the ratio between proteins, glucids and lipids (LCT only) of free, spontaneous feeding was 23, 46 and 31% respectively, their absorption rates being 61 $\pm$ 19, 79 $\pm$ 15 and 52 $\pm$ 16%, respectively, the net total absorption being 67 $\pm$ 12% (Messing *et al.*, 1991).

Mineral supplementation

Hypokalaemia is secondary to either a Na or a Mg deficiency (Shils, 1969; Whang *et al.*, 1992). Hypocalcaemia is secondary to Mg and/or vitamin D deficiency (Haderslev *et al.*, 2003). Treatment of hypocalcaemia relies on the active metabolites of vitamin D (1-α + Mg supplements) (Ducreux *et al.*, 1991; Jeejeebhoy, 2002; Chagas and Kelly, 2003). One can encounter difficulties with oral Mg supplements because they have a laxative effect with a variable tolerance between patients. They can be given in doses of up to 20–30 mmol/day (Jeejeebhoy, 2002). If hypomagnesaemia persists, it is necessary to give Mg salts IM or IV.

Micronutrient supplementation

Lipid malabsorption after ileal resection ≥ 1 m is followed by malabsorption of fat-soluble vitamins (A, D, E and K) (Jeppesen *et al*., 2000) and requires careful supplementation (Jeejeebhoy, 1994). Parenteral supplementation by vitamin B_{12} (1000 μg/3 months) after resection of the terminal ileum ≥ 60 cm is prescribed indefinitely (Behrend *et al*., 1995; Compher *et al*., 2001; Jeejeebhoy, 2002). When these patients need IM supplementation (or a series of same) it is necessary to precede the injection by 24 or 48 h with vitamin K_1 supplementation when the prothrombin time is < 70%. If patients need anticoagulation treatment at curative dosage rates, we recommend the administration of vitamin B_{12} SC at a dosage of 1000 μg/month. If diarrhoea is ≥ 1000 ml/day, oral zinc supplementation should be given in the form of gluconate or pyroglutamate, and not of sulphate, as the latter has a laxative effect. (Behrend *et al*., 1995; Jeejeebhoy, 2002).

Treatment of complications secondary to intestinal resection

Peptic ulcer

This occurs secondary to hypersecretion of gastric acid and is seen in up to 20% of patients (Nightingale, 1994); its frequency has decreased dramatically with the widespread use of PPI and the use of antibiotic treatment effective against *Helicobacter pylori*.

Cholelithiasis (gallstones)

This is secondary to either: (i) ileal resection, i.e. the bile becomes lithogenic through deficiency in biliary salts, with an increase in cholesterol saturation and ongoing cholesteral crystals; or (ii) bowel rest, inducing gall bladder stasis with Ca-bilirubinate precipitates. Its frequency, associated with HPN, has been seen as occurring in up to 40% of patients (Nightingale *et al*., 1992). Biliary sludge can be seen more rapidly after intestinal surgery (< 2 weeks) and with ileal disorders – either resection or disease – and gall bladder lithiasis is seen in up to 20% of patients. Prophylactic cholecystectomy is therefore proposed when digestive surgery is performed with the existing presence of either gall bladder sludge or lithiasis (Thompson, 1996).

Renal lithiasis (kidney stones)

This occurs secondary to hyperoxaluria, and is seen in up to 25% of patients with SBS having steatorrhoea and a whole or part of the colon in continuity (Nightingale *et al*., 1992). Its preventive treatment relies on: (i) diuresis of more than 1 l/day; (ii) a low-oxalate diet; and (iii) the prescription of Ca salts (1.5–3.0 g/day) before meals. This treatment, in our

experience, removes this complication from more than 95% of cases. If these measures are insufficient, citrate salts – as well as a reduction in lipid feeding – are indicated (Jeejeebhoy, 2002).

D-lactic encephalopathy

This occurs secondary to the production of d-lactate by the colonic bacterial flora. D-lactate, having no systemic metabolism, plays the role of false cerebral neurotransmitter and induces pseudo-ebriety (drunkenness) with cerebellar signs (Stolberg *et al.*, 1982; Nightingale, 1994). This complication, seen in fewer than 5% of patients, is not always associated with acidosis since only a few mmol of d-lactate are sufficient to provoke this encephalopathy. It can be either acute or subacute and recurrent, and can be induced by any of the following: (i) the ingestion of a large quantity of milk products (possible increase in lactobacillus activity); (ii) vitamin B_1 deficit; or (iii) by the use of broad-spectrum antibiotics which, prescribed for other reasons, modify the colonic bacterial flora (Flourie *et al.*, 1990; Hudson *et al.*, 1990).

The treatment relies on a 24-h bowel rest phase, followed by restriction of glucose/milk and sometimes the administration of the antibiotic metronidazole. If acidosis is present, urgent treatment relies on fasting, IV rehydration and IV bicarbonate (Gurevitch *et al.*, 1993).

Summary

Short bowel syndrome refers to an aggregation of clinical signs and symptoms caused by malabsorption, characterized primarily by intractable diarrhoea, dehydration, malabsorption of macronutrients, weight loss, malabsorption of vitamins and trace elements and malnutrition. Based on a description of the pathophysiology of the short bowel syndrome, the clinical presentation of the syndrome is presented, pharmacological and dietary treatment options are given and complications summarized.

Optimization of 'classical' dietary, nutritional and gastroenterological treatments is the cornerstone of treatment of SBS patients, as should be complementary HPN for those who cannot be autonomous via the enteral route only. Today, better ways of delineating transient from permanent IF in SBS patients allow for proper additional indications for hormonal and/or surgical treatments in the hope of weaning off HPN patients classified as having permanent IF. Care of these patients requires the expertise of centres devoted to the whole-spectrum treatment of IF.

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7 Gastrointestinal Fistulae

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Key points

- Fistulae are a complication of, e.g. Crohn's disease, cancer, diverticular disease, or may appear secondary to gastrointestinal surgery or trauma.
- The importance of sepsis identification and control cannot be minimized.
- The mainstay of therapy for closure of fistulae is parenteral nutrition and giving the patient nil by mouth.
- HPN (home parenteral nutrition) for patients with fistulae may be instigated for a number of months, but only to allow appropriate conditions for definitive surgery.

Introduction

A fistula from the gastrointestinal tract to an adjacent organ (bladder, vagina, skin or more distal bowel) can lead to nutrition and fluid deficiencies, depending on its anatomical origin. Thus, a proximal jejunal enterocutaneous fistula associated with underlying sepsis will result in devastating fluid and nutrient losses which, untreated, can lead to a mortality rate of 50% (Soeters *et al*., 1979; Dudrick *et al*., 1999). By contrast a recto-vaginal fistula, whilst having an important impact on a patient's quality of life, has little effect on mortality or nutrition. Primary, spontaneous fistulae are a complication of an underlying disease process, e.g. Crohn's disease, cancer or diverticular disease. Much commoner are secondary fistulae shortly after gastrointestinal surgery or trauma (Haffejee, 2004). These are almost always associated with local sepsis and it

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is the management of the sepsis that dominates the therapeutic approach. Up to 60% of post-operative fistulae will spontaneously heal with appropriate nursing and nutritional care within 6 weeks. Factors associated with failure to heal include the following:

- persistent sepsis;
- muco-cutaneous continuity;
- local disease, e.g. Crohn's, causing fistulation;
- distal obstruction to the fistula;
- wide discontinuity of bowel;
- multiple, complex fistulae;
- untreated undernutrition; and
- unstable metabolic disease.

The overriding importance of sepsis identification and control cannot be minimized. In a specialist intestinal failure unit, fistulae account for between 44 and 80% of referrals (Scott *et al.*, 1991; Teubner, personal communication, 2005). The principles of care are: (i) the provision of nutritional support, including fluid balance; (ii) expert nursing and stoma care; (iii) identification of anatomical structures; (iv) control and drainage of sepsis; and (v) definitive surgery.

Care of the patient

Nutritional support

The mainstay of therapy is parenteral nutrition and giving the patient nil by mouth. Certainly in those patients for whom it is known that spontaneous healing will not take place, they may eat and drink to the limits of food and fluid replacement. In those patients in whom an attempt is being made to allow the fistula to heal without surgery, it is unclear whether oral restriction leads to fistula closure. In the author's experience it makes little difference, and the factors described above are more important; there have been no appropriate controlled studies to give a definitive answer. Enteral nutrition may be used again, providing it does not lead to uncontrollable fluid losses. The practice of intubating the distal limb of a fistula (if accessible) allows a number of patients to be enterally fed who would otherwise require parenteral nutrition (Teubner *et al.*, 2004).

Medical therapy

Octreotide will non-specifically reduce an output by approximately 1 l, but is unlikely to result in an increase in fistula healing (Sitges-Serra *et al.*, 1993; Jamil *et al.*, 2004). The recommended dose is 25–50 mcg two to three times daily, and the treatment can be continued quite safely long term. It is confined to those patients in whom standard management of a

high output (opiates, acid suppression, oral rehydration solutions) is inadequate. Infliximab is helpful in controlling active Crohn's disease and has a role in the management of peri-anal fistulae, but has little effect on internal or enterocutaneous fistulae (Miehsler *et al*., 2004; Parsi *et al*., 2004). Experimental therapies include vacuum aspiration (Medioros *et al*., 2004) and adipose mesenchymal stem cells (Garcia-Olmo *et al*., 2005).

Nursing/stoma care

Multiple/complex fistulae provide a considerable challenge in the maintenance of skin, fluids, wound and psychological care. Excellent results are seen in specialized 'intestinal failure units', that can provide the multidisciplinary care required. The successful closure of fistulae is more likely with the following criteria: (i) low output; (ii) distal small bowel involvement; (iii) good post-operative nutritional status; and (iv) the patient's ability to eat and drink normally; unsuccessful closure would be expected with these criteria: (i) high output (> 500 ml/day); (ii) very proximal involvement; (iii) mucocutaneous continuity; (iv) distal obstruction disease, e.g. Crohns; (v) cancer active at the site; (vi) poor nutritional status; and (vii) inability to provide appropriate nursing and nutrional care. Spontaneous closure time is usually within 6 weeks of adequate care, but can be much longer.

Delineating anatomy

Patients with resistant fistulae require radiological contrast studies, including fistulography, to delineate the length, relationships and connections. Ultrasound, CT – and, if need be, MR and white cell scans – are mandatory in identifying any underlying sepsis. This can be prominent on scanning even though the patient may not be systemically ill or the usual inflammatory markers not markedly elevated.

Sepsis control

Radiological drainage of abscesses and collections of infection may need to be repeated. In complex cases drains should be inserted to allow repeated washouts of septic areas and to prevent reaccumulation of material. If it is clear that sepsis management cannot be obtained by this method, a stoma proximal to the site of the (first) fistula may be required.

Definitive surgery

The importance of avoiding fistula resection in the presence of sepsis is reiterated. Serum albumin > 30 mmol/l is a reasonable target, but may not be achievable for many weeks. The presence of widespread sepsis after multiple attempts at surgery may lead to obliteration of the peritoneal

cavity and a very demanding surgical environment. Home parenteral nutrition for a number of months (average 6) can provide this interval and allow the patient to return to home, often after many months in hospital (Carlson, 2003; Evans *et al*., 2003). Reconstruction is then possible in a non-septic, controlled environment. Mortality rates of over 50% have fallen to 20% or less, but seemingly the greater the delay in surgical repair of the fistula the better the outcome (mortality 2–7%) (Carlson, 2003; Lynch *et al.*, 2004; Olaison *et al*., 2005).

Home parenteral nutrition and fistulae

HPN has been used in the management of fistulae for many years (Byrne *et al.*, 1979, Mughal and Irving, 1986), partly as a means of providing for prolonged spontaneous closure but also as a means to allow timing for definitive surgery. The percentage of HPN patients with fistulae as their underlying problem is relatively small – currently in our Acute Intestinal Failure Unit we admit approximately 60 new patients per year, and nearly 50% have a fistula but only four or five will go home on parenteral nutrition. This is always for a number of months, and only to allow appropriate conditions for definitive surgery. Some of these may require long-term HPN, but this is because they have SBS. This compares with figures of 6 and 7% in the two HANS surveys (Van Gossum *et al*., 1996, 1999). Most of these patients had either Crohn's disease or GI cancer as their underlying diagnosis.

Nutritional regimen

There are no specific differences in the nutritional requirements of these patients from other patients, other than that many will have a very proximal fistula with correspondingly high outputs. This will necessitate both high volumes of fluid and long periods of infusions.

Outcome

The prognosis is dependent on the underlying disease. Thus, Crohn's disease as the cause of the fistula requires HPN prior to surgery, whilst cancer fistulae usually involve HPN only as a terminal treatment.

Summary

The management of gastrointestinal fistulae is both supportive and dependent on the underlying disease. Persistent post-operative fistulae are usually associated with sepsis, malnutrition and fluid and electrolyte losses. In complex fistulae or patients in whom surgery is best delayed as long as

possible, HPN for a number of months can play a useful role. In those patients with cancer as the cause of the fistula, HPN can provide helpful palliation.

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8 Chronic Intestinal Pseudo-obstruction

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Key points

- Chronic intestinal pseudo-obstruction (CIPO) is defined as a rare, severe, disabling disorder characterized by chronic and/or recurrent symptoms suggesting bowel obstruction, in the absence of fixed lumen-occluding lesions.
- CIPO is classified either as idiopathic (most common in children) or secondary (most common in the adult population).
- Recurrent episodes of obstruction are the most frequent clinical presentation, together with malabsorption and diarrhoea.
- Diagnosis is based on the clinical presentation, with longstanding symptoms and the absence of mechanical obstruction and – in some cases – a family history.
- Prokinetic drugs are systematically used in CIPO but their effectiveness is generally poor.
- Nutritional support is of great importance and HPN (home parenteral nutrition) is required in 60–80% of infants and in 20–50% of adults.
- Surgery, explorative or with resection, may be an option, or alternatively diversion of the stoma.
- Long-term outcome is characterized by a 10–25% infant mortality rate. In the adult, the clinical course, long-term outcome and prognostic factors are less well known because of the limited data on the small numbers of patients with heterogeneous onset and severity of the disease.

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Definition and classification of CIPO

According to a consensus working group in the 1980s, CIPO is defined as a rare, severe, disabling disorder characterized by chronic and/or recurrent symptoms suggesting bowel obstruction, in the absence of a fixed lumen-occluding lesion (Rudolph *et al*., 1997). Essentially, CIPO represents a wide and heterogeneous group of gastrointestinal nerve and muscle disorders. In most patients, CIPO is a sporadic disease (De Giorgio *et al*., 2001). Usually, CIPO is classified either as idiopathic or secondary. Idiopathic CIPO is the most prominent paediatric cause and occurs in 40% of adult CIPO patients (De Giorgio *et al*., 2001). It usually refers to hollow visceral disorders (see Box 8.1).

The secondary form of CIPO occurs in 60% of adult patients and rarely in children. The list of potential causes of CIPO is not exhaustive (see Box 8.1). The most common causes are: (i) metabolic disorders (diabetes mellitus, hypothyroidism); (ii) neuropathic, drug-related conditions (vincristine, anticholinergic drugs); and (iii) paraneoplastic and post-infectious syndromes and amyloidosis (Rudolph *et al*., 1997; Schuffler *et al*., 1981; Connor and Di Lorenzo, 2006; Joly *et al*., 2006).

In parallel with aetiological classification, a histopathological classification has also been made, taking into account abnormal pathological

Box 8.1. Principal aetiology of chronic intestinal pseudo-obstruction (CIPO).

Idiopathic CIPO

- MNGIE (Mitochondrial neuro-gastrointestinal encephalomyopathy) and other mitochondrial cytopathies.
- Intestinal neuronal dysplasia.
- Hirschsprung disease and diffuse aganglionosis.
- Multiple endocrine neoplasia type Iib.
- Neurofibromatosis type I.
- Others.

Secondary CIPO

- Smooth muscle disorders (connective tissue disease, amyloidosis, diffuse lymphoid infiltration of the small intestine, muscular dystrophies).
- Diseases of the central nervous system (Parkinson's disease, other causes of dysautonomia).
- Visceral sporadic neuropathies (paraneoplastic syndrome, post-infectious syndromes (Chagas disease, Epstein Barr Virus, Cytomegalovirus, Varicelle Zoster Virus, rotavirus).
- Drug-related toxicity (isoniazide, vincristine, anthraquinone, adriamycine, calcium channel inhibitors, anticholinergic drugs).
- Metabolic disorders (hypothyroidism, diabetes mellitus, acute intermittent porphyria, Fabry's disease, hyperparathyroidism).
- Miscellaneous (coeliac refractory sprue, radiation enteritis, Crohn's disease, post-surgical disorders).

and manometric findings (Stanghellini *et al*., 1987; Wood, 2002). Digestive motility is a highly coordinated process of mixing, absorption and propulsion of ingesta throughout the gastrointestinal tract, eventually leading to the expulsion of residues. Many actors are involved in digestive motility, from the central neural network, through the enteric nervous system to digestive smooth muscle (Goyal and Hirano, 1998). Digestive motility is also regulated by a pacemaker activity evoked by the interstitial cells of Cajals (ICC), which generate slow waves of phasic changes in intraluminal pressure (Thomsen *et al*., 1998; Lee *et al*., 1999). Recently, loss of ICC in the digestive tract has been associated with the idiopathic form of CIPO (Isozaki *et al*., 1997; Feldstein *et al*., 2003). CIPO can now, therefore, be classified into three different entities: mesenchymopathies, visceral neuropathies and visceral myopathies (De Giorgio *et al*., 2004).

Diagnosis

CIPO remains a diagnostic challenge because of its non-specific symptoms, the rarity of the disease, its insidious onset and, generally, lack of laboratory and morphologic tests. Frequently, between the onset of symptoms and the time of diagnosis, CIPO history is marked by multiple, non-contributive laparotomies or non-indicated bowel resection (Mann *et al*., 1997; Hanks and Weber, 1981). Following clinical evaluation, there are two factors which might lead to a diagnosis of CIPO: (i) a high degree of suspicion; and (ii) the exclusion, with certainty, of a mechanical bowel obstruction (Rudolph *et al*., 1997; Di Lorenzo, 1999). Stable, intermittent or long-standing symptoms of incomplete bowel obstruction are often present years before diagnosis (Di Lorenzo, 1999; Stanghellini *et al*., 2005). In two retrospective studies, mean time between onset of symptoms and diagnosis varied from 5.8 to 8 years (Mann *et al*., 1997; Stanghellini *et al*., 2005). A positive family history background of such disorders and the presence of extra-intestinal symptoms should also alert the physician.

Epidemiology

The heterogeneity of the disease and the lack of research are factors in the epidemiological uncertainty of CIPO. Based on the registry of the American Pseudo-Obstruction and Hirschsprung's Society (now part of the international Foundation for Functional Gastrointestinal Disorders), prevalence was estimated in the USA at 100 new cases born per year (0.3 paediatric cases/millions of births/year) (Di Lorenzo, 1999). These data, however, concern only the neonatal form of CIPO. The French web registry of Home Parenteral Nutrition (HPN) collects data on patients with intestinal failure requiring HPN; in this database, CIPO accounts for 10% of adult and infant patients, equivalent to 0.3 patients/million population/year.

Clinical findings

The paediatric form of CIPO normally begins at birth or in early infancy (Vargas *et al*., 1988; Faure *et al*., 1999). The adult form also occurs in young people (20–40 years of age), with more women affected than men in a ratio of 2:3 (Pitt *et al*., 1985; Stanghellini *et al*., 2005). Symptoms of CIPO are caused directly by ineffective propulsion and include the classic signs of bowel obstruction, including nausea, vomiting, abdominal pain and/or distension, loss of weight and anorexia. Symptoms are often chronic and continuous, progressively increasing with time. There seems to be no difference between symptoms at onset and at follow-up (Stanghellini *et al*., 2005).

Sometimes CIPO is revealed by an acute obstructive episode mimicking mechanical bowel obstruction, thus involving futile surgery. In some cases, severe clinical forms of CIPO present as total oral intolerance, permanent obstruction, intractable pain and rapid loss of weight, with protein energy malnutrition and life-threatening deficiencies, requiring HPN.

Complications

Long-term outcome is generally poor despite surgical and medical therapies. Three types of complication are often reported during the course of CIPO: (i) HPN-related complications (catheter-related sepsis, thrombosis, PN liver-related disease (Howard and Ashley, 2003); (ii) associated disease complications of, e.g., the renal and urinary, cardiac and central and peripheral nervous systems; and (iii) specific complications of CIPO: dehydration, metabolic disturbances, bacterial translocation, peritonitis, gastro-oesophageal reflux disease (± Barret mucosa, inhalation pneumonia) (Joly *et al*., 2006).

In the literature, the incidence of PN-related complications did not seem to differ from that of other causes of intestinal failure. It is to be expected that PN-related liver disease may develop more rapidly due to bacterial overgrowth and bacterial translocation.

Prognosis

Children

There is an HPN requirement in 60–80% of infants and in 20–50% of adults (Hanks and Weber, 1981; Faure *et al*., 1999; Mousa *et al*., 2002; Stanghellini *et al*., 2005). Considering infants, the long-term outcome is characterized by a 10–25% mortality incidence before adulthood. Although part of morbidity and mortality are attributable to complications of treatment, including surgery and parenteral nutrition, studies have shown

certain factors contributing to a poor prognosis in children: (i) short small bowel; (ii) exclusive parenteral nutrition with no prospect of enteral feeding; (iii) urinary tract involvement; (iv) neonatal form; (v) no MMC on manometry findings; and (vi) visceral myopathy.

Congenital CIPO has also been associated with increased morbidity and mortality compared to those in acquired forms (Huang *et al.*, 1995).

Adults

In adults the clinical course, long-term outcome and prognostic factors are less well known because data derive from clinical series reporting only small numbers of patients with heterogeneous onset and severe disease. In our experience (57 adult patients), CIPO prognosis appears to be mostly related to the aetiological prognosis (unpublished personal data). Initial reports showed a 25–30% mortality rate at early follow-up (Hanks and Weber, 1981; Vargas *et al.*, 1988). Recently, two studies reported a 10% mortality rate after a mean follow-up of 17.5 and 4.6 years, respectively (Mann *et al.*, 1997; Stanghellini *et al.*, 2005). This possible decrease in mortality rate achieved in recent years is probably due to improvements in overall management, including nutritional support.

Nutritional support and overall management

The main goals of management of CIPO are: (i) improvement of intestinal propulsion; and (ii) maintenance of adequate nutritional status, including fluid and mineral balances. Indeed, as a consequence of chronic dysmotility, inadequate oral intake, increased losses (vomiting, diarrhoea) and malabsorption aggravated by chronic intestinal malfunction, malnutrition should be systematically evaluated. If treatment of bacterial overgrowth is to be systematic, different modes of therapy are available according to the severity of the disease. Dietary education may be sufficient for patients with mild and moderate symptoms, but if oral nutritional intake becomes inadequate, nutritional support must be set up with enteral or parenteral nutrition.

Prokinetics

Despite their poor efficacy with regard to clinical symptoms, prokinetic drugs are systematically used in CIPO, probably because of their potential for improving digestive motility on manometry findings (Soudah *et al.*, 1991; Tack *et al.*, 1992; Quigley, 1999). Lack of efficacy is possibly explained by the poor intestinal bio-availabity of oral drugs. In some cases, combined use of prokinetics could improve digestive motility (Verne *et al.*, 1995). New prokinetic drugs should be evaluated in the near future.

Treatment of bacterial overgrowth

Intestinal bacterial overgrowth has often been described during digestive motility disorders (Parson *et al*., 1969; Riordan *et al*., 1996) and it has been shown that improvement in digestive motility reduces bacterial overgrowth (Soudah *et al*., 1991). Sequential antibiotic therapy is very effective in treating intestinal bacterial overgrowth and in reducing malabsorption (Attar *et al*., 1999). Correlation between bacterial translocation and absence of MMC activity has been demonstrated and can result in a worsening of a digestive motility disorder (Nieuwenhuijs *et al*., 1998). A potential life-threatening consequence of bacterial overgrowth relates to bacterial translocation (Berg, 1999; Madl and Druml, 2003).

Dietary measures

The dietary regimen is influenced by the disease phenotype and is aimed at attaining sufficient oral levels of micro- and macronutrients (Scolapio *et al*., 1999). Patients with gastroparesis usually have a lowered oral intake and early satiety, whereas patients with predominantly small bowel involvement often experience nausea, abdominal pain and diarrhoea. In patients with decreased gastric emptying, liquid or semi-liquid food is better tolerated than is solid food (Camilleri and Phillips, 1991). Oral intake should also be fractionated into five or six meals per day. Dietary measures also include the use of a low-lactose, low-fibre, low-fat diet in order to optimize gut motility and to decrease the risk of bacterial overgrowth and gastric bezoar. Associated multivitamin and micronutrient supplementation is also needed (Fe, folate, Ca, and vitamins D, K, and B_{12}) in order to prevent specific deficiencies (Smith *et al*., 2003).

Enteral nutrition

Enteral feeding by ostomy is a potentially effective method of nutritional support, which could be used despite oral feeding intolerance. However, it should be used carefully with iso-osmolar nutrients at slow, continuous infusion rates to prevent poor tolerance and enteral nutrition-related pneumonia. If a trial period gives positive results, infusion rates and volumes can be increased progressively. Ostomy could be also helpful for venting procedures.

Parenteral nutrition

HPN is necessary in severe CIPO patients where other supportive methods have failed (Messing and Joly, 2006). Because of higher cost, morbidity and mortality and low probability of HPN weaning-off, it should not be started before an oral and/or enteral nutrition trial (Smith *et al*., 2003). Specificities of HPN in CIPO patients related to chronic bowel obstruction and lowering of oral intake include the following:

- Higher fluid volume requirement for prevention of dehydration, especially in the case of refractory vomiting or permanent suction ostomy. Fluid volume requirements must also be adapted because of frequent and variable increased digestive losses (diarrhoea, vomiting). The same is true for hydroelectrolytic adaptation, especially in the maintenance of Na, K and Mg balances.
- Higher number of infusions required per week (six to seven per week versus four to five for SBS (unpublished personal data).
- To prevent PN-related liver disease, especially in exclusive HPN (patients with intractable obstruction), parenteral lipid intake should be limited to prevent, for example, fatty acid deficiency.
- Micronutrient and vitamin supplementation (e.g. Selenium (Se), vitamins B_1, B_6, E) should be given and adapted during the routine nutritional survey.
- Necessity of maintaining minimal oral feeding in order to: (i) reduce parenteral caloric needs; (ii) prevent complications with exclusive HPN (bacterial translocation, liver disease, biliary involvement, partial intestinal villous atrophy – especially that induced by bacterial overgrowth).
- Mitochondrial cytopathies could require specific vitamin supplementation, e.g. coenzyme Q_{10}, ubiquinone or its synthetic variant, idebenone (Geromel *et al*., 2002).

Surgical procedures

Surgical intervention occurs often before and/or during CIPO management (Hanks and Weber, 1981; Mann *et al*., 1997; Stanghellini *et al*., 2005). Surgery cannot offer curative treatment, so its use is usually limited to the refractory form of CIPO, after careful case selection. The most common and efficient surgical procedure is the venting or feeding ostomy. Venting ostomy decreases the frequency of both admissions for acute obstructive symptoms and vomiting, and also prevents abdominal pain and retching in patients who have undergone anti-reflux surgery. In addition, gastrointestinal motility may improve as the bowel becomes less dilated (Di Lorenzo, 1999). Furthermore, a combined nasogastric-nasojejunal tube is available which allows simultaneous gastric suction and jejunal infusion (Patrick *et al*., 1997).

Explorative laparotomy may be performed for viscerolysis in the case of suspected mechanical bowel obstruction caused by previous laparotomy. In these cases, full-thickness biopsies or limited small bowel resection during the surgical procedure could be undertaken for full histopathological examination. Bowel resection or surgical by-pass must be considered with great caution, as few patients with an isolated diseased segment can benefit from this kind of procedure (Murr *et al.*, 1995). On the contrary, extensive CIPO cases did not benefit, and often experienced peri-operative complications.

In a few cases, patients with CIPO non-responsive to maximal medical and surgical therapy, and with complications such as dehydration or severe intestinal translocation, benefited from sub-total bowel resection (Schuffler *et al*., 1985; Mughal and Irving, 1988; Joly *et al*., 2003) or intestinal transplantation (Buchman and Scolapio, 2003; Masetti *et al*., 2004; Blondon *et al*., 2005; Grant *et al*., 2005). Intestinal transplantation has become a life-saving procedure for patients with irreversible intestinal failure. The indications were defined as: (i) life-threatening complications of home parenteral nutrition (HPN); (ii) lack of venous access for HPN; (iii) chronic intestinal failure with a high risk of mortality; and (iv) primary, disease-related poor quality of life despite optimal HPN.

In total, approximately 1300 intestinal transplantations were performed (40% in adult patients). Eight per cent of adult patients suffering from intestinal failure due to CIPO were transplanted (Grant *et al*., 2005). Multi-visceral transplantation was often performed, with 1-year patient and transplant survival rates of approximately 80 and 65%, respectively, relatively similar to that in cases of other aetiology (Masetti *et al*., 2004). Intestinal transplantation should be considered in adult patients suffering from CIPO and with PN-related life-threatening complications.

Summary

Chronic intestinal pseudo-obstruction (CIPO) is an important indication for home parenteral nutrition (HPN) in both adults and children. CIPO refers to a heterogeneous group of disorders (Box 8.1) characterized by symptoms of intestinal obstruction in the absence of mechanical evidence of obstruction. It is caused by ineffective intestinal contractions. CIPO may be classified either as a primary disease, usually limited to the hollow viscera, or as a secondary disease, associated with an existing systemic disorder. CIPO may predominate as a 'total' gut disease from oesophagus to anal sphincter or as a 'localized' disease which is gastric and intestinal or intestinal alone; segmental gut disease is not the rule, with the exception of an isolated megaduodenum.

Recurrent episodes of obstruction follow the usual clinical presentation, together with malabsorptive diarrhoea; pseudo-pseudo CIPO may also be the case, i.e., malabsorptive diarrhoea without obvious obstruction.

Besides nutritional support, symptomatic treatment usually consists of prokinetic drugs, such as low doses of octreotide and erythromycin. In the case of a systemic disease causing CIPO, specific treatments are also the cornerstone here, such as, for example, in systemic lupus erythematosus.

The most severe forms may require ostomy for nutrition and/or decompression. Otherwise, surgery should be avoided with the exception of surgical complication associated with CIPO, such as peritonitis due to perforation (with or without diverticula) or bowel ischaemia. Patients

severely affected by CIPO with an intestinal 'functional' insufficiency, especially those affected by diffuse forms of the disease, may need long-term HPN. In the latter case, when there is a failure of HPN, alternative treatment such as extensive resection or intestinal transplantation should be discussed case by case in an intestinal tertiary care centre.

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9 Radiation Enteropathy

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Key points

- Radiation enteropathy may require HPN (home parenteral nutrition) in subacute conditions since a prolonged period of bowel rest can allow a regression of the lesions and an improvement in bowel function.
- In chronic radiation enteropathy long-term HPN represents a life-saving procedure because of the irreversible intestinal failure due either to the disease or to the consequences of surgical complications.
- The final outcome of patients on HPN for radiation enteropathy depends both on the potential complications of long-term HPN and progressive damage to other (neurological, urological, bony, etc.) structures included in the radiation field.

Introduction

Within 2 years of Roentgen's discovery of ionizing radiation in 1895, the detrimental effects of radiation on the gastrointestinal tract were described (Walsh, 1897). The effect of photons is due to the interaction of the electromagnetic waves with normal tissues through the production of electrons, which combine with intracellular water and induce the formation of hydroxyl radicals. These radicals cause cell death through single or double DNA breaks and through interaction with the cell membrane.

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Pathophysiology

The cells are most vulnerable to the killing effect of radiation during the G2 and M phases, and consequently rapidly proliferating tissues such as small intestinal crypt cells are particularly sensitive to radiation; they undergo apoptosis and are shed from the intestinal villus.

Furthermore, ionizing radiation activates the translation of gene coding for the transforming growth factor-β, which is a multifunctional peptide growth factor acting as a potent fibrogenic and pro-inflammatory cytokine. Transforming growth factor-β promotes fibrosis by stimulating the expression of collagen and fibronectin genes and the chemotaxis of fibroblasts, and it also inhibits the degradation of the extracellular matrix.

Histopathologically, the damage from radiation enteropathy (RE) initially involves mucosa, which suffers cellular devitalization, and submucosa, which becomes oedematous; subsequently, damage is characterized by diffuse collagen deposition and progressive occlusive vasculitis. The fibrosis and vasculitis progress over time and result in the narrowing of the intestinal loops with dilation of the bowel proximal to the stricture, which then thickens the affected segments of intestine and serosa. Severe stenosis, ulceration, necrosis and perforation of the intestinal wall may sometimes occur.

Clinical signs

The clinical scenario of RE encompasses nausea, vomiting, abdominal cramping and watery, blood-tinged diarrhoea, which are all present in the acute phase of RE. This clinical picture is also concurrent with the treatment and may last days or weeks, but usually reverses spontaneously after a few weeks before progressing to the more dramatic scenario of the chronic and established RE. This appears after several months, years or decades after initial exposure to radiation, and is characterized by intestinal obstruction, perforation and bleeding, which require hospitalization and – sometimes – surgery. Between these two types of RE there is a subacute type, which clinically appears within 3–18 months after completion of radiation therapy (Schier *et al*., 1964), and it may progress for several years or even regress and/or exhibit long periods of quiescence.

The Radiation-Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer (RTOG) proposed in 1991 (Trott and Herrmann, 1991) the criteria for scoring the radiation morbidity of irradiation of the lower gastrointestinal tract and pelvis, which is reported in Table 9.1.

Incidence

Whereas the prevalence of acute RE is difficult to estimate because of the large variety of radiation protocols and chemotherapy schedules, the

Table 9.1. Radiation morbidity scoring criteria for lower GI tract including pelvis.

	Lower GI tract including pelvis
0	No change
1	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics
2	Diarrhoea requiring parasympatholytic drugs (e.g. Lomotil)/mucous discharge not necessitating sanitary pads/or rectal or abdominal pain requiring analgesics
3	Diarrhoea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)
4	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion

frequency of subacute and chronic RE is better known. However, the mildest types may escape the radiologist, whereas the later and more severe types occur years after the end of radiation therapy and patients may then be admitted to other institutions or undergo emergency surgery.

The prevalence of RE has increased in recent years because of the use of radiation as part of a multidisciplinary approach to cancer (Galland and Spencer, 1987). Data quoted for those patients who have received radiation therapy and who subsequently have developed RE usually vary between 0.5 and 16.9% (Shamblin *et al.*, 1964; Poddar *et al.*, 1982; Harling and Balslev, 1988). A recent investigation carried out by the Institute of Radiological Sciences of the University of Milan on the prevalence of severe ileitis defined it as a 'requiring surgery' complication (Cerrotta *et al.*, 1995); this survey showed that such a complication occurred in 7.3% of 191 patients within a mean period of 23 months (range 4–87) after receiving standard adjuvant post-operative radiation therapy following a radical resection for rectal cancer. A more recent paper, which included 164 patients receiving adjuvant radiotherapy for cervical cancer, reported that after a median follow-up of 60 months (range 38–119) 22 (13.4%) patients developed a RTOG Grade II radiation injury to the intestine, four (2.4%) had Grade III complications requiring surgery and three (1.8%) had died (Chen *et al.*, 2004).

Epidemiology and the Role of HPN

The epidemiology of chronic RE is that of a progressive and relentless disease, with further complications becoming apparent in about 50% of those surviving the initial lesions; 5% of patients eventually require surgery (Galland and Spencer, 1987) and 10–25% die either as a direct result of the injury or as a result of complications arising from corrective surgery (De Cosse, 1969; Russel and Welch, 1979).

Galland and Spencer (1985) followed the progress of 70 patients presented to a surgical unit with RE which had appeared after an average interval of 2 years from the time of radiation therapy. None of them had received home parenteral nutrition (HPN), median survival was about $2\frac{1}{2}$ years and the 5-year survival rate was 42%. It is noteworthy that RE accounted for 62% of the deaths, directly (1/3) or indirectly (2/3), as a consequence of surgical complications.

In the acute phase of RE these patients are parenterally fed in hospital for a few weeks. In the past, however, patients often underwent explorative surgery and resection, in an erroneous attempt to correct a transient, reversible acute condition which finally resulted in a chronic intestinal failure, requiring permanent HPN.

The first attempts to keep patients suffering intestinal failure due to RE alive through HPN date back to the pioneers of HPN (Broviac and Scribner, 1974), and the results from this first small series of patients were then published by the University of Washington in Seattle (Miller *et al*., 1979), followed by the Cleveland Clinic (Lavery *et al*., 1980).

Reports from databases or registers from different countries show that RE accounts for a percentage ranging from 4% to 6% in Canada (Detsky *et al*., 1986), the USA (Howard *et al*., 1991, 1995) and the UK (Mughal and Irving, 1986) to 13–21 in Europe (Messing *et al*., 1989) and France (Messing *et al*., 1988). The 1993 European survey (Van Gossum *et al*., 1996) reported that RE accounted for 8% of underlying diseases of patients receiving HPN, with Spain, France and Belgium registering the highest number of subjects.

The percentage of new patients receiving HPN for RE appears to have decreased over the past few years (Howard, 1993), which is probably due to improvements in both radiation field delivery and surgical treatment.

Indications for HPN

Appropriate factors for involvement of HPN comprise the following: (i) chronic sub-obstruction; (ii) pain caused by oral/enteral nutrition; (iii) long-standing wasting; or (iv) frequently, a combination of these factors. Moreover, a common indication is intestinal failure as a consequence of extensive surgical resection, which has resulted in small bowel syndrome (SBS) or severe post-operative complications. For these reasons the potential indications for surgery, HPN or both in patients affected by RE should be considered and discussed together with the patient.

As a general rule, patients with acute RE should never be considered for surgery; symptoms usually subside with time and intravenous fluids/nutrition can be provided for a limited period of bowel rest. On the contrary, patients affected by complicated, chronic RE are almost always candidates for surgery because obstruction or stenoses are by this time irreversible and one cannot expect bleeding, perforation or obstruction to

resolve spontaneously. However, if the damage to the gut is widespread or if an extensive small bowel resection is required, patients usually will require long-term HPN if they are to survive. A more flexible approach is required for patients with subacute RE. Every effort should be made to determine whether the RE is localized or diffuse while the patient is still receiving a short course of parenteral nutrition. The diagnostic work-up includes a plain X-ray of the abdomen and a contrast X-ray study (if possible) of the small bowel, a colonoscopy and an abdominal CT scan. A careful evaluation of symptoms and their association with the oral intake of nutrients is also crucial for a proper assessment of the extent of the disease. Quite often the enteropathy is more diffuse than would be expected.

If RE is limited (usually confined to the distal ileum because of the loops of small intestine trapped in the pelvis during radiotherapy) and there is no improvement (or there is rapid relapse) of symptoms after a short course of parenteral nutrition and medical therapy, the patient is a candidate for resective or bypass surgery.

The problem is much more complex when RE involves long tracts of the small bowel or compromises the intestinal motility of a large part of the jejunum and ileum. Husebye *et al*., (1994) have shown that late RE is characterized by impaired fasting motility and attenuated postprandial motor response. This dysfunction of intestinal motility is typical of intestinal pseudo-obstruction, a condition characterized by the absence of structural luminal occlusion and due to the presence of adynamic intestinal segments acting as functional stenoses (Conklin and Anuras, 1981).

In such conditions one should persevere with parenteral nutrition as long as possible because the only role of surgery is the removal of large parts of the gut to relieve a state of permanent obstruction with the strong possibility of eventual SBS, with or without a stoma. Therefore, if symptoms subside, one should consider a long period (several months) of HPN. Only if symptoms do not subside – or quickly recur when enteral nutrition is resumed after a long period of HPN – should surgery be considered. In fact, since the patient is already on HPN, the inability of surgery to solve the problem and the consequent need to maintain the patient indefinitely on HPN cannot be considered as a total failure. In such cases, the possibility of the eventual requirement for permanent HPN (due to the unresolved obstruction or the need for an extensive small bowel resection) should be discussed with the patient and his/her family prior to surgical intervention.

Nutritional regimen

There is no specific nutritional regimen for patients on HPN because of RE. Energy and nitrogen requirements follow the standard guidelines of the intravenous nutrition of malnourished patients, and administration is usually nocturnal cyclical. However, if patients have a short bowel remnant or a high-output stoma, water and electrolyte requirements can be

extremely high and require long periods of HPN infusion, as occurs in patients with SBS.

Outcome

The outcome of patients on HPN for RE is described in terms of survival, rehabilitation, discontinuation of HPN and resumption of a full oral intake.

Survival

Data on survival are biased because it is often impossible to be sure that patients with RE do not harbour a residual tumour, and a high percentage of these patients succumb because of a recurrent cancer. Sometimes the nutritional response to parenteral nutrition, which is much better in simply malnourished patients than in wasted cancer patients, may help us understand whether the patient has RE only, or both RE and a recurrent cancer.

Mortality due to cancer accounts for 13–33% of patients on HPN according to different series (Miller *et al*., 1979; Lavery *et al.*, 1980; Silvain *et al*., 1992; Scolapio *et al*., 2002) and reflects varying methods of selecting patients. The overall survival of patients varied and was as follows: 93% at a 6–12 month interval (Van Gossum *et al*., 1996); 87% at 1 year (Howard *et al.*, 1995); 65% at 3 years (Howard *et al*., 1991); 64% at 5 years (Scolapio *et al.*, 2002); and 53% at 15 years, according to the Italian Society for Parenteral and Enteral Nutrition.

If one considers patients affected by severe RE, the prognosis is less favourable: Silvain *et al*. (1992) stated that survival probability was 58% at 1 year and 36% at 5 years, and Girvent *et al*. (2000) reported that of the 15 patients referred with intestinal failure after surgery for complications of RE and actively treated, one-third died in hospital and a further third required the instigation of HPN.

Thus, it appears that surgical complications and recurrence of cancer account for the high immediate and early mortality of patients on parenteral nutrition for RE. A multivariate study showed that at the age of 60+, vascular disease or the occurrence of intestinal perforation or fistula portend a poor prognosis (Silvain *et al*., 1992).

Rehabilitation

The rehabilitation of patients can also be a challenge because of the damage extending beyond the gut, e.g. radiation nephritis, myelopathy and neuritis. Approximately 50% of patients have been reported to be partially rehabilitated and to have achieved reasonable (or better) quality of life (Lavery *et al*., 1980; Howard *et al*., 1995).

Resumption of oral intake

Baticci and Bozzetti (1982) first published reports that HPN and bowel rest for some months could achieve a spontaneous resolution of intestinal obstruction and allow the resumption of oral alimentation without surgical intervention. A further report of one case was published (Selby *et al*., 1983). Bozzetti *et al*. (1995) reported that five out of ten patients with subacute RE were able to achieve oral nutritional autonomy after 19 months (range 1–32) of HPN. More recently, Silvain *et al*. (1992) and Scolapio *et al*. (2002) showed that approximately one-third of patients were able to discontinue HPN and resume oral intake.

Summary

Acute RE is frequently reversible and patients have to be treated in a conservative way, with total bowel rest and parenteral nutrition. In chronic RE, HPN may have a role when enteropathy involves large parts of the small bowel, or in short bowel syndrome (SBS) due to previous resective surgery. In these patients, HPN may be required indefinitely. In subacute RE, not amenable to surgery because of multiple, scattered lesions or a scenario of poorly localized pseudo-obstruction, HPN is recommended; it may allow resolution of the intestinal obstruction in about one-third or one-half of patients.

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10 Cancer

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Key Points

- Patients suitable for HPN should not be terminal, even if they are incurable.
- Incurable cancer patients may enter an HPN programme if they have a life expectancy (due to the disease) longer than 3 months, symptoms are controlled and they are aware of the limitations of the treatment.
- The suggested regimen should include about 30 kcal/kg/day (1:1 glucose/fat ratio, 1 mEq/Na/kg/day in a total fluid volume of 30 ml/kg/day).
- Median survival of these patients exceeds that usually allowed by a total macronutrient starvation in most series.
- Maintenaince of quality of life for a short period of time is more common than a true improvement.
- Crucial issues include: (i) the estimate of the life expectancy; (ii) the communication with the patient and his/her family for balancing their expectations with the realistic benefits of HPN; and (iii) definition of the criteria for withholding and withdrawing the nutritional support.

Introduction

Indications for nutritional support of the cancer patient which are commonly accepted by the scientific community include: (i) treatment of malnourished patients while they are receiving oncological therapy; and (ii) treatment of patients suffering from severe iatrogenic complications or chronic sequelae following chemotherapy, radiation therapy or surgery.

On the contrary, indications for HPN in incurable cancer patients

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represent a continuous source of debate and controversy not only among various specialists but even among physicians working in the same field.

There are two main reasons for this: on one hand there is the clear awareness by clinicians that current medical care has evolved to the point that, by transforming previously lethal diseases into chronic conditions, malnutrition and the inability to feed may finally represent in some patients the main determinants for the length of survival, even in malignant diseases. On the other hand, all physicians involved in HPN practice know perfectly well that patients with benign intestinal failure survive 'thanks' to HPN whereas cancer patients finally die 'despite' nutritional support.

Besides these two pivotal points, there are a number of psychological, cultural and economical factors which can affect the options of the caregiver, patient and his/her relatives. The decision whether or not to start and whether or not to withdraw an incurable cancer patient from an HPN programme is always difficult (Weiss *et al*., 1982).

Areas of Controversy

The incurable versus the terminal cancer patient

When discussing with different specialists (surgeons, oncologists, palliativists, nutritionists, etc.) involved in the care of those cancer patients generically defined as 'terminal', and who are potential candidates for an HPN programme, it is important to be sure that they all refer to the same type of patient.

It should be clear that while all terminal cancer patients are 'oncologically' incurable, not all incurable cancer patients are 'biologically' terminal. The oncologic definition of 'terminal' often means that no oncologic therapy is available for the patient whose survival may range from a few days to several months. However, in common parlance, 'terminal' refers to patients in a state of agony or pre-agony where palliation of symptoms and not nutritional support is the absolute priority.

In order to avoid any ambiguity in defining the severity of the state of the patients and potential candidacy for HPN, it is better to adopt the term 'incurable' to focus on cancer patients for whom all available oncologic therapies have been exhausted and who might sometimes require nutritional support if aphagic and not agonizing (Bozzetti, 2003).

Nutritional support: a therapy versus basic human care

This question is not merely academic. Many state laws and professional groups consider artificial nutrition as a form of medical therapy (Capron, 1991; Dyer, 1993; MacFie, 1996; Huang and Ahronheim, 2000), a point of view which is not universally shared (Hodges *et al*., 1994).

A therapy needs to be validated through randomized clinical trials in order to be accepted as an evidence-based medicine and, in such a trial, one arm may receive no treatment, or merely the standard treatment. However, in aphagic/obstructed cancer patients it would be impermissible to have a randomized, no-treatment arm, which means progressive undernutrition until death, as the standard treatment simply does not exist.

Miles (1989), emphasizing the cultural and symbolic value of nourishment, which is traditionally viewed as an expression of love and care for both the living and the dying, made the important distinction that while physicians tend to see 'nourishment' as a medical treatment aimed at achieving physiological objectives, families see 'feeding' as an act of community.

It is common experience that anorexia and hypophagia of a dying cancer patient represent a major concern for both the patient and their family members (Holden, 1991; McClement *et al*., 2003; Orreval *et al*., 2004). A specific study on the nutritional situation prior to the introduction of HPN from the perspective of patients with advanced cancer and their family members in order to understand factors contributing to the decision to accept HPN has been recently published (Orrevall *et al*., 2004). Patients reported wanting and trying to eat, but being unable to do so; family members experienced powerlessness and frustration, as they could not enable the patient to eat. This desperate and chaotic nutritional situation for the family influenced the patient's willingness to accept HPN.

The point that nutrition cannot be completely equated to a therapy was clearly recognized in the ASPEN Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients, where the Board of Directors wrote:

> A major distinction between therapeutic trial of efficacy of a drug or a procedure and the feeding of nutrients known to be essential to maintenance of human health and survival must be made. Withholding a drug or invasive procedure will not produce disease in otherwise healthy humans, whereas essential nutrients must be provided to both healthy and ill people.
>
> (ASPEN, 2002)

The above-mentioned considerations lead to the final conclusion that the value of HPN in incurable cancer patients has to be assessed regardless of the absence of randomized clinical trials and keeping in mind that absence of evidence is not evidence of absence (Altman and Martinbland, 1995).

In this context it is appropriate to report the position of the Roman Catholic Church (National Conference of Catholic Bishops, 1995) on the use of artificial nutrition and hydration near the end of life: 'There should be a presumption in favour of providing nutrition and hydration to all patients who require medically assisted nutrition and hydration', and this approach should be warranted as long as 'there is sufficient benefit to outweigh the burdens involved in the patient'.

Natural History of the Incurable Cancer Patient and Prevalence of HPN

Cachexia occurs during the terminal course of cancerous disease in approximately 70% of patients, and it is recognized as the cause of death in 5–23% (Warren 1932; Klastersky *et al*., 1972; Inagaki *et al*., 1974; Ambrus *et al*., 1975) of terminal cancer patients.

Anorexia, hypophagia and continuing negative energy balance are prominent features of cachexia. Hypermetabolism and weight loss are significant predictors of decreased survival (Bosaeus *et al*., 2002). These factors may explain why cancer patients account for a high percentage – sometimes even the majority – of the subjects enrolled in HPN programmes.

Registers of HPN patients in various countries report the following figures for cancer: Italy 57% (De Francesco, 1995), Japan 55% (A. Okada, 1995, personal communication), the USA 46% (Howard *et al*., 1991, 1995) and France 18% (Messing *et al*., 1988). In a recent European survey of 500 patients receiving HPN in 1997 (Van Gossum *et al*., 1999), it was found that cancer patients accounted for 60, 39, 27, 23, 8 and 5% in The Netherlands, Spain, France, Belgium, Denmark and the UK, respectively.

A recent evaluation reported that the prevalence of HPN in adults, in Italy, was 22.3 per million inhabitants and that cancer patients accounted for 60.9% of those (L. Pironi, personal communication).

Indications for HPN

The clinical status

The incurable cancer patient who is the ideal candidate for HPN has the following characteristics: (i) he/she is aphagic because of malignant obstruction (or sub-obstruction); (ii) without severe or untreatable symptoms; and (iii) without any important functional organic impairment of organs/apparatus. Hence, he/she has a relatively good performance status (> 50 according to the Karnofsky-Burchenal index), with no (or minimal) involvement of vital organs such as the liver or the lung.

Notably, the life expectancy of this patient is likely to depend more on starvation and the continuing deterioration of the nutritional state than on tumour progression.

In clinical practice the conditions with the most appropriate indications for HPN are: (i) peritoneal carcinomatosis; and (ii) some slow-growing tumours, (e.g. ovarian carcinoma, retroperitoneal tumours, relatively indolent gastrointestinal tumours and intra-abdominal recurrences). The worst candidate (indeed, a non-candidate) is a heavily symptomatic elderly patient in poor condition, with altered function of many organs and in need of intensive palliative care.

Life expectancy and its predictability

The most crucial point is the assessment of life expectancy, which is extremely important with regard to patient suitability for HPN. There is in fact no rationale for feeding intravenously a subject who is going to succumb from cancer rather than from starvation/undernutrition.

In healthy adult subjects, a nitrogen loss critical for survival occurs after a loss of 33–37% of the usual/ideal body weight (Kotler *et al*., 1989), i.e. after 60–75 days of starvation, as demonstrated by the tragic experiences of the Leningrad siege, the Warsaw ghetto and the Irish hunger strike (Brozek *et al*., 1946; Fliederbaum, 1979; Winick, 1979). However, we can assume that it would take even less time to achieve a weight loss of this magnitude in patients affected by a catabolic disease or in a wasting condition when they are under consideration for a programme of HPN.

Nevertheless, prediction of length of survival has proved to be unreliable in several studies (Parkes, 1972; Yates *et al*., 1980; Mor *et al*., 1984; Evans and McCarthy, 1985; Rueben *et al*., 1988; Addington-Hall *et al*., 1990; Bruera *et al*., 1992; Viganÿ *et al*., 2000), with just a few exceptions (Maltoni *et al*., 1995, 1999; Pirovano *et al*., 1999; Caraceni *et al*., 2000).

In a recent report, Caraceni *et al*. (2000) have shown that patients with a favourable palliative score (< 5.5) have > 70% probability of surviving 2 or 3 months, depending on the presence or absence of delirium. However, in a prospective investigation (Cristakis and Lamont, 2000) in which 343 physicians were asked to estimate the length of survival of 468 patients (with a median survival of 24 days), there was an overestimation of the survival time by a factor of 5.3. Overall, only 20% of the predictions were accurate, i.e. within 33% of the number of days that the patient actually survived; 63% were optimistic and 17% were pessimistic.

This tendency to overestimate the survival time has long been recognized (Forster and Lynn, 1988; Pearlman, 1988; Llobera *et al*., 1990; Schonwetter *et al*., 2000). It is interesting to note that physicians in the upper quartile of practical experience were the most accurate, which leads to the supposition that the senior director of care may be the best judge (Cristakis and Lamont, 2000).

Unfortunately, accuracy is generally higher when predicting short-term survival, delirium being a strong indicator in this case (Caraceni *et al*., 2000); conversely, it is definitely lower when considering patients who are not actually dying.

However, it may be difficult to apply these scores to patients who are potential candidates for HPN, because some of these indices include variables such as dysphagia or weight loss that are responsible, *per se*, for nutritional deterioration – apart from reflecting the severity of the disease – and that could be partially reversed through nutritional support. Therefore, the judicious use of HPN in this setting requires careful clinical assessment on a patient-by-patient basis (Hoda *et al*., 2004).

Symptom palliation

HPN should not be provided in the presumption of preventing hunger or thirst. These symptoms are rarely experienced by terminally ill cancer patients (McCann *et al*., 1994) and even in less advanced conditions patients are usually anorectic. Thirst, if present, is not always a consequence of dehydration and may be managed with assiduous oral care. These points should be clarified to the patient and to the family.

Nutritional Regimen

Many cancer patients on HPN have requirements for macronutrients and micronutrients comparable to those of other patients receiving intravenous nutrition, provided they do not have short bowel syndrome (SBS).

However, since patients with peritoneal carcinomatosis are frequently represented in many series of HPN, this suggests the use of a 'modified' diet with reference to the content of water and sodium and the composition of energy. Such a diet, even if not strictly specific for cancer patients, may be accepted as a prudent diet.

Water

A restriction in water administration is advisable for several reasons:

1. Cachexia is often associated with the expansion of the extracellular fluid volume.
2. If patients have peritoneal carcinomatosis, an overzealous administration of water, glucose and sodium can sharply precipitate an impending ascites. Gamble (1946) first demonstrated that glucose reduces renal sodium excretion and, for the same reasons, the loss of extracellular fluid; and Bloom (1962) suggested that this effect was mediated by insulin through an increased sympathetic activity. The effects of a glucose-based parenteral nutrition on positive water and sodium balance have been demonstrated by Rudman *et al*. (1975) and subsequently described in oncologic patients by Bozzetti *et al*. (1996).
3. In cancer patients there may be excessive production of antidiuretic hormone (ADH) due to the presence of nausea, which frequently occurs in the advanced stages of disease, or to the administration of morphine. Furthermore, the wasting syndrome is associated with loss of intracellular water and solutes which affect the hypothalamic osmoreceptor cells by stimulating ADH release at levels which maintain serum sodium osmolality at subnormal levels (Steiner and Bruera, 1998). In consequence, the clearance of free water is decreased, also because the urea load presented to the kidney is reduced secondary to protein undernutrition, whereas the

synthesis of endogenous water is maintained by the oxidation of carbohydrates and fats (Kerndt *et al*., 1982), and insensible water loss drops due to reduced physical activity (Bruera *et al*., 1996).

The total amounts of fluid and sodium given should not exceed 30 ml/kg/day and 1 mol/kg/day, respectively.

Energy

Many investigators have reported that cancer patients may be hypometabolic, normometabolic or hypermetabolic. When energy expenditure is expressed by unit of body cell mass a consistent percentage of patients are shown to be hypermetabolic. However, since physical activity accounts for about 25% of total energy expenditure, and dietary-induced thermogenesis for about 5%, given that most of these subjects are confined to bed or to a chair and are hypophagic, the energy supply cannot be excessive, and a value of between 20 and 30 kcal/kg/day seems to be appropriate.

Since there is also evidence in human cancer host uses that the subject ingests fat whilst the preferred fuel for cancer cells is glucose, a high lipid:glucose calorie ratio (i.e. 50:50) is desirable.

Nitrogen

Finally, a supply of 1–1.5 g amino acids/kg/day is adequate in most cases.

Outcome

Survival

Survival of cancer patients on HPN depends on the severity of the basic disease, i.e. type and stage of tumour.

Unfortunately, many series pool together patients with simple iatrogenic complications of oncological therapy (radiation enteropathy or chronic surgical sequelae), patients with active cancer receiving chemotherapy or radiation therapy and patients with advanced, incurable cancer. Therefore, disparity in the composition of the series and indications for HPN can account for different survival rates in different reports.

In small, retrospective series of patients receiving HPN (Hurley *et al*., 1990; King *et al*., 1993; Cozzaglio *et al*., 1997; Pironi *et al*., 1999; Bozzetti *et al*., 2002; Pasanisi *et al*., 2002) the median survival ranged from 53 to 120 days. In the recent experience of the Mayo Clinic, the median time from initiation of HPN to death was 5 months (range 1–154 months) (Hoda *et al*., 2004).

More reliable are those studies that report large institutional experiences, data from national registers and/or pooled data from several

nations. Table 10.1 summarizes these main reports and shows that most of the 1-year survival rates range between 20 and 30% (Howard, 1993, 2000; Howard *et al*., 1995; Messing *et al*., 1988; Van Gossum *et al*., 1999). These figures are in keeping with the data of the British Artificial Nutrition Survey (Elia *et al*., 2000) which, in 1999, reported a 26% survival rate at 1 year. If one considers more favourably selected patients (non-terminal cancer patients), a 38% 5-year survival rate is observed (Scolapio *et al*., 1999).

The survival rates from the Register of the Italian Society for Parenteral and Enteral Nutrition are shown in Fig. 10.1.

Quality of life

Before attempting to clarify the effects of HPN on the quality of life for the patient, it should be noted that if anxiety, depression, shortness of breath

Table 10.1. Main reports on 1-year survival rates in cancer patients on HPN.

Reference	Period of study	Number of patients	Survival
Howard, 1993	1985–1990	1672	28% at 1 year; median 6 months; mean 4 months
Howard *et al*., 1995	1985–1992	2122	37% at 1 year
Messing *et al*., 1998	1993–1995	524	19.5% at 6 months
Van Gossum *et al*., 1999	1997	200	26% at 6–12 months
Howard, 2000	1984–1988	1073	25% at 1 year; median 6 months
SINPE Register, 2004	1980–2004	1103	20% at 1 year, median 6 months

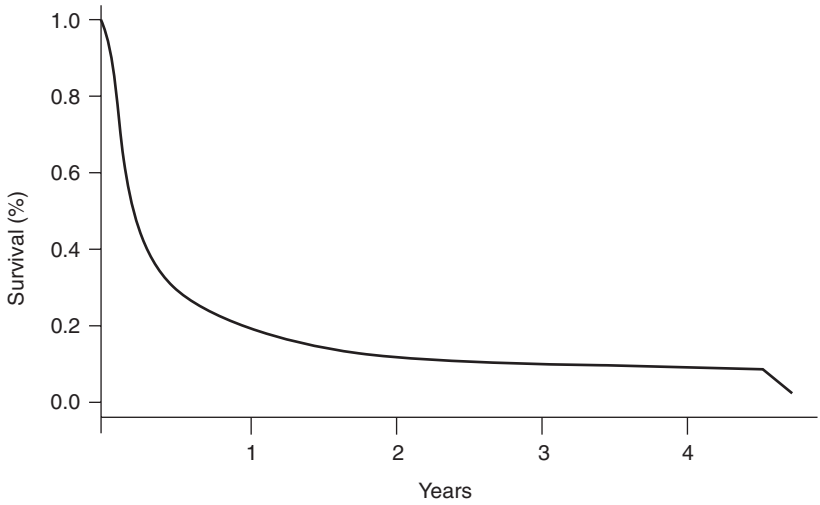

Fig. 10.1. Survival of incurable cancer patients on HPN (1103 patients).

and sense of wellbeing are the major determinants of the will to live, as recently pointed out by Chochinov *et al*. (1999), then a lack of control over these symptoms will have a major impact on the response to HPN.

Data on quality of life are sparse. Some retrospective analyses (King *et al*., 1993; Cozzaglio *et al*., 1997; Scolapio *et al*., 1999) would suggest a limited benefit in cancer patients on HPN: the Karnofsky performance index increased in 7% of patients after 1 month (Pironi *et al*., 1999) and in 68% of patients surviving longer than 3 months (Cozzaglio *et al*., 1997); the ability to sustain daily activities and oral alimentation in 27% of patients was reported by Torelli *et al*. (1999). According to the data of the North American Home Parenteral and Enteral Nutrition Registry Register (Howard, 2000), 29% of patients appeared to be fully rehabilitated at the 1-year mark.

Bozzetti *et al*. (2002) undertook a prospective study on 69 advanced cancer patients enrolled in an HPN programme in six different Italian centres. The main end points of the study were: (i) the change of nutritional status and determination of the length of survival; and (ii) the evaluation of the impact of HPN on quality of life measured by the Rotterdam Symptom Checklist questionnaire. These parameters were collected at the start of HPN and thereafter at monthly intervals. These patients were severely malnourished, almost aphagic, and beyond any hope of oncologic cure. The median survival was 4 months (range 1–14), one-third of patients survived longer than 7 months and nutritional status was stable until death. Indices of quality of life remained stable until 2–3 months before death.

The authors concluded that HPN may benefit a limited proportion of patients, who might survive longer than the time normally allowed by a condition characterized by depletion and starvation. This time is probably less than 2 months, and is half the expected survival time of healthy subjects undergoing voluntary or forced starvation (Brozek *et al*., 1946) or of those on hunger strike. Provided that patients survive more than 3 months, there was some evidence that quality of life remained stable and acceptable for several more months.

Conclusions

The traditional goals of medicine are cure sometimes, relief occasionally and comfort always.

We should realize that although we are no longer dealing with the ‘curative’ dimension of treatment, there is nevertheless a constant danger that decisions in this field may become expressions of futility and therapeutic obstinacy or of palliative extremism, unless they are rationalized and shared by physicians, patients and/or their families.

In addition, it is common experience that some ethical and emotional problems can be ‘pre-empted’ by discussing them with the patient, his/her family and the healthcare team from the outset.

Therefore, we think that the approaches to the potential enrolment of an incurable cancer patient in an HPN programme should follow three subsequent steps: (i) communicating; (ii) differentiating between effects and benefits; and (iii) the trial-and-error approach.

Communicating

The worst experience for any patient is to believe that there is no consistency among the options of care proposed by different specialists, i.e. the surgeon, medical oncologist, palliativist, nutritionist and other caregivers, and that these options fluctuate from day to day. Therefore, the physician should discuss the specific treatment options with patients only after having made a decision regarding the treatment goals.

At this point there is the delicate problem of the patient's awareness and consent. In southern Europe, only 25–38% of patients are aware of the diagnosis when their disease is at an advanced stage (Mosconi *et al*., 1991; Pronzato *et al*., 1992; Centeno-Cortes and Nunez-Olarte, 1994; Grassi *et al*., 2000), and less than half of those wanted to be given more information.

A 1999 survey of 2088 patients with metastatic disease found that 39% believed it to be 'difficult to cure' and 47% considered their disease 'severe' (IGEO, 1999). In Spain only 11.5% of patients with a fatal prognosis knew about their short-term inexorable future (Espinosa *et al*., 1993). Relatives may sometimes be responsible for the patient's ignorance about their diagnosis and prognosis because, in 73–84% of cases, they want to avoid the patient being informed in a straightforward manner about the status of disease advancement (Espinosa *et al*., 1993; Grassi *et al*., 2000).

More importantly, according to a recent investigation (Lo *et al*., 1997), only 12% of cancer patients wanted to discuss, personally, the matter of life-sustaining treatments.

We have to respect the right of patients not to know: the Council of Europe, in Chapter III, Article 10, paragraph 2 of the Convention of Human Rights and Biomedicine, which came into force on 10 September 1996, states that 'everyone is entitled to know any information collected about his or her health. However, the wish of an individual not to be so informed shall be observed'. As a matter of fact, one-third of physicians believe that patients never want to know the truth (Grassi *et al*., 2000), and an equal proportion believe that informed consent is necessary in order to respect patient autonomy (Ordine dei Medici, 2001).

Whilst adequate information should always be given to patients when actively or implicitly requested, there is much uncertainty about the true comprehension of communication. Indeed, the ability of the patient to actively negotiate a decision with the caregiver requires four intact cognitive functions: (i) the ability to clearly understand the information relevant to the decision; (ii) the ability to fully appreciate the situation and the consequences of alternative approaches; (iii) the ability to elaborate and weigh the information rationally in the context of a coherent set of values

and goals; and (iv) the ability to communicate or transfer choices to the physician regarding care.

It is noteworthy that a recent study carried out in an important Canadian palliative care centre has reported the presence of cognitive deficit in 44% of patients at the moment of hospitalization, and in 55% at the time of death or upon hospital discharge (Pereira *et al*., 1997).

If diagnosis – and especially prognosis – are not disclosed to the patient, the physician and/or relatives should, collectively, together take a decision according to the presumed will of the patient. This is quite a difficult task.

In fact, a self-report measure of the desire for death distributed to 92 terminally ill cancer patients with a life expectancy of < 6 months has demonstrated substantial fluctuations in will-to-live score within various intervals of time (12–24 h, 7 days, 1 month) (Chochinov *et al*., 1999). Therefore, the assessment of a patient's will to live should be repeated several times and only if the answers are consistent should this information be utilized to determine whether to initiate or to withdraw a life-sustaining treatment.

Asking for informed consent by anticipating some situations before they actually occur is also fraught with difficulties. Coppola *et al*. (1999) have shown, in 2536 patients, that there was no constancy in the choices of preferences regarding life-saving treatments expressed in advance, both verbally and in writing. Specifically, the desire to undergo artificial nutrition as a life-sustaining procedure ranged from a very low percentage of subjects by Coppola *et al*. (1999) to about 70% of patients by Pearlman *et al*. (2000).

In Italy, for instance, the Italian National Bioethics Committee issued a document on advanced directives which accepts such practice and yet states that advanced directives may not be mandatory for the physician, and thus were termed 'advanced declaration of treatment' (Comitato Nazionale per la Bioetica. Dichiarazioni anticipate di trattamento. Roma: Presidenza del Consiglio dei Ministri, Dipartimento per l'Informazione e l'Editoria).

Differentiating between effects and benefits

The goals to be attained through an HPN approach should be realistically discussed with the patient and the family. The metabolic effects of short-term parenteral nutrition (Bozzetti, 1989) and HPN (Bosaeus *et al*., 2002) in cancer patients are reported in the literature. Do these effects translate into a clinical benefit for the patient? If the goal of HPN is simply to blunt progressive nutritional deterioration and to ensure a longer survival for the patient while he/she remains with the family home, the answer is probably 'yes', at least for a certain number of patients who are considered good candidates.

If the goal of HPN is to improve the patient's quality of life, the answer is quite uncertain. This is because the quality of life of the patient is not

only strictly an individual matter, but may be related more to the symptoms of the primary disease and the previous oncologic treatment than to intestinal failure or malnutrition.

A predefinition of the goals of HPN and the chances of success is essential not only to avoid over-optimistic expectations such as: 'my husband was condemned to die because he could not eat … now HPN will avoid it!', but also because if HPN cannot attain those endpoints, to withdraw it as an alternative will be less traumatic for the family and ethically acceptable for the physician.

The trial-and-error approach

Since the discrimination between good candidates and bad candidates will select/exclude only a small percentage of patients, for the majority of them the benefit of HPN is unpredictable and its indication very uncertain.

Especially in this group of patients it is worthwhile to adopt the trial-and-error method. That is, one can initiate HPN and withdraw it if it is found to be inappropriate or not beneficial on subsequent reassessment. This was also the final conclusion of the Consensus Meeting launched by the European Association for Palliative Care in 1996 (Bozzetti *et al*., 1996).

Summary

The use of HPN in incurable cancer patients is still controversial because this type of support may be considered as a life-saving procedure in aphagic patients, and consequently unsuitable for a randomized comparison with a 'no intravenous feeding' approach.

Moreover, patients and relatives do not understand that HPN, even if able to prevent a starvation-dependent death, will not be able to prevent a cancer-dependent death.

HPN may be recommended in aphagic patients if they are going to die prior to starvation (that could occur in about 2 months) than from tumour progression.

Furthermore, asymptomatic patients, with a good performance status, could maintain an acceptable quality of life during HPN.

Our ability to recommend or withhold an HPN programme is very limited and many series report that only 30–50% of the patients have a prolongation of the presumed survival through HPN. For this reason patients and relatives should be actively involved in the decision process concerning HPN.

There is some empirical knowledge that patients with a good Karnofsky index, who are aphagic because of gastrointestinal obstruction/sub-obstruction, relatively asymptomatic and with tumours confined to non-vital organs (usually the peritoneum) are probably the best candidates.

The nutritional regimen should be water- and salt-restricted (especially in patients with an impending ascites), with a glucose:fat calorie ratio of about 1:1 and an energy provision of about 30 kcal/kg/day.

Future clinical research should focus on investigating which patient-dependent or tumour-dependent factors can predict the response to HPN in terms of nutritional benefit, longer survival, maintenance and/or improvement of quality of life.

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11 Mucosal Damage and Immunodeficiency

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Key points

- Control of the inflammatory process is essential at any stage of Crohn's disease and HPN (home parenteral nutrition) is only an adjunct supportive therapy.
- Short bowel syndrome (SBS) is the most common indication for HPN in patients with inflammatory bowel disease.
- Radiation enteritis is a relatively common indication for HPN, usually due to intestinal resection and SBS.
- Prognosis of HPN in radiation enteritis is hampered by the age of the patient and other radiation complications, either intestinal or extra-intestinal.
- HPN in refractory coeliac disease is indicated in the case of complications with intestinal lymphoma or as a general nutritional support.

Introduction

This chapter concerns HPN for inflammatory bowel disease, i.e. Crohn's disease and radiation enteritis, both of which remain important indications for HPN. Two other immune diseases, i.e. AIDS and conditions with villous atrophy – mainly coeliac disease – are less frequently an indication for HPN (Table 11.1).

Table 11.1. HPN indications in adult patients for mucosal diseases (from Van Gossum *et al.*, 1996; Messing *et al.*, 1998; F. Joly *et al.*, personal communication). Data are presented as a percentage of total indications.

	Crohn's	Radiation enteritis	AIDS	Others medical[a]
1993	15	8	4	5
1993–95	17	12	13	5
2001–2004	6	6	0	2

[a] Other malabsorption syndromes (mainly villous atrophy diseases) excluding CIPO, cancer and SBS syndrome.

Crohn's disease and SBS

Epidemiology

The incidence of Crohn's disease is 0.7–14.6 per 100,000 population in Europe and North America (Loftus and Sandborn, 2002). The nature of Crohn's disease predisposes to multiple surgical resections, which can lead to intestinal failure and SBS (Bernell *et al.*, 2000). Hurst *et al.* (1997) noted that 5% of patients with Crohn's disease were left with an intestinal remnant of less than 180 cm after multiple resections, and were at risk for the development of SBS. Other studies have reported an incidence of SBS associated with Crohn's disease of between 0.1 and 4.0% (Post *et al.*, 1996; Yamamoto *et al.*, 2001).

Natural history

In diffuse jejuno-ileal Crohn's disease, there may be a higher incidence of post-operative complications and recurrence because of extensive and severe disease, compared with localized disease. Diffuse jejuno-ileal Crohn's disease is associated with a high incidence of recurrence, and most patients required reoperation. Advances in medical and surgical treatment probably have resulted in a reduction in SBS associated with Crohn's disease despite the increased incidence. Some authors recommended performing stricturoplasty or limited resection, when feasible, to conserve bowel and minimize the risk of the development of SBS (Post *et al.*, 1996; Hurst *et al.*, 1997; Agwunobi *et al.*, 2001; Yamamoto *et al.*, 2001).

Indications for HPN and outcome

The outcome of SBS patients with inflammatory conditions related to Crohn's disease and radiation enteritis was compared to the outcome for non-inflammatory SBS patients, including mesenteric vascular disease as well as other benign disorders and malignancy (Thompson *et al.*, 2003). Patients with Crohn's disease were less likely to have an ileocaecal junction or a stoma compared to those with radiation enteritis. Patients with

inflammatory conditions were less likely to require PN after the first year, particularly so in the group with > 120 cm remnant small bowel. Thirty-day mortality was higher in the non-inflammatory group. One- and five-year survival was similar in inflammatory and non-inflammatory groups.

However, survival was better in Crohn's disease than in the radiation enteritis group. Patients with SBS resulting from Crohn's disease appear to have a better prognosis, while they are more likely to have multiple resections.

Radiation enteritis

Epidemiology

The frequency of radiation enteritis varies between 0.5 and 15.0% of patients treated with abdominal radiotherapy.

Natural history

Small-bowel complications are correlated with the radiation dose and the volume of small bowel exposed. Radiation injury to the intestine has both acute and chronic phases that impair intestinal epithelial and endothelial functions, respectively. In the days following radiation ± chemotherapy, citrulline reduction has been shown to be an indictor of epithelial loss (Crenn *et al*., 2003; Lutgens *et al*., 2004). After recovery from the acute injury, approximately 40% of patients develop chronic intestinal damage comprising fibrotic and ischaemic lesions. Some patients develop fistulae or perforations either during the acute/subacute phase (during and in the 18-month period following radio- or curie-therapy) or during the chronic phase, which can occur for over 30 years (Dubois and Earnest, 1998).

The chronic phase is characterized by stenosis, telangiectasia and ulcerations of the gut with occult or overt blood loss. At the chronic stage, recurrent malignancy is observed in about 20% of cases. Decades after radiotherapy, some patients develop stenosis of the blood vessels and lymphangiectasia.

Indications for (H)PN and outcome

Malabsorption is a frequent finding, which can be related to the different types of intestinal damage, bacterial overgrowth and/or intestinal resection. In the subacute phase, bowel rest and steroids may accelerate epithelial recovery and decrease the fibrotic process (Cosnes, 1996), with the risk of masking surgical complications. Resolution of chronic enteritis is unlikely and HPN is only supportive. Even in the absence of recurrent malignancy, chronic radiation enteritis necessitating HPN has a poor prognosis and results in a poor quality of life, especially when there are associated extra-intestinal lesions (e.g. uro-renal or neuronal).

Nutritional support may be considered as a useful adjunct therapy with a low peri-operative mortality rate, and PN followed by curative abdominal surgery may be the best strategy (Bories *et al*., 1987). Timing of surgery is a very important point, taking into account the natural history of the disease, and should be 'not too early, not too late' to avoid iterative surgery, especially during the 6–24-month period where is observed transition between subacute and chronic lesions (Thompson *et al*., 2003).

The reported 5-year survival rate varies from 42 to 67% (Galland and Spencer, 1985; Deitel and To, 1987). Resection of multifocal, severe stenotic lesions is considered a better strategy than bypass and is associated with the best prognosis (Messing *et al*., 1995; Dubois and Earnest, 1998). Indeed, a significantly better prognosis was observed in patients with PN-dependent SBS than in patients with a longer but non-functioning gut, i.e. no possibility of significant oral feeding, and this is especially true for patients with chronic radiation enteritis (Messing *et al*., 1995).

AIDS

Epidemiology

Before the era of anti-retro viral therapy, administering HPN to AIDS patients was controversial, considering the cost of therapy, the increased risk of infection with intravenous catheters and the poor prognosis for the patient. HPN was almost never used for AIDS patients in the UK or in Australia, whereas in 1994, it represented 5 and 18% of HPN indications in the USA and France, respectively (Howard *et al*., 1991; Howard and Malone, 1996; Messing *et al*., 1998). Incidence and prevalence of overall indications for HPN increased slightly in seven European countries between 1989 and 1993, although they decreased from 7 to 2% for AIDS. Outcomes did not change significantly in this 4-year period with the exception of AIDS, where mortality decreased from 88 to 34%; this was obviously related to newer specific anti-AIDS therapies (Bakker *et al*., 1999).

Natural history

In patients with HIV infection, wasting has been associated with increased mortality (Kotler *et al*., 1989; Thiebaut *et al*., 2000), accelerated disease progression (Wheeler *et al*., 1998), loss of muscle protein mass and impairment of strength and functional status. Weight loss in HIV infection features depletion of both lean and fat tissue (Kotler *et al*., 1985; Grinspoon *et al*., 1997). The loss of fat and lean body masses (LBM) could depend on the severity of illness and previous body composition. A number of studies suggest that loss of LBM and/or weight are independent predictors of survival in adult HIV patients. An early study (Kotler *et al*., 1989) demonstrated that loss of body cell mass, as determined by K-40 isotope analysis, was an important determinant of increased mortality in patients with advanced HIV disease.

In studies performed before the current treatment era, a statistically greater survival in AIDS patients with a body cell mass > 30% of weight or albumin > 30 g/l was demonstrated (Suttmann *et al*., 1995). Progressive weight loss over 4 months indicated also an increased risk of death, increasing from 1.26 (OR) to 2.22 with a weight loss of 0% to 5% and 5% to 10%, respectively (Wheeler, Gilbert *et al*., 1998). Similarly, in outpatients, risk of death increased 8.3-fold with weight < 90% ideal body weight (Guenter *et al*., 1993).

More recently, adjusted survival hazard ratios were 1.9 (95% CI, 1.4–2.6), 3.3 (95% CI, 2.4–4.4) and 6.7 (95% CI, 5.2–8.6) for weight losses of < 5%, 5% to 10% and >10% from baseline, respectively, over a mean follow-up 20-month period (Thiebaut, Malvy *et al*., 2000). BMIs of 16 to 18 and < 16 were associated, respectively, with a 2.2- (95% CI, 1.6–3.0) and a 4.4-fold (95% CI, 3.1–6.3) increased risk of death (Thiebaut, Malvy *et al*., 2000). On the basis of the published data, the Working Group on the Prevention and Treatment of Wasting and Weight Loss recommended extending the existing CDC standards for wasting to include patients with rapid but lesser degrees of weight loss, i.e. a weight loss of 5% within 6 months (Grinspoon and Mulligan, 2003).

Indications for HPN

The indication for nutritional support in AIDS patients is similar to that of other chronic intestinal diseases (Melchior and Messing, 1999; ASPEN, 2002). PN would be linked with better nutritional results if associated with specific wasting-directed therapy (Melchior and Messing, 1999; ASPEN, 2002; Grinspoon and Mulligan, 2003). There are several approaches to achieving appropriate intake, including: (i) testosterone in hypogonadal men; (ii) anabolic agents and appetite stimulants (megoestrol acetate) for those with decreased appetite; and (iii) progressive resistance training (ASPEN, 2002; Grinspoon and Mulligan, 2003).

Outcome

Initially, the benefits of HPN with regard to survival were overshadowed by the high rate of opportunistic infections, and the poor prognosis was related to severe, irreversible, acquired immunosuppression. Indeed, only 10% of patients were alive after 1 year of HPN (Howard *et al*., 1991). However, in a series of 22 patients with a mean weight loss before HPN of 21.4% during a mean 2.5 months of HPN, weight gain and clinical improvement in 15/22 patients without increased risk of sepsis were reported (0.12/100 catheter days) (Singer *et al*., 1991). The latter study and others (Corcoran and Grinspoon, 1999) attributed the excellent metabolic response to increased fuel delivery through PN.

In 1998, a randomized study demonstrated increased survival duration in the HPN group (mean 212 days, range 102–417) in comparison to patients treated by dietary counselling and oral supplementation (57 days,

45–193). This result was obtained before the use of protease inhibitors and/or associated triple therapies. At that time, HPN was a supportive adjunct, but efficient treatment of wasting syndrome in severely immunodepressed AIDS patients. Today, with the use of multiple antiviral therapies indications for HPN are the exception, due to the control of diarrhoea previously associated with severe infections of the gastrointestinal tract (Modigliani *et al*., 1985). Indeed, no AIDS patient was enrolled in the French HPN registry of 476 adult patients between June 2001 and June 2004.

Coeliac disease

Epidemiology

Symptomatic coeliac disease (CD) is associated with substantial morbidity caused by chronic diarrhoea with malabsorption, weight loss, osteomalacia, anaemia and malnutrition. Serological screening studies have shown that the worldwide prevalence of CD is 1 in 266 (Fasano and Catassi, 2001). Similar prevalence has been reported in most European countries, South America and the USA (Catassi *et al*., 1999; Gandolfi *et al*., 2000; Pratesi *et al*., 2003).

Natural history

Between 7 and 30% of CD patients fail to respond to gluten-free diet (GFD) treatment. Non-responsiveness may be either primary, i.e. the patient fails to respond to treatment following initial diagnosis, or secondary, where the patient who has previously had a documented response to GFD becomes non-responsive to therapy. The commonest causes of non-responsiveness are poor education or non-adherence to a strict GFD (Vahedi *et al*., 2003). Less frequent causes include, in order of decreasing frequency: (i) enteropathy-associated T-cell lymphoma; (ii) ulcerative jejuno-ileitis; (iii) pancreatic insufficiency; and (iv) intolerance to dietary constituents other than gluten (e.g. milk, soya).

Enterocyte loss and PN requirements

Intestinal failure requiring HPN was recently recognized through the enterocyte loss due to villous atrophy in CD and non-CD patients, with citrulline as a biomarker: in 52 villous atrophy patients, citrulline correlated with a composite score which integrated the degree as well as the extent of the villous atrophy. ROC curves indicated that citrulline was more powerful than albumin levels in predicting the degree of reduction of the enterocyte mass (Crenn *et al*., 2003).

In this study, the citrulline threshold for assessment of intestinal failure was two-fold less (i.e. 10 μmol/l – 25% of control values) than for SBS cases (i.e. 20 μmol/l). Citrulline was also shown to be a marker of response to

GFD (Crenn *et al*., 2003). Different sites of reduction of the enterocyte mass (proximal in CD versus distal in SBS), as well as adaptive functional changes in SBS, are preliminary and partial explanations of the differences between these two models of enterocyte mass reduction.

Specific PN needs are anticipated in CD patients based on the recognized increased protein turnover rate explored with 1–13C Leucine (Carbonnel *et al*., 1995). Explanation of increased protein needs relies less on protein-losing enteropathy than on crypt hyperplasia associated with villous atrophy. Micronutrients (e.g., B_{12}, folic acid, Zn) are better provided two- to three-fold more than basal requirements to compensate for increased intestinal synthesis or losses. In our experience, Cu is frequently very low in such cases (personal unpublished data).

Indications for HPN and outcome

All non-responsive CD patients may require (H)PN course(s), sometimes long-term, to maintain or correct malnutrition due to villous atrophy leading to severe malabsorption (O'Mahony and Howdle, 1996). Sometimes, short periods (around 3 months) of bowel rest are also required to demonstrate a false or a true non-responsiveness to GFD (Messing *et al*., 1986). Other villous atrophy disease unresponsive to GFD which may require a HPN course is common variable immunodeficiency (Messing *et al*., 1985). In a series of 15 CD patients requiring 22 HPN periods of mean duration 13 (6–19) months PN was efficient in all cases, with correction of dehydration and an improvement in nutritional status.

All patients had a severe malabsorption with a severe (20 cases) or moderate (2 cases) malnutrition (Messing, Halphen *et al*., 1986). In three cases (three periods) the disease had been recently discovered and was severe, without complications and was responsive to GFD. Seven patients (ten periods) had a refractory CD without detected complications and six patients (eight periods) had a refractory CD with complications (two with lymphoma). Overall, the prognosis of refractory CD was poor. Five out of the 15 patients died (two with lymphoma, one with ulcerative jejuno-ileitis and two with refractory sprue without overt complications).

Summary

Control of the inflammatory process is essential at any stage of Crohn's disease and HPN is only an adjunct supportive therapy, the most common indication being SBS. This means that, most of the time, HPN is not exclusive and should be conducted with the lowest possible PN dependency, implying a state of hyperphagia in order to be at the nadir of HPN support complications. Therefore, HPN support is associated with the commonly used immunosuppressive treatments for Crohn's disease with the exception of some patients with end-enterostomy. HPN treatments imply a risk of catheter-related sepsis and thus the best

education that patients can be offered with reference to HPN self-management is very important.

Subacute or chronic radiation enteritis requiring HPN is also frequently complicated by SBS. The prognosis has indeed been ameliorated by the possibility of performing radical surgery while on HPN, and also by having the option to choose the best timing for surgery without fear of eventual SBS – compared to having a longer but non-functioning bowel. The aim of attaining minimal HPN dependency can also be achieved through dietetic counselling of the patient. Prognosis of HPN in radiation enteritis is hampered by the age of the patients and by other radiation complications, either intestinal (telangiactasia/haemorrhage) or extra-intestinal (mainly uro-renal).

Definition and diagnosis of intestinal failure due to villous atrophy and the consequent need for HPN are now facilitated by the use of citrulline as a biomarker of enterocyte loss associated with the extent and grade of villous atrophy. HPN in refractory coeliac disease has two specific aspects: (i) the associated need for either immunosuppressive therapy – similar to that used in Crohn's patients – or chemotherapy in the case of cryptic or overt T-cell lymphoma; and (ii) specific HPN needs – based upon the high protein turnover rate of the enterocyte cell mass and increased losses – required to achieve faster and better nutritional rehabilitation. Better specific therapies are also awaited to increase the poor prognosis of these patients.

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12 Home Parenteral Nutrition in the Elderly

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Key points

- About 40% of all patients who received parenteral nutrition were over age 65 in studies from the USA; in Europe the proportion of elderly receiving home parenteral nutrition (HPN) was in the range 10–20%.
- Radiation enteritis and ischaemic bowel diseases are the most common benign underlying diseases among the elderly on HPN.
- In general, age negatively influences the rehabilitation of HPN patients.
- Re-nutrition with parenteral nutrition and the gain of body cell mass is slower in the elderly patient population.
- TPN formulas and/or flow rates should be specifically adapted for the elderly and glucose tolerance of TPN should be carefully checked.

Introduction

Home parenteral nutrition (HPN) was initially proposed for young patients with short bowel syndrome (SBS) and severe malabsorption, but due to the ageing of the general population and the progress of medical care, elderly patients more and more have become candidates for HPN. In this chapter we discuss the specific points of HPN in the elderly patient.

Prevalence of the Elderly in HPN Programmes

A 1987 report by the US Office of Technology Assessment on Life-Sustaining Technologies and the Elderly has discussed current utilization

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of total parenteral nutrition (TPN) for elderly people and the related issues of patient access to treatment, decision-making practices and quality of care. It has been shown that about 40% of all patients who received parenteral nutrition were aged over 65. Data from commercial home nutrition services and small registries indicated that about 20% of people on HPN were over 65 (Maslow, 1988).

In another study, the use of HPN in geriatric patients and the effect of ageing on the clinical outcome of HPN therapy were assessed between 1985 and 1992. Data were obtained from the following US sources: (i) Medicare parenteral and enteral nutrition workload statistics; (ii) Blue Cross and Blue Shield of South Carolina; and (iii) the North American HPEN Patient Registry. On the basis of these data it was estimated that in 1992 there were 40,000 HPN patients nationwide. One-quarter to one-third of the HPN group was aged ≥ 65 years, depending on the underlying diagnosis (Howard and Malone, 1997).

The percentages of geriatric patients starting HPN within the major diagnostic groups are represented in Table 12.1. As expected, the proportion of elderly on HPN was the highest in the radiation enteritis and ischaemic bowel diseases groups. In the ESPEN-Home Artificial Nutrition Working Group survey conducted in 1993, 14% of patients were 61–70 years of age and 9% > 70 (Van Gossum *et al*., 1996). In the second survey conducted by the same group in 1997 the proportion of elderly patients was higher, and 18% of patients were 61–70 and 10% > 70 (Van Gossum *et al*., 1999). In the 1993–1995 3-year epidemiological survey of HPN performed in France in approved centres for adults, 17% of patients started HPN programmes between 61 and 70 years of age, and 12% when over 70 years of age (Messing *et al*., 1998).

The lack of recent epidemiological studies does not allow us to update these data. However, we estimate that more and more elderly (> 75 years) patients are currently being treated with HPN. The proportion of HPN patients with malignant diseases varies between countries. In North America 40% of patients receiving HPN had malignant diseases (1985–1991) compared with 5% in the UK (1977–1991) (Elia, 1995). The proportion of patients is also relatively low in Denmark, intermediate in France and Belgium, and high in Italy and The Netherlands (Van Gossum

Table 12.1. Proportion of geriatric patients starting home parenteral nutrition within the major diagnostic groups (from Howard and Malone, 1997).

Diagnosis	Number of patients in total	Number of patients aged ≥ 65 years (%)
Cancer	2122	470 (22)
Crohn's disease	562	45 (8)
Ischaemic bowel disease	331	95 (29)
Motility disorders	299	63 (21)
Radiation enteritis	145	53 (37)

et al., 1996, 1999). These differences contribute to the wide variation in the age distribution of HPN patients. In future, HPN will be used more and more in patients with malignant disease, and this will increase the average age of patients treated.

Prognosis and Rehabilitation of Elderly Patients on HPN

In a study conducted in 1997, Howard and Malone (1997) evaluated the outcome of geriatric patients in receiving HPN in the USA. They selected patients with Crohn's disease, ischaemic bowel disease and motility disorders and compared patients over 65 to middle-aged patients (aged 35–55 years). As expected, the 12-month survival rate was lower in the elderly (71%) than in middle-aged patients (92%). However, the complication rate was similar in the two groups of patients. The percentage of re-hospitalizations for an HPN-related complication was 0.9 in the two groups of patients, and the number of re-hospitalizations related to non-HPN complications was 0.7 in the elderly group and 0.9 in the middle-aged group. The 12-month rehabilitation status in the two groups of patients is represented in Fig. 12.1.

The gradual manner in which age influences rehabilitation in patients on HPN has been evaluated in Crohn's disease, and this is represented in Fig. 12.2. These results clearly show that age negatively influences rehabilitation in HPN patients. They also suggest that illness leading to HPN therapy has more devastating effects in geriatric than in middle-aged patients. However, the quality of outcome is still good overall, which makes it reasonable to conclude that age *per se* should not disqualify geriatric subjects from HPN therapy.

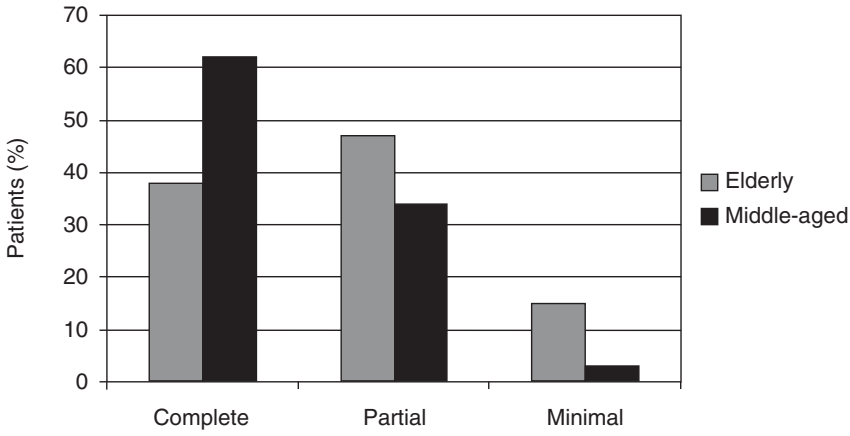

Fig. 12.1. Rehabilitation status at 12 months of elderly (≥ 65 years) and middle-aged patients (35–55 years) receiving home parenteral nutrition. Adapted from Howard and Malone (1997).

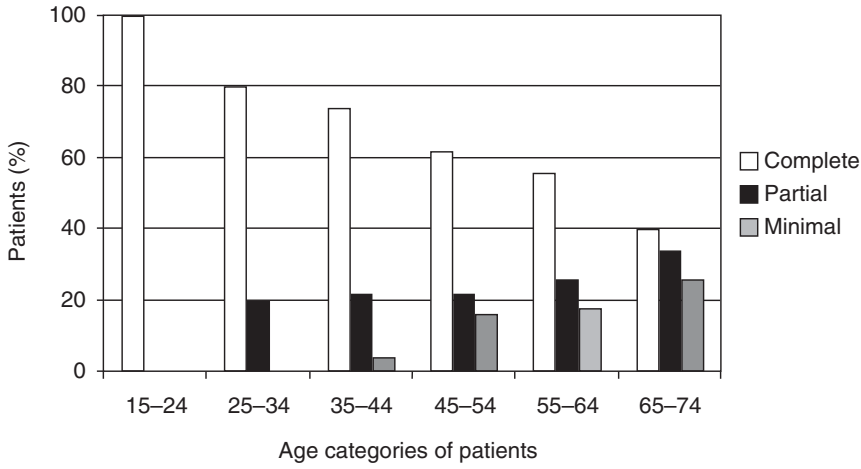

Fig. 12.2. Influence of age on the degree of rehabilitation in patients with Crohn's disease receiving home parenteral nutrition. Adapted from Howard and Malone (1997).

Metabolical Specificities of Parenteral Nutrition in the Elderly

In malnourished elderly patients, dietary supplementation increases protein synthesis and induces a gain in fat-free mass (Bos *et al*., 2000). However, many clinical observations suggest that the repair of a malnourished state is more difficult in the elderly than in the younger patient. The excess energy requirements for 1 kg of weight gain in young females with anorexia nervosa was shown to be about 7500 kcal/kg (Walker *et al*., 1979); in contrast, that requirement was shown to be between 8856 and 22,620 kcal/kg in malnourished nursing home patients (Abbasi *et al*., 1994).

The comparison of the efficacy of cyclic enteral nutrition in 51 middle-aged (45 ± 15 years) patients with 46 elderly (77 ± 6 years) suggested that the repair of a malnourished state is more difficult in the elderly (Hébuterne *et al*., 1995). For similar energy intakes during a mean 27 days of enteral nutrition, the weight gain was 6.3 kg in patients ≤ 65 years old and only 4.7 kg in elderly patients, and some biological nutritional parameters increased more in the younger patients than in the elderly. In particular, the gain in nutritional proteins (albumin, transferrin, transthyretin) was much lower in the elderly than in the younger patients, whereas inflammatory status was similar in the two groups. However, in this study, the duration of re-feeding was not standardized and body composition was not measured.

We therefore conducted another study of a 3-week re-nutrition programme to compare the effects of cyclic enteral nutrition on the nutritional assessment parameters and body composition in middle-aged and elderly patients, in order to determine if age alone could affect the

nutritional effects of tube feeding (Hébuterne *et al*., 1997). This study clearly demonstrated a reduced efficacy of re-nutrition in the elderly and the gain of body cell mass was lower in the elderly (1.6 kg) than in younger patients (2.7 kg). This result was not due to differences in patients' condition, and nutrient absorption was satisfactory and similar in both groups of patients.

During parenteral nutrition, Shizgal *et al*. (1992) have evaluated the effect of age on the response to TPN in 325 patients by measuring body composition by multiple-isotope dilution at the onset and at 2-week intervals during the course of TPN. With advancing age more energy was required to maintain the body cell mass of malnourished patients (Fig. 12.3).

A study of re-nutrition in young and old malnourished rats clearly demonstrated that ageing was a significant variable affecting the response to nutritional support (Walrand *et al*., 2000). Interestingly, it was shown in this study that the nitrogen balance was lower in re-fed old rats than in a similarly malnourished group of adult rats, and that a higher protein intake was needed in aged rats to achieve the same nutritional effect to that in the younger group. The decreased efficiency of re-nutrition in repairing a malnourished state in the aged is not a consequence of maldigestion nor of malabsorption of nutrients, which is not affected by ageing (Russell, 1992) but is possibly a consequence of age-related changes in the metabolic state.

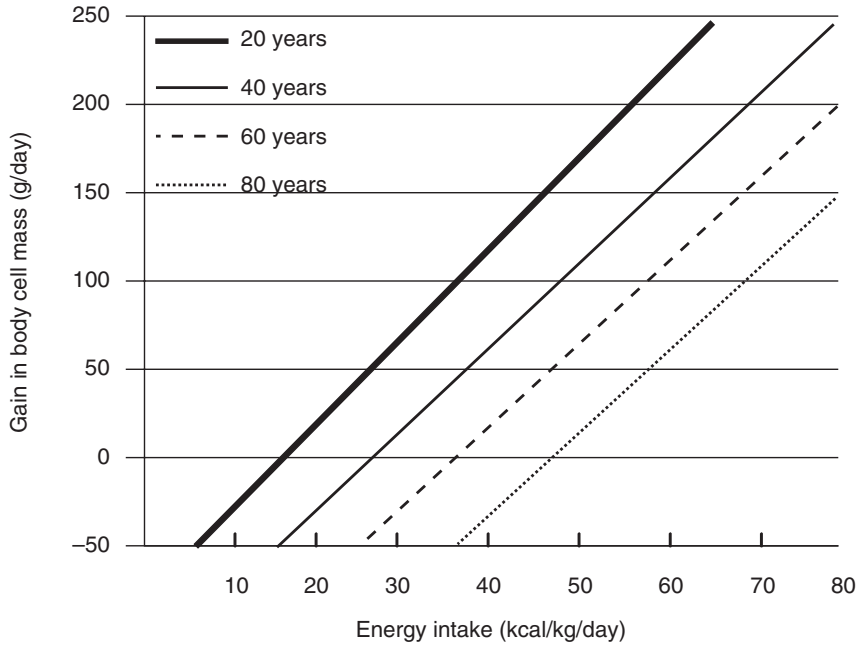

Fig. 12.3. Influence of age on the relationship between the daily changes in body cell mass and energy intake. Adapted from Shizgal *et al.* (1992).

Energy expenditure and body composition in well-nourished and elderly patients

It is well known that advancing age is accompanied by changes in body composition and energy metabolism. Owing to the decrease in fat-free mass (FFM) with age (Forbes and Reina, 1970), older individuals generally have a lower resting energy expenditure (REE) than do younger normal subjects (Keys *et al*., 1973; Bloesch *et al*., 1988; Thorne and Wahren, 1990; Vaughan *et al*., 1991; Roberts *et al*., 1995). When REE is adjusted for FFM, some authors have reported a lower REE in the elderly than in younger subjects (Fukagawa *et al*., 1990; Roberts *et al*., 1995; Visser *et al*., 1995), but others have not observed any difference between the two groups (Keys *et al*., 1973; Bloesch *et al*., 1988).

In one study comparing elderly and middle-aged women, the elderly subjects had a higher REE/FFM (Voorrips *et al*., 1993). However, these investigations were all carried out on healthy and non-malnourished subjects. In malnourished elderly subjects, Campillo *et al*. (1992) demonstrated that the REE/FFM was higher in those patients with BMI < 20 than in those with a BMI > 20.

We have also demonstrated a dramatic increase in REE/FFM in very severely malnourished patients with a BMI > 20 (Schneider *et al*., 2002). The FFM accounts for 85% of the individual variation in REE (Cunnigham, 1991). Sarcopenia occurs with ageing, and the decrease in FFM is due essentially to a decrease in muscle mass (Rosenberg, 1997; Janssen *et al*., 2002). Malnourished elderly individuals with a low FFM have probably lost a great quantity of muscle mass.

In patients under 70 years of age, weight loss leads to a homogeneous decrease of FFM, BCM and fat mass (FM), whereas patients over 70 lose only FFM and BCM, and maintain their absolute values of FM that represent a higher percentage of total body weight (Schneider *et al*., 2002). Recent investigations on the relative contribution of different organs to REE have shown that while muscle mass represents almost 40% of FFM, it represents only 20% of REE (Gallagher *et al*., 1998).

In contrast, organs such as the heart, brain and kidney account for a very small percentage of FFM and a proportionally greater percentage of total REE. Extensive loss of muscle mass in malnourished elderly individuals may increase the contribution of other organs to FFM, thereby increasing REE when expressed as a ratio of FFM.

In particular, the adaptation to starvation and re-feeding could be lesser in the elderly because of the reduction of active cell mass and the inability to increase both protein synthesis and degradation. During illness, nitrogen must be mobilized from muscle to provide amino acids to the immune system, liver and other organs. If adequate nitrogen cannot be provided, either exogenously from the diet or endogenously from muscle, the body's capacity to withstand an acute insult declines, and – at about 60% of baseline nitrogen throughput – the body ceases to function (Roubenoff, 1999).

Glutamine is the most abundant free amino acid in the human body and has several important metabolic roles during malnutrition and

re-feeding, since it may promote protein synthesis and inhibit protein catabolism in muscle (Smith and Wilmore, 1990). Skeletal muscle is a major site for glutamine synthesis in the body and serves as a glutamine store. Any decrease in muscle mass induces a decrease in the glutamine pool and both impairment of glutamine metabolism and depletion of the glutamine pool have been demonstrated in old, stressed rats (Minet-Quinard *et al*., 1999). Many studies suggest that a glutamine supplement in stressed and/or malnourished patients may have a positive effect on the clinical outcome (Ziegler *et al*., 2000). Specific studies of glutamine or glutamine precursor supplementation in the aged should be of great interest.

Boirie *et al*. (1997) have demonstrated that a higher splanchnic extraction of amino acids during feeding in the elderly induced a lower peripheral availability. This could contribute to a decreased muscle protein synthesis during feeding, explaining the lower efficacy of the nutritional support in the aged. It is now clear that sarcopenia is the backdrop against which the drama of disease is played out: a body already depleted of protein because of ageing is less able to withstand the protein catabolism that accompanies acute illness or inadequate protein intake (Roubenoff and Castaneda, 2001).

Many hormonal changes that may reduce the efficacy of re-nutrition have also been demonstrated in the elderly; for instance, growth hormone has showed interesting anabolic effects in the elderly (Lange *et al*., 2000), and growth hormone supplement has been shown to improve the outcome in elderly patients with accidental hip fracture (Van der Ley *et al*., 2000).

Substrate oxidation and thermogenic response to TPN

A study by Volpi *et al*. (2000) suggested that the anabolic response to a mixed glucose/amino acid meal was reduced in older men. This study suggested that insulin resistance occurs even in healthy, elderly volunteers. In a study conducted on patients managed by TPN for intestinal failure, important metabolic differences between elderly and middle-aged patients were demonstrated (Al-Jaouni *et al*., 2002). For similar energy supplies, elderly patients oxidized more fat and less glucose than did middle-aged patients.

Twelve elderly patients (8F/4M; 72 ± 5 years) and 12 middle-aged patients (9F/3M; 39 ± 13 years) who were on cyclic TPN for intestinal failure were investigated in stable condition after at least 15 days of TPN. In the fasting state, REE was significantly higher in the elderly patients than in the middle-aged patients. During TPN, lipid oxidation was significantly higher in the elderly patients than in the middle-aged patients, and glucose oxidation was significantly lower in the elderly patients than in the middle-aged patients (Fig. 12.4).

Areas under the curves of glycaemia and free fatty acids were significantly higher in the elderly patients whereas insulin was lower, suggesting insulin resistance in the elderly (Fig. 12.5). The reduction in

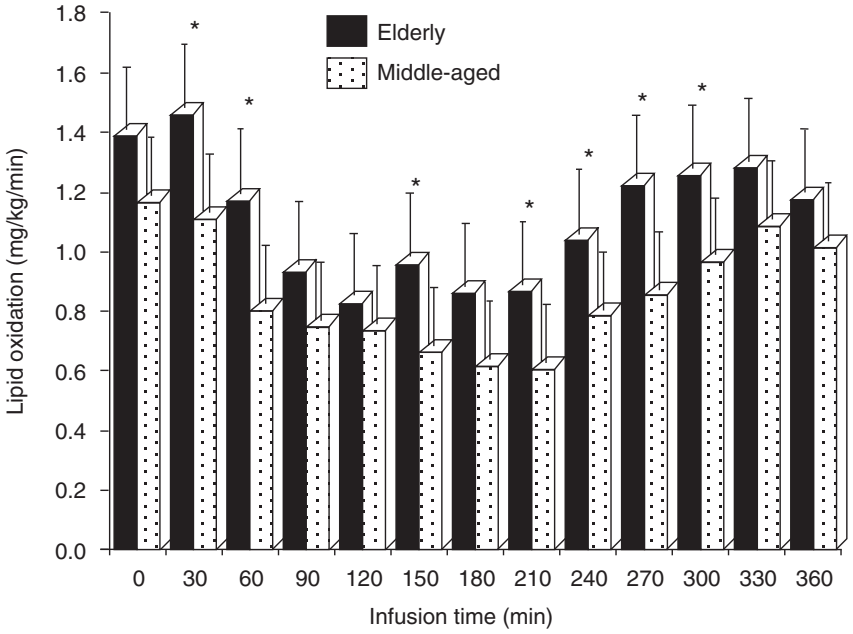

Fig. 12.4. Fat oxidation in elderly and younger patients during TPN. Adapted from Al-Jaouni *et al.* (2002).

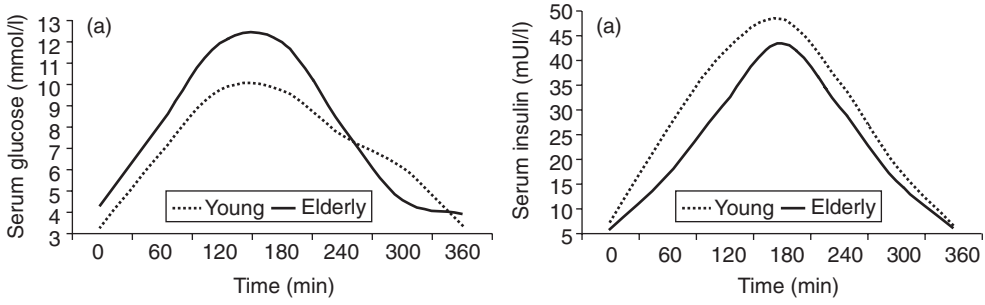

Fig. 12.5. Serum glucose (a) and serum insulin (b) during TPN in non-diabetic young and elderly patients. Adapted from Al-Jaouni *et al.* (2002).

glucose oxidation during TPN may affect treatment tolerance. Therefore, knowing the importance of glucose control in critically ill patients (Van den Berghe *et al.*, 2001), glucose control of elderly patients on TPN is an important issue.

In the same study, the authors failed to observe any effect of age on the thermogenic response to TPN. Previously published results concerning the effect of age on thermogenic response are contradictory. In some studies, glucose-induced thermogenesis was apparently decreased in elderly

subjects compared to that in young subjects (Golay *et al*., 1983; Bloesch *et al*., 1988). In other investigations, the thermogenic response after ingestion of a liquid mixed meal was found to be decreased in elderly men (Thorne and Wahren 1990; Visser *et al*., 1995) but not in elderly women (Visser *et al*., 1995). Other authors reported that the thermogenic response to a protein load was no different in elderly individuals compared to young subjects (Tuttle *et al*., 1954).

However, none of these studies concerned malnourished patients fed by TPN. We observed a thermogenic effect of TPN between 9.8 and 13.6% of the energy infused, a finding consistent with studies on young subjects in whom the thermogenic effect of TPN varied between 5 and 17% (Lindmark *et al*., 1986; Vernet *et al*., 1986; Sobotka *et al*., 1991).

Social Particularities of HPN in the Elderly

Transferring a geriatric patient from hospital to home to continue HPN therapy requires a good deal of advanced planning. HPN is 65% more cost effective than in-hospital TPN, but has potentially life-threatening complications and requires close cooperation and the effective organization provided by a multidisciplinary team of healthcare professionals. However, the most elderly patients are sometimes unable to grasp the importance of strict asepsis despite prolonged training and support, and many candidate patients are not suitable for training due to ongoing problems related to both their underlying disease and co-morbidity.

Because home professional nursing is rarely available for more than 2 h per day, most of the parenteral nutrition therapy has to be supervised by the patient or his/her family. Unfortunately, most hospitals and institutions in many Western countries do not even have a multidisciplinary nutrition team to cater for patients receiving parenteral nutrition, and it is often difficult to find an institution able to perform HPN. So, dependency levels of HPN patients are rising, making care from remote centres difficult (Freshwater *et al*., 2005).

Summary

About 25% of HPN patients are > 65–70 years of age. Because of the ageing of the general population and medical progress the prevalence of elderly patients treated with HPN will increase in the future. Due to the metabolic particularities of the elderly, TPN formulas and/or flow rates should be specifically adapted for the elderly and glucose tolerance of TPN should be carefully checked. Transferring a geriatric patient from hospital to home may sometimes be difficult, and institutions where a nutrition team is able to take care of parenteral nutrition should be developed.

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Part III
Complications

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13 HPN-related Liver Disease

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Key points

- Home parenteral nutrition (HPN)-associated liver disease is related to both the HPN regimen and to underlying disease.
- Risk factors include: (i) a LCT/glucose ratio > 40% or more than 1 g LCT/kg/day; (ii) presence of short bowel, no remnant ileum or < 150 cm and colon exclusion; (iii) infection; (iv) hyperalimentation; (v) glucose administration > 7 mg/kg/min; and (vi) continuous versus cyclic HPN.
- Prevention (absence of chronic cholestasis) is of utmost importance.
- Therapy includes, besides the optimization of the nutritional regimen: (i) the use of ursodeoxycholic acid, taurine and alpha-tocopherol supplementation; (ii) short-term antibiotic cover; (iii) re-establishment of colon continuity; and (iv) implementation of enteral feeding.

Introduction

HPN-related liver disease would be better termed HPN associated liver disease (HPNALD), because not only the HPN regimen (quantity, quality, rhythm of administration) plays a role but also the underlying disease, leading to a widely varying duration of HPN (1 month to long-term or indefinite HPN). Optimization of HPN delivery in the last 25 years has now delineated favourable conditions avoiding, most of the time, the occurrence of jaundice, i.e. an intra-hepatic cholestasis, which is the most frequent clinically encountered situation with HPNALD (Howard and Ashley, 2003).

However, this progress has been hampered by the huge increase in the

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use of industrial nutritive mixtures in HPN patients (Van Gossum *et al.*., 2001), mixtures which should be considered unsuitable for the specific IV nutritional needs of any HPN patient (Cavicchi *et al.*, 2000). Therefore, specifically tailored nutritive mixtures (all-in-one container) must remain the rule rather than the exception for HPN patients, especially for those who are expected to be long-term HPN (LTHPN) patients, i.e. those with benign but chronic (permanent) intestinal failure. Alternative treatments to LTHPN should be considered, especially in those potential HPN candidates for reconstructive surgery or transplantation (Tx) (Chan *et al.*, 1999; Buchman *et al.*, 2003; Grant *et al.*, 2005).

This approach is of primary importance when it is known that in the past two decades HPNALD led to liver failure (LF) in 20% of patients on LTHPN (Messing *et al.*, 1995), being at that time responsible for either death or being put on a waiting list for combined liver–intestinal Tx (Buchman *et al.*, 2003). Prevention of HPNALD is therefore of crucial importance from the first days of PN, and the regimen in that first PN phase (i.e. 6 months) has to be managed carefully in order to avoid chronic cholestasis. These facts favour the management of PN patients in centres expert in the whole spectrum of intestinal failure therapy (Buchman *et al.*, 2003).

Prevalence

Chronic abnormalities as identified by liver function tests have been reported as occurring during HPN in both children and adults, with a wide frequency ranging from 15–85% in several series (Bowyer *et al.*, 1985; Stanko *et al.*, 1987; Clarke *et al.*, 1991; Ito and Shils, 1991; Messing *et al.*, 1992; Quigley *et al.*, 1993).

In a prospective cohort study of 90 LTPN patients enrolled between 1985 and 1996 in two approved HPN centres, actual occurrence of severe liver disease (SLD; bilirubin level > 60 μmol/l, factor V < 50%, portal hypertension, encephalopathy, ascites, gastrointestinal bleeding, histologically proven extensive fibrosis or cirrhosis) was determined by the Kaplan-Meier method: 58 patients (65%) developed chronic cholestasis and 37 (42%) developed SLD after 6 (3–132) and 17 (2–155) months, respectively.

Amongst these patients, 22 showed histologically proven extensive fibrosis (n = 17) or cirrhosis (n = 5) after 27 (2–148) months. The prevalence of SLD was found to be 26 ± 9% and 50 ± 13% at 2 and 6 years, respectively. Liver disease was responsible for the death of 7% of patients (22% of the deaths). In these LTPN patients, mean non-protein calorie intake was 88 ± 13% REE (glucose at 4.0 ± 1.2 g/kg/day and soya-based rich triglyceride (LCT) – or standard 20% lipid – emulsions at 0.64 ± 0.20 g/kg/day), thus intending to avoid the deleterious effect of 'hyperalimentation' (Cavicchi *et al.*, 2000).

This LTHPN regimen included, however, a wide range of LCT:glucose ratios: 8–40% (cf. below). Indeed, after 2 years of HPN, glucose-based LTHPN was associated with macrovacuolar steato-hepatitis and SLD in fewer than 25% of patients (Bowyer *et al.*, 1985), whereas lipid-based LTHPN, i.e. ternary mixtures including standard LCT emulsions of > 1 g/kg/day, was associated with portal inflammation, ductular abnormalities, microvacuolar steatosis and cholestatic SLD in 50% of patients (Cavicchi *et al.*, 2000).

Diagnosis

Mild increases in LFT, indicative mainly of cholestasis (total alkaline phosphatase and γGT), with a lesser increase in the levels of ASAT/ALAT enzymes, are usually seen with (in 50% of cases) an increase in conjugated bilirubin. Intra-hepatic cholestasis implies non-obstructed and non-dilated bile ducts, a fact that should be verified with liver imaging (Nanji and Anderson, 1985; Burnes *et al.*, 1992). If HPNALD persists, severe histological changes consisting of extensive portal fibrosis and/or cirrhosis have been reported, leading – over months to years – to liver failure and death (Stanko *et al.*, 1987; Clarke *et al.*, 1991; Ito and Shils, 1991; Burnes *et al.*, 1992).

When LFT becomes abnormal, the occurrence of extensive fibrosis and liver failure can be seen within several months if a high degree of PN dependence was involved, i.e. poor oral intake and ongoing IV hyperalimentation (Stanko *et al.*, 1987; Messing *et al.*, 1992). On the other hand, at least in adults, optimized HPN is compatible with a long-standing (> 5 years) uncomplicated HPNALD-associated cirrhosis (personal unpublished observations).

Peculiar clinical findings are: (i) absence of pruritus despite 'bronze' jaundice; this is probably due to the disrupted enterohepatic cycle of bile acids in short-gut patients with no remnant ileum; (ii) portal hypertension, although lessened by decreased portal blood flow associated with the resected intestinal organ, may be present in enterostomy patients with blood losses (overt or occult), requiring careful stoma care; (iii) in HPN patients, jaundice with increased conjugated and unconjugated bilirubin, splenomegaly and thrombocytopenia (but not hepatomegaly, anaemia or leucopenia) can be particularly associated with noticeable sea-blue histiocytes (activated macrophages CD 68^+) and infiltration of bone marrow without haemophagocytosis (Stanko *et al.*, 1987; Messing *et al.*, 1992; Bigorgne *et al.*, 1996, 1998).

This latter phenomenon is the expression of an accumulation of polyunsatured fats (PUFA) – resulting from an overly high long-term standard lipid delivery through ternary mixtures – in the reticuloendothelial cells (Stanko *et al.*, 1987; Messing *et al.*, 1992; Bigorgne *et al.*, 1996, 1998). This sea-blue histiocyte syndrome could be present in adults as a chronic manifestation (Silverstein *et al.*, 1970) or, especially in

children, as a flare-up revealed by underlying infection (Colomb *et al.*, 2000). Phytosterolaemia has been described in HPNALD in children and in preliminary adult studies as a biological marker of IV fat infusion (Moss and Amii, 1999).

After having excluded bile duct stone(s) by imaging, positive HPNALD diagnosis relies on liver biopsy; histological elemental lesions include micro-/macrovacuolar steatosis, portal inflammation and ductular abnormalities and hepatocyte necrosis; these lesions, although non-specific, form a suggestive pattern. They can be of very early occurrence, ≥ 30 days of PN (Levecq *et al.*, 1988), and when chronic cholestasis is seen, extensive or bridging fibrosis and cirrhosis have been documented in 35 and 11% of cases after a median duration of 2 and 3 years, respectively (Cavicchi *et al.*, 2000).

Indeed, in the study looking at the natural history of HPNALD, the probability of developing either abnormalities in liver function tests or histological HPNALD were very close and non-significantly different during the mean 5-year follow-up (Cavicchi *et al.*, 2000).

Microvacuolar steatosis, phospholipidosis (Degott *et al.*, 1988), accumulation of phospholipids, polyunsaturated triacyl glycerol within hepatocytes and hyperplasia of macrophages, i.e. Kupffer cells in and around sinusoids or in and around portal areas (Levecq *et al.*, 1988; Imamura *et al.*, 2005) all need special staining to be revealed (Oil red O and Otan Baker +), and are seen especially when ternary nutritive mixtures are used. This explains why microsteatosis was not described with the use of IV fat infusions, whereas hepatocyte macrosteatosis was easily demonstrated, for instance, with high glucose infusions (Messing *et al.*, 1977, 1979).

Pathophysiology

HPNALD is multifactorial and recent reviews have listed implicated variables (Buchman *et al.*, 1993). We favoured pragmatical – but as yet incomplete – physiopathology, best delineated between nutrition- and patient-related variables, because this allows practical management (prophylaxis and curative treatment) of such a complication. Indeed, pathogenesis of HPNALD, if intricate and multifactorial, involves patient-dependent factors, especially SBS (Stanko *et al.*, 1987; Clarke *et al.*, 1991; Ito and Shils, 1991; Cavicchi *et al.*, 2000) and nutrition-dependent factors, especially 'intravenous hyperalimentation' (Luman and Shaffer, 2002) or soya-rich PUFA triglyceride emulsion (> 1 g/kg/day) even without hyperalimentation (Stanko *et al.*, 1987; Bigorgne *et al.*, 1996; Cavicchi *et al.*, 2000).

Patient-related variables

In univariate analysis the following conditions were related to the development of chronic cholestasis during HPN: (i) ileal resection (Messing

et al., 1994), in multivariate analysis; (ii) SBS with no remnant ileum – either < 150 cm, odd ratio (OR) 3.2, 95% confidence interval (CI); 1.5–5.3 (Luman and Shaffer, 2002) or < 50 cm, OR 2.1, CI 1.2–3.7 (Cavicchi *et al.*, 2000); and (iii) colon exclusion, OR 3.9, CI 1.7–5.6 (Messing *et al.*, 1994). In the former study, chronic cholestasis was associated with the development of SLD (OR 4.8 (CI 1.6–13.7)) (Cavicchi *et al.*, 2000).

In very short bowel, especially if protein enteral absorption is < 25% of total needs in children (Geggel *et al.*, 1985), the systemic taurine pool is depleted (plasma, platelets and lymphocytes levels are significantly lower than in controls) (Kopple *et al.*, 1990; Iglicki *et al.*, 1996). Indeed, in nine SBS HPN-dependent patients receiving taurine-free HPN, taurine turnover was one-third less than reference values (A.M. Badran *et al.*, personal unpublished data).

In addition, despite normalization of plasma taurine levels in SBS patients using long-term taurine-enriched (300 mg/day) amino acid solutions, a huge persistent depletion of taurine- versus glycine-conjugated bile salts – irrespective of the length of the remnant jejunum – was documented (Schneider *et al.*, accepted in World Journal of Surgery). This indirect evaluation of the enterohepatic bile salt pool through dosage of plasma bile salts suggests that huge bile salt losses due to a ruptured enterohepatic cycle (Ferezou *et al.*, 1993) are not easily corrected by the IV provision of taurine (Kopple *et al.*, 1990).

Other factors implicated in the occurrence of HPNALD occur through intestinal bacterial overgrowth and translocation (Chazouilleres *et al.*, 1987) and/or disruption of the enterohepatic bile acid pool with the occurrence of tertiary deconjugated 'toxic' bile acids (Fouin-Fortunet *et al.*, 1982). Again, colon exclusion of several months' duration, with morphopolynuclear inflammation of the mucosa (Harig *et al.*, 1989) and changes in bacterial flora (Neut *et al.*, 1989), induces translocation with ensuing cholestasis.

Along similar pathways, sepsis – either systemic or gut-induced – is a factor increasing the occurrence of cholestasis in juvenile or adult PN (Messing *et al.*, 1992; Matsui *et al.*, 1993; Beau *et al.*, 1994a). It has been postulated that PN-associated chronic cholestasis could be exacerbated by sepsis and that Kupffer cell dysfunction may participate in its pathogenesis (Scott-Conner and Grogan, 1994; Cavicchi *et al.*, 2000; Pironi *et al.*, 2003a).

Nutrition-related variables

When short-term ternary hyperalimentation was utilized (45–60 kcal/kg/day), cholestasis was seen more frequently (alkaline phosphatase 25–60%, bilirubin 12–30%) than with lower ternary PN levels (30–40 kcal/kg/day; alkaline phosphatase 15–25%, bilirubin 5–10%) (Allardyce *et al.*, 1978; Bengoa *et al.*, 1985; Messing *et al.*, 1992).

Malnourished patients are more prone to liver damage provoked by extra loading of excess macronutrients (Lerebours *et al.*, 1986; Braxton and Lowry, 1995), focusing again on an appropriate IV infusion when a

diagnosis of intestinal failure is made. Glucose infusion of more than 7 mg/kg/min is associated with an RQ of > 1, signifying *de novo* lipid synthesis in the liver with saturated triglyceride depots in hepatocytes (Wolfe *et al.*, 1988; Just *et al.*, 1990). A parallel increase in blood triglycerides can also be observed (Messing *et al.*, 1977).

Essential fatty acid deficiency or choline deficiency decreases lower extrusion of liver triglycerides, producing higher macrosteatosis (Fleming *et al.*, 1976; Jeejeebhoy *et al.*, 1976; Reif *et al.*, 1991; Demetriou, 1992; Buchman *et al.*, 1995; Reimund *et al.*, 2001; Howard and Ashley, 2003).

A contributing factor to the development of fatty liver is bacterial translocation (Neut *et al.*, 1989; Moss and Amii, 1999). It is therefore logical to anticipate steato-hepatitis under the above-cited conditions. A large volume of the lipid infusion is not oxidized and is thus stored, especially if simultaneous infusion of glucose is realized with ternary mixtures (Just *et al.*, 1991). These deposits are loaded within the reticuloendothelial cells, especially those of the spleen and liver (Degott *et al.*, 1988; Levecq *et al.*, 1988; Zoli *et al.*, 1998; Reimund *et al.*, 2001).

Lipoprotein X (LPX) comprises equimolecular amounts of cholesterol and phospholipids, the former being taken up from cell membranes. LPX is a marker of the abnormal metabolism of lipid infusion: its blood level increases with the triglyceride IV load but its production is greater with the 10% in comparison with the 20% lipid emulsion due to a two-fold higher ratio of phospholipids:triglycerides (Messing *et al.*, 1990). LPX, like PUFA lipids, is deposited in Kupffer cells and hepatocytes, thus explaining the phenomenon of microsteatosis (cf. above).

It was observed that liver function test abnormalities were more frequent ($P < 0.02$) in ternary AIO ($n = 48$; 54%) than when lipids were infused separately ($n = 58$; 29%) (Beau *et al.*, 1988). Stability of ternary mixtures was one possible explanation of this finding (Gerard-Boncompain *et al.*, 1992). In multivariate analysis, an IV lipid input (20% soya emulsions, rich in PUFA) of more than 1 g/kg/day was clearly associated during PN with both chronic cholestasis (OR, 2.3; CI, 1.6–5.9) and SLD (OR, 3.4; CI, 1.6–6.8) (Cavicchi *et al.*, 2000). This was linked only to IV lipid intake and observed without hypercaloric feeding (cf. above).

The probability of being free of SLD after 2 years of HPN was only 50% when more than 1 g/kg/day of soya lipids was used, whereas the figure was > 80% when < 1 g/kg/day was given. In the latter case, < 25% of cases developed SLD after 6 years of HPN for intestinal failure (Cavicchi *et al.*, 2000). Therefore, standard 20% lipid emulsions (soya-rich PUFA) are dramatically deleterious for the liver when used at a dosage rate of more than 1 g/kg/day.

In general, haemic essential fatty acid (EFA) profiles in HPN patients indicate normal arachidonic levels, even with low amounts of IV PUFAs, i.e. 5–10% of calorie load, but decreased docohexanoic acid (DHA) even with large volumes of IV PUFAs (up to 50% of calorie load). Thus, a relative balance/deficit of N-3 lipids is observed with a further, specific negative effect of very short bowel (Chambrier *et al.*, 2002).

The use of MCT/LCT emulsion – 50 g per infusion – during 4 months did not change most of the EFA profiles (Chambrier *et al.*, 2004). These observations suggest that pro-inflammatory leucotrienes and cytokines might be increased with ternary mixtures (Reimund *et al.*, 2004a).

Lipoperoxidation induced by acute IV lipid infusion is a well-known phenomenon (Lemoyne *et al.*, 1988; Van Gossum *et al.*, 1988) and it is further increased by: (i) the HPN duration; (ii) the PUFA soya load (1 (0.0–1.8) g/kg/day); and (iii) a lower vitamin E status (Pironi *et al.*, 1998). In effect, the ratio of vitamin E (α-tocopherol)/g of PUFA that induces the lowest lipid peroxidation had been estimated to be ~ 0.6, depending on the degree of unsaturation (Valk and Hornstra, 2000; MacDonald *et al.*, 2001), a ratio that is rarely found in most lipid emulsions, i.e. concentration of total tocopherols/g with PUFA is normally 0.33 (0.15–3.3).

Furthurmore, tocopherols are considered as having poor availability in lipid emulsion and competition exists between α- and γ – more abundant but less active forms – whereas exchange is very active at the time of chylomicron metabolism (Kelly and Sutton, 1989; Steephen *et al.*, 1991). In the short term (10 days), 3.4 g of α-tocopherol/g of PUFA (MCT/LCT enriched with vitamin E) reduced the peroxidation versus LCT controls (ratio of 0.2) in ternary mixture PN (Jonas *et al.*, 2000; Manuel-y-Keenoy *et al.*, 2002).

In addition, storage of AIO may induce the following: (i) vitamins C or E degradation/losses in EVA bags (Gomis Munoz *et al.*, 1996; Silvers *et al.*, 2001; Pironi *et al.*, 2003b); (ii) light-induced peroxidation, which may necessitate darkened storage/delivery conditions; or (iii) an increase in the amount of oversized fat globules in some AIO mixtures (Allwood and Martin, 2000; Driscoll *et al.*, 2001, 2003). The latter change induces enhanced fat trapping in the reticulo-endothelial system (RES) and peroxidation.

Liver tolerance of new or semi-recent lipid emulsions (mixed MCT/LCT, olive oil based, enriched ω-3, etc.) have been poorly studied with reference to HPN (Chambrier *et al.*, 2004; Reimund *et al.*, 2004b, 2005) and a clear-cut conclusion cannot be made at this point. Decreased choleresis is a contributing factor to HPNALD: no food intake (i.e. exclusive PN), continuous instead of cyclic PN delivery, excess or imbalance of amino acid infusion (deficit in taurine or S-adenosyl donors) were seldom associated with cholestasis in clinical studies (Messing *et al.*, 1982), but frequently in experimental studies (Belli *et al.*, 1987; De Bandt *et al.*, 1999).

Lastly, either excess contaminants – e.g. Al, Mn and Cu – in nutritive mixtures (Quigley *et al.*, 1993; Reynolds *et al.*, 1998; Van Gossum and Neve, 1998; Blaszyk *et al.*, 2005), Fe delivery or a deficit in antioxidants such as Se, glutathione and vitamin C may also facilitate peroxidation of macronutrients. The ensuing inflammatory liver fibrosis secondary to excess Fe deposits (or others metals) cannot be treated by antioxidant supplementation.

Treatment: Preventive and Curative

Patient-related

After a case report of efficient sequential ursodeoxycholic acid (UDCA) treatment (Lindor and Burnes, 1991), it was demonstrated that UDCA *per os* (15 mg/kg/day) can improve HPN-associated cholestasis in both children ($n = 7$) and adults ($n = 9$) (Geggel *et al.*, 1985; Beau *et al.*, 1994a; Spagnuolo *et al.*, 1996). Biological improvement could be achieved in 2–8 weeks (Beau *et al.*, 1994a; Spagnuolo *et al.*, 1996). At 30 mg/kg/day, even in SBS, incorporation at a level of 40% in the bile salt pool was demonstrated (Iglicki *et al.*, 1996). UDCA improves the reduced choleresis, protects hepatocytes from overproduction of cytotoxic biliary acids (Poupon and Poupon, 1995) and reduces HLA Class I antigen over-expression on hepatocytes (Innes *et al.*, 1988; Calmus *et al.*, 1990).

Parenteral taurine supplementation has been reported as improving PN-associated cholestasis through improved bile flow (Guertin *et al.*, 1991, 1993) and as preventing lithocholic, acid-induced cholestasis in guinea pigs (Guertin *et al.*, 1991). In children, it has been proposed to include taurine in parenteral nutrition solutions (Cooke *et al.*, 1984; Howard and Thompson, 1992; Helms *et al.*, 1999).

Taurine may be beneficial by virtue of its effects on increasing the amounts of hydrophilic, tauro-conjugated bile acids and by preventing cell membrane changes caused by oxidative stress (Guertin *et al.*, 1991; Redmond *et al.*, 1998). Taurine has also been shown to reduce pro-inflammatory cytokine production in Kupffer cells and to improve upon defective phagocytic and pro-inflammatory cell microbicidal capacities (Redmond *et al.*, 1998).

In 15 patients with portal fibrosis at baseline, receiving UDCA with ($n = 6$) or without ($n = 9$) taurine, we have found ten responders who had a better response to both treatments and were, in general, those with the shortest HPN duration. Our policy is to treat intestinal failure due to very short gut with taurine-enriched amino acid solutions (Hardison, 1978) and to instigate oral UDCA earlier, as we can do in the course of the disease.

Multicentre trials are necessary to confirm whether the association of UDCA and taurine could prevent SLD in LTHPN.

Short-term courses of oral or IV antibiotic treatments were shown to reduce cholestasis of (H)PN (Beau *et al.*, 1994a) patients. Our policy is to give sequential oral antibiotic treatment oriented against Gram-negative or anaerobic bacteria, especially when patients have a dysmotile bowel or incomplete bowel stenoses. Re-establishment of colon continuity – rather than diversion – is associated with a lower risk of cholestasis during HPN (Messing *et al.*, 1994). Meanwhile, our policy is to nourish the excluded segment with SCFA enemas (Harig *et al.*, 1989).

Nutrition-related

Drastic reduction – just sufficient to prevent essential fatty acid deficiency – or suppression of soya lipid emulsion during several months was demonstated to reduce chronic cholestasis and lipid thesaurismosis in both children and adults (Gerard-Boncompain *et al.*, 1992; Colomb *et al.*, 2000). Our policy is to give cyclic nocturnal PN with an energy component no more than 1.2-fold the REE, with less than 1 g/kg/day, or no more than 33% of total calories as 20% lipid emulsion (Cavicchi *et al.*, 2000).

Replacement of standard soya emulsions with either LCT/MCT or oleic-based emulsions might represent an advantage (Reimund *et al.*, 2004b; Thomas-Gibson *et al.*, 2004), but should be tested through large multicentre trials. Reducing as much as possible the HPN regimen, i.e. the number of cycles per week and the quantity of each cycle (Messing *et al.*, 1999), implies maximal use of enteral feeding and optimal treatment of the underlying disease which led to intestinal failure.

For SBS, dietetic advice and optimization of absorption now includes, beside usual gastroenterological medications, indications for growth hormone and bowel reconstruction (see Chapters). In most cases, HPN is just complementary, but complete, individualized feeding avoiding both excess and deficits of minerals and micronutrients.

Supplementation by α-tocopherol according to IV PUFA (cf. above) and reduction of trace metals when cholestasis is present (Howard and Ashley, 2003) should not be omitted. Adjustment to both IV supply and remnant gut absorption, depending on the aetiology of the intestinal failure, is beyond the scope of this review.

However, it can be stated that there is no documented carnitine deficiency during long-term HPN (Bowyer *et al.*, 1988, 1989; Messing *et al.*, 1999), and therefore no obvious benefit from using MCT-enriched IV lipids for increasing oxidation during HPN in unstressed, stable patients – with the exception being that in cases due to underlying diseases such as the following: (i) CIPO due to mitochondrial cytopathies; (ii) severe renal insufficiency; and (iii) cirrhosis (Goulet *et al.*, 1992; Richelle *et al.*, 1993).

Future Developments

The natural history (Cavicchi *et al.*, 2000) and main contributing factors – nutrition- and patient-related – of HPNALD have been described. These suggested factors act in combination rather than as isolated factors. Intervention-controlled studies, at a multicentre level, need to be performed to establish the primary prophylaxis of HPNALD through choleretic treatment, in association with new IV fat sources at an appropriate level, plus antiperoxidative treatment such as α-tocopherol and other supplementation.

These therapeutic long-term trials, difficult to inaugurate, have to be decided upon as soon as possible through expert consensus in order to

implement them on an international level in centres managing all the facets of intestinal failure treatment (Buchman *et al.*, 2003). The main goal is to reduce SLD to a minimum; this still remains too frequent, as illustrated by the large number of combined liver/intestinal transplants described in the last report of the international transplant registry, i.e. 50 and 51% in children and adults, respectively (Grant *et al.*, 2005).

Summary

HPNALD can be reduced to less than 20% after 5 years of HPN for intestinal failure (Cavicchi *et al.*, 2000). HPN need to be tailored, from the outset, to each single patient deemed to be dependent on HPN for more than 6 months. Presently, industrial nutritive mixtures do not fulfil that goal, mainly because the IV lipid load is too high. To prevent HPNALD, optimized HPN and optimized disease treatments are the two sides of the same coin, because minimal PN dependency is one way of avoiding excess delivery of IV macronutient infusion within each complete PN cycle.

It is also necessary to focus on perfect nursing care in order to obtain complete autonomy of patients in managing the PN infusion cycle; indeed, reducing the rate of line sepsis can be achieved through patient autonomy (Nahon *et al.*, 1997). It is therefore a pity that a recent European survey (Van Gossum *et al.*, 2001) indicates that complete education of patients is poorer now than in the past (Messing *et al.*, 1988). Indeed, line sepsis control is as important as any other physiopathological contributing factor of HPNALD.

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14 Metabolic Bone Disease in Long-term HPN in Adults

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Key points

- Metabolic bone disease (MBD) characterized by bone pain and fractures, osteopenia or osteoporosis at bone densitometry and by osteoporosis or osteomalacia at bone histology is present in almost all patients on home parenteral nutrition (HPN) for benign intestinal failure.
- In most of these cases, the disease is present before starting HPN, whereas long-term HPN is not necessarily associated with a worsening of bone structure.
- The pathogenesis of bone disease may be multifactorial: (i) general factors, such as ageing and post-menopausal status, and (ii) factors related to the underlying disease play the major pathogenetic role, but an unbalanced HPN formula may be involved too.
- Diagnosis and monitoring rely on bone mineral density assessment and the evaluation of biochemical markers of bone turnover, which should be performed at the outset of HPN and at yearly intervals.
- Prevention and treatment are based on lifestyle and dietary recommendations, active treatment of the underlying disease-related factors and on optimization of the composition of the parenteral infusion. Bisphosphonates may prevent further bone demineralization.

Introduction

Patients on long-term home parenteral nutrition (HPN) often present with a metabolic bone disease (MBD). (Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000). In most cases MBD is due to general factors, such as ageing and post-menopausal status, or to factors

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related to the patient's underlying disease (HPN-associated MBD) already present before the patient enters the HPN programme (Bjarnason *et al*., 1997; Schulte *et al*., 2000; Haderslev *et al*., 2003). However, accelerated bone loss has been reported during HPN therapy, raising the question of the specific role of HPN-related factors in the pathogenesis of MBD (HPN-related MBD) (Foldes *et al*., 1990; Klein and Coburn, 1991; Verhage *et al*., 1995).

Epidemiology

Studies of bone histology or bone mineral density (BMD) carried out in individual centres and including small populations showed the presence of MBD in 40–100% of patients (Shike *et al*., 1980; De Vernejoul *et al*., 1985; Shike *et al*., 1986; Lipkin *et al*., 1987, 1990; Goodman *et al*., 2000).

A multicentre, cross-sectional survey (Pironi *et al*., 2002) on 165 HPN patients evaluated the prevalence of MBD by dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and femoral neck. A BMD T-score (number of standard deviations (SD) below the mean BMD of young subjects) value < -1 was observed in 84% of patients. In 41%, the BMD T-score was < -2.5, which is a condition defined as osteoporosis according to the World Health Organization diagnostic criteria (WHO, 1994). Also, the BMD Z-score (number of SD from the normal BMD value corrected for sex and age) was measured and was < -1 in 62% (< -2 in 31%).

The incidence of MBD is unknown. Both earlier longitudinal studies, including small patient groups (Foldes *et al*., 1990; Klein and Coburn, 1991; Saitta *et al*., 1993) and recent follow-ups on large patient populations (Cohen-Solal *et al*., 2003; Haderslev *et al*., 2004; Pironi *et al*., 2004), showed that long-term HPN was not necessarily associated with a worsening of bone health, and in some cases an improvement could occur.

Cohen-Solal *et al*. (2003) studied a cohort of 88 patients, of whom 56 entered a follow-up study. At both lumbar spine and femoral neck, the baseline BMD Z-score was positively associated with: (i) age at diagnosis of intestinal failure (lower Z-score in younger patients), which may have occurred several years before starting HPN; and (ii) with body mass index (higher Z-score with higher BMI). During the follow-up the changes in Z-score were dependent on the age when intestinal failure had occurred and on the duration of HPN, with a synergistic effect between them (the older the patient, the higher the increase in Z-score during HPN). At the femoral neck, there was no significant change in the Z-score during long-term HPN.

Haderslev *et al*. (2004) performed a subsequent study on a cohort of 75 patients. The estimated spinal and hip BMD Z-scores at the commencement of HPN were lower than normal in patients with Crohn's disease but not in patients with non-Crohn's disease. During the follow-up, the decrease in both the lumbar spine and femoral neck BMD Z-scores did not change significantly in comparison to healthy subjects in both disease groups, although the decline in BMD was significantly higher in non-

Crohn's disease patients. Regarding the individual trends over time in BMD, Crohn's disease patients might even evidence improved bone mineral density during HPN treatment. It is noteworthy that the Crohn's disease group was younger, and had a lower percentage of females as well as post-menopausal females compared to the non-Crohn's group.

Pironi *et al*. (2004) carried out a multicentre longitudinal study on 65 patients. At both lumbar spine and femoral neck the baseline BMD Z-score was positively associated with age at the commencement of HPN (lower Z-score in younger patients). During the follow-up, the BMD Z-score increased at spine and remained stable at hip. The variations of Z-score at spine were negatively associated with female sex and with age at commencement of HPN (the older the patient the greater the decrease in BMD).

The follow-up studies including large numbers of HPN patients also analysed the relationship between the BMD Z-score changes and the characteristics of the HPN programme (nutrient content, time schedule), but no statistically significant association was observed. It is suggested that, with the current practice of HPN programmes, the annual change of BMD variation is no greater than in age- and sex-matched healthy subjects, and that a considerable part of MBD variation is related to the patient's sex and age at the commencement of HPN or at the onset of intestinal failure, as well as to factors related to the underlying disease. These results do not rule out the risk of BMD decrease primarily due to HPN in the individual patient. This may be the case with non-appropriate and/or unbalanced HPN formulas (Klein and Coburn, 1991), as well as the way in which the patient reacts to HPN-related factors interfering with bone metabolism (Schulte *et al*., 2000).

Clinical Features

MBD in long-term HPN may be characterized by asymptomatic osteopenia, bone pain localized mainly at the spine and lower joints or by bone fractures which occur with no or minimal trauma. A prevalence study (Pironi *et al*., 2002) showed that, during the course of HPN, bone pain occurred in 35% of patients (mainly at the spine, knee, hip, ankle, feet and hands) and bone fractures in 10% (spine, rib and hip), which were associated with the lowest values of T- and Z-scores. MBD may have a negative impact on the patients' rehabilitation status which may otherwise be achieved partly or totally by about two-thirds of patients (Van Gossum *et al.*, 2001; Pironi *et al.*, 2003).

Histology

Histomorphometric studies showed the presence of either osteomalacia (Klein *et al*., 1980; Shike *et al*., 1980; Lipkin *et al*., 1987; Saitta *et al*., 1993;

Goodman *et al*., 2000) or osteoporosis (De Vernejoul *et al*., 1985; Shike *et al*., 1986; Lipkin *et al*., 1987; Saitta *et al*., 1993; Goodman *et al*., 2000). Osteomalacia is characterized by defective mineralization and increased osteoid, which is the unmineralized bone matrix. Osteoporosis is characterized by an equal reduction in bone mineral and bone matrix, so that bone is decreased in amount but is of normal composition (Kanis, 2002).

The analysis of the dynamic histomorphometric indexes showed a low bone formation rate in most of the patients (Klein *et al*., 1980; Shike *et al*., 1980; De Vernejoul *et al*., 1985; Lipkin *et al*., 1987; Saitta *et al*., 1993; Goodman *et al*., 2000; Kanis, 2002). Increased bone turnover (Shike *et al*., 1986; Lipkin *et al*., 1987) or defective mineralization (Shike *et al*., 1980) was also reported.

Low bone turnover seems characteristic of HPN-associated MBD. In the solitary follow-up observation performed by bone histology, a group of patients was studied after both a few months of HPN and 6–12 months later (Shike *et al*., 1980). Bone histomorphometry showed – in most of the patients – the feature of hyperkinetic bone turnover at the first assessment, which evolved later into a low rate of bone formation. It has been demonstrated that in patients on HPN too, serum osteocalcin (OC), a biochemical marker of bone formation rate, significantly correlates with the bone formation rate measured by histomorphometry (Lipkin *et al*., 1990).

In an observation using serum OC and urinary pyridinium cross-links as markers of bone resorption, data consistent with the early results by bone histomorphometry were obtained (Pironi *et al*., 2000). Patients who were at the beginning of the treatment showed high concentrations of serum OC and of urinary cross-links, suggesting hyperkinetic turnover. During HPN low, or low-normal, OC concentrations were observed, consistent with the presence of a low bone formation rate.

Pathogenesis

The pathogenesis of MBD associated with HPN is multifactorial (Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000), (Box 14.1). General factors and lifestyle-related factors such as age, menopause, alcohol and tobacco abuse may be involved.

Underlying disease-related factors may also play a role, such as: (i) malabsorption of calcium and vitamin D; (ii) calcium losses in the gut lumen; (iii) chronic inflammation (increased bone resorption by tumour necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6) and prostaglandin E2; (iv) decreased bone formation by TNF and IL-6; and (v) drugs, such as chronic corticosteroid administration.

Patients with a short bowel may develop a metabolic acidosis due to the diarrhoea-induced losses of bicarbonate. Some patients may have a d-lactic acidosis due to bacterial overgrowth syndrome. The underlying disease

may also be responsible for the development of malnutrition; reduced physical activity and lower sunlight exposure can also have a negative impact on bone mineralization.

Several hypotheses have been advanced about the HPN-related factors. Aluminium overload was the first one. In the 1970s the amino acid solutions derived from caseine hydrolysis were highly contaminated with aluminium (Klein *et al*., 1991). The feature was that of high serum concentration and high urinary excretion of aluminium associated with osteomalacia, positive aluminium staining in bone, hypercalciuria and low serum concentrations of both parathyroid hormone PTH and 1,25-dihydroxyvitamin D (Klein *et al*., 1980; Ott *et al*., 1980). This feature was reversible by replacing casein hydrolysate with crystalline amino acid solutions, which contain negligible quantities of the metal (Vargas *et al*., 1988).

Aluminium overload causes the accumulation of the metal at the mineralization zone of bone, thus impairing bone mineralization. Furthermore, aluminium reduces the parathyroid gland's secretion of PTH, thus impairing the physiological activity of stimulating bone formation. Aluminium may block the enzymatic conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the specific renal enzyme (Klein, 1995). Nowadays caseine hydrolysate solutions are no longer produced, but it must be observed that other nutrient solutions currently used in PN formulations still may be contaminated with aluminium, such as phosphate salts, calcium gluconate, vitamins and trace metal solutions (Klein, 1995).

High serum aluminium concentrations may still be observed (De Vernejoul *et al*., 1985; Advenier *et al*., 2003). Even though high serum aluminium may not necessarily be associated with positive aluminium staining in bone histology (De Vernejoul *et al*., 1985), it should be avoided because *in vitro* studies have showed that aluminium may directly inhibit proliferation of osteoblasts (Klein, 1995).

The hypothesis of vitamin D poisoning has been advanced on the basis of a few studies from the same research group. In the first one (Shike *et al*., 1981) it was observed that after a 6-month withdrawal of intravenous vitamin D there was a decrease in un-mineralized bone matrix and an increase in the bone mineralization rate in bone histology associated with the normalization of serum 1,25-dihydroxyvitamin D and PTH concentrations, which were lower than normal before the withdrawal. The second was a follow-up study in a group of patients on long-term HPN who had osteopenia associated with low PTH and 1,25-dihydroxyvitamin D serum concentrations (Verhage *et al*., 1995).

After 4.5-year withdrawal of intravenous vitamin D, BMD at lumbar spine increased, serum 1,25-dihydroxyvitamin D and PTH concentrations normalized. However, BMD did not change at the femoral neck and significantly decreased at Ward's Triangle, equalling the increase in spinal BMD. It has been suggested that the daily intravenous infusion of 25-hydroxivitamin D amounts – equal to the RDA for adult healthy people – may impair PTH secretion. Consequently, there would be a lack of its

physiological actions such as bone mineralization and 1,25-dihydroxyvitamin D synthesis, which had recovered after vitamin D withdrawal.

Several cross-sectional studies have shown a positive correlation between renal calcium loss and the amount of infused amino acids, glucose, sodium and calcium with the PN solution, which could result in a PN-induced hypercalciuria (Klein and Coburn, 1991). On the contrary, urinary calcium was negatively correlated with intravenous phosphate load, which appears to enhance calcium reabsorption by the renal tubules independently of PTH (Klein and Coburn, 1991; Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000).

Calciuria is greater with cyclic infusion than with continuous infusion (Klein and Coburn, 1991). Furthermore, metabolic acidosis, due to titratable acids produced mainly by the metabolism of neutral and sulphur-containing amino acid, can induce bone calcium reabsorption (Klein and Coburn, 1991; Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000).

The exact mechanisms for HPN-induced hypercalciuria have not been completely clarified. Both increased the glomerular filtration rate (IV fluids, calcium and sodium, metabolic acidosis) and decreased reabsorption by the renal tubules (excessive IV amino acids, glucose and calcium and low IV phosphate) (Klein and Coburn, 1991). High urinary calcium excretion is a frequent finding in patients on HPN (Klein *et al*., 1980; Shike *et al*., 1980, 1986; De Vernejoul *et al*., 1985; Lipkin *et al*., 1987; Saitta *et al*., 1993), even though some human studies suggested that during HPN adaptation occurs allowing a reduction of renal calcium losses (Lipkin *et al*., 1988).

In a non-human primate model of parenteral nutrition (Lipkin, 1998), calciuria in response to parenteral nutrition was elevated initially but decreased after 2 weeks of therapy. Hypercalciuria was due to an increased urine-filtered calcium load. The decrease of calciuria with time was associated with a decrease in the calcium filtration fraction, an index which inversely mirrors the renal tubular reabsorption of calcium. The decrease of calciuria was associated with the increase of serum PTH concentration, suggesting that adaptations may occur with time in parenteral nutrition therapy which result in calcium conservation, including a diminished filtered calcium load and increased PTH secretion.

Urinary calcium excretion can be reduced by increasing inorganic phosphorus content of the parenteral solution. The decreases in urinary calcium excretion seem to be due to an increase in renal tubular calcium reabsorption by the direct action of inorganic phosphorus on the renal tubules (Wood *et al*., 1986; Berkelhammer *et al*., 1998).

The development of an altered response to PTH is a more recent hypothesis. Parenteral nutrition might alter the balance of the effect of PTH on bone between resorption and formation in the direction of resorption (Jeejeebhoy, 1998; Whitfield *et al*., 1999).

A study on diurnal regulation of serum calcium and PTH concentrations during HPN showed that patients on long-term HPN had abnormal

parathyroid gland function and mild secondary hyperparathyroidism (Goodman *et al*., 2000). The nocturnal infusion of HPN solutions containing calcium disrupted the normal diurnal variations in serum calcium and PTH concentrations. The authors suggested that long-term HPN would increase the regularity of PTH secretion, together with moderate but persistent elevations in serum PTH concentrations. These might lower the PTH/PTH-related peptide receptor expression and diminish the response to physiological blood concentrations of PTH in target tissues. This would imply a reduced bone formation and turnover and a reduced renal calcium reabsorption (Jeejeebhoy, 1998; Whitfield *et al*., 1999).

HPN-related MBD may be due to the development of deficiency or toxicity of micronutrients known to interfere with bone metabolism (Shike *et al*., 1986; Lipkin *et al*., 1987; Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000). This is the case for vitamin K, vitamin C, copper, fluoride, boron and silicon deficiencies and for vitamin A, cadmium, strontium and vanadium toxicities. However, no consistent data have yet been provided on the relationship between MBD and the content of these nutrients and toxins in patients on long-term HPN.

Finally, a direct role of HPN in inducing the release and/or regulating the activity of cytokines known to impair bone metabolism has been suggested (Jeejeebhoy, 1998). Animal studies have shown that parenteral nutrition enhances the catabolic effects of tumour necrosis factor (TNF-a, Matsui *et al*., 1993). Increased serum and urine concentrations of IL-6 and soluble TNF receptor II, not associated with clinical and biochemical signs of inflammation, were observed in patients on long-term HPN (Ling *et al*., 2001). Increased mRNA expression for inflammatory cytokines (IL-1, IL-6, TNF-a) in the intestine of parenterally fed rats has been demonstrated (Ogle *et al*., 1995).

Diagnosis

The diagnosis of MBD relies on: (i) bone densitometry, both for the definition of the degree of bone demineralization at commencement of HPN as well as for its evolution during the treatment; and (ii) on biochemical parameters, for the assessment of bone turnover and investigation of the potential pathogenetic mechanism. Bone densitometry measures BMD, independently of the presence of osteomalacia or osteoporosis. When a differential diagnosis is needed, bone histology is mandatory. Investigations concerning the general and lifestyle pathogenetic factors and the underlying disease-dependent factor(s) must also be performed to classify the MBD as HPN-associated or HPN-related.

Table 14.1 shows the instrumental and biochemical parameters for the diagnosis of BMD and the timing of measurement for each parameter. DEXA is considered the gold standard and currently the preferred method for the measurement of BMD. Assessment is usually made at the lumbar spine and/or hip and the result is expressed as the number of

Box 14.1. Pathogenesis of metabolic bone disease in patients on long-term home parenteral nutrition.

General and lifestyle factors

- Ageing
- Female gender and physiological menopause
- Alcohol and tobacco abuse

Underlying disease-related factors

- Malabsorption and intestinal losses of nutrients (calcium, magnesium, vitamin D)
- Protein calorie malnutrition
- Chronic inflammation
- Metabolic acidosis
- Reduced physical activity
- Reduced sunlight exposure
- Secondary oestrogen or androgen deficiency (through drugs, surgery or malnutrition)
- Drugs (corticosteroids, immunosuppressants, loop diuretics, long-term anti-coagulation with heparin or warfarin)

HPN-related factors

- Aluminium poisoning[a]
- Vitamin D poisoning[b]
- Hypercalciuria due to IV nutrient loads (excess of amino acids, calcium, sodium, glucose; deficiency of phosphate; non-appropriate Ca:P molar ratio in the PN solution; excess of fluids)[c]
- Impaired PTH secretion/function[d]
- Micronutrient deficiency or toxicity (vitamins C, K, zinc, copper, fluoride, boron and silicon deficiencies; vitamin A, cadmium and strontium toxicities)[e]
- HPN-induced pro-inflammatory cytokine[f]

[a] Aluminium poisoning proved for amino acid solutions derived from casein hydrolysate; not reported with the current crystalline amino acid solutions.
[b] Vitamin D poisoning supported by only two studies from the same HPN centre.
[c] Hypercalciuria due to IV nutrient loads; demonstrated by cross-sectional studies.
[d] Impaired PTH secretion/function: hypothesized in one study.
[e] Micronutrient deficiency or toxicity; only hypothesized, no studies.
[f] HPN-induced pro-inflammatory cytokine; only hypothesized, no studies.

standard deviations from mean BMD value of: (i) young adult reference mean (T-score); and (ii) age- and sex-matched healthy subjects (Z-score).

The WHO Study Group (1994) defined the severity of MBD as osteopenia or osteoporosis on the basis of the T-score value. The relative risk of any fracture has been estimated to be 1.4–1.6 for every decrease in BMD of 1 SD below the BMD Z-score (Kanis, 2002). The WHO's diagnostic categories of BMD and the degree of fracture risk were established for post-menopausal women in whom osteoporosis is by far the most common bone disease. Epidemiological studies suggest a predictive value of BMD for the assessment of fracture risk in HPN patients too (Pironi *et al*., 2002).

Biochemical assessment of MBD requires measurement of the following: (i) serum concentrations and 24-h urinary excretion of minerals (Ca, P, Mg); (ii) serum concentrations (and/or urinary excretion) of biochemical markers of bone turnover (Calvo *et al*., 1996); and (iii) serum PTH, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations. Serum aluminium concentrations should also be measured in patients with a pathologic BMD T-score.

Treatment and Prevention

Prevention and treatment depend upon the potential pathogenetic mechanisms (Table 14.2). Patients should be advised to have regular physical exercise and sunlight exposure, to stop smoking and to limit alcohol consumption. Normal weight should be reached and maintained. Dairy foods should not be forbidden unless contraindicated by the underlying intestinal failure condition.

No study concerning oestrogen replacement therapy in post-menopausal women – or on other hormone therapies such as testosterone and anabolic hormones – has been performed in patients on HPN. The indication and the usefulness of these medications must be evaluated in the single patient, also taking into account the associated risks of deep vein thrombosis and breast cancer.

Underlying disease-related factors must be strictly controlled, by treating inflammation and minimizing the dosage of bone-damaging drugs. Oral calcium and magnesium supplementation should be prescribed whenever possible. Acid–base balance may be maintained by preventing d-lactic acidosis, giving oral bicarbonate supplementation and optimizing the parenteral nutrition infusion.

Prevention of MBD related to HPN factors is based on the optimization of the parenteral infusion. Aluminium contamination should be < 25 mg/l (Klein, 1995). The mineral levels should be aimed at maintaining normal serum concentrations and 24-h urinary excretion. Particular attention must be paid to the Ca:P ratio in the infusion (Wood *et al*., 1986; Berkelhammer *et al*., 1998), even thought the optimal ratio cannot be always achieved because of problems of stability in the mixture.

Amino acids and sodium should not be added in amounts greater than losses because of the risk of sodium-induced hypercalciuria (Klein and Coburn, 1991). Acetates are useful in avoiding acidosis and in maintaining serum bicarbonate in the normal range. However, it must be considered that *in vitro* studies showed that large quantities of acetate may inhibit osteoblast activity (Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000).

The recommended IV vitamin D for adults is 200 IU/day (Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000). Normal vitamin D nutritional status is represented by normal serum concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. Vitamin D

Table 14.1. Instrumental and biochemical parameters for the diagnosis and follow-up of metabolic bone disease (MBD).

Parameter	Frequency of measurement
Bone mineral density Method: by dual-energy X-ray absorptiometry (DEXA) at lumbar spine (trabecular bone) and at femoral neck (cortical bone) Diagnosis: WHO diagnostic criteria: T-score (No. of Standard Deviations below mean BMD of young subjects); > –1.0 = normal; –1.0 to –2.5 = osteopenia; ≤ –2.5 = osteoporosis Follow-up: Z-score (No. of SD from normal BMD values corrected for sex and age); > –1.0 = normal; –1.0 to –2.0 = reduced; ≤ –2.0 = severely reduced	At commencement of HPN, then yearly
Bone biopsy after double tetracycline labelling	In cases of doubtful diagnosis between osteomalacia and osteoporosis
Markers of bone turnover Formation: serum Osteocalcin	Stable patient: yearly
Resorption: serum cross-laps or urinary cross-links of bone collagen	Additional measurements in cases of: (i) bone pain appearance; (ii) change in the metabolic and the clinical features; (iii) treatment with bone-damaging drugs
Serum and 24-h urinary excretion of Ca, Mg and P	Stable patient: every 4 months Additional measurements as for markers of bone turnover
Plasma intact parathyroid hormone (PTH 1-84)	Stable patient: yearly Additional measurements as for markers of bone turnover
Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D	Stable patient: yearly Additional measurements as for markers of bone turnover
Serum aluminium	In case of pathologic bone mineral density, T-score
Other nutrients potentially involved in MBD in HPN patients	Measurements according to the clinical suspicion

stimulates intestinal absorption of calcium, phosphorus and magnesium and has a key role in the regulation of bone turnover (Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000).

However, excess of vitamin D should be avoided because it may result in net bone resorption, and thus in bone demineralization (Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000). Patients with low BMD, low serum PTH, low serum 1,25-dihydroxyvitamin D concentrations

and normal 25-hydroxyvitamin D might be considered candidates for vitamin D withdrawal (Verhage *et al*., 1995).

No data have yet been provided on the optimal glucose:lipid ratio as non-protein calories in the parenteral solution. Finally, in some patients, slowing the infusion rate may reduce hypercalciuria (Klein and Coburn, 1991).

Drug therapy may be useful for the prevention and treatment of MBD in HPN patients, but to date only one randomized controlled study on bisphosphonates has been carried out in patients on HPN (Haderslev *et al*., 2002b). Intravenous clodronate was able to decrease the urinary excretion of markers of bone resorption and to contain BMD at the lumbar spine in patients on HPN after 12 months, but no significant increase in BMD was observed.

Only anecdotal reports or no data have been provided on therapy with calcitonin, PTH, fluoride and vitamin K in HPN patients (Koo, 1992; Buchman and Moukarzel, 2000; Seidner and Licata, 2000). Recent controlled studies have shown a role for growth hormone and glucagon-like peptide-2 as intestinotrophic drugs in stimulating intestinal adaptation in short bowel patients on HPN. Preliminary reports suggest that these drugs may also improve BMD (Haderslev *et al*., 2002a; Mauras *et al*., 2002).

Future Developments

MBD in patients on long-term HPN is a challenging issue for the clinician. Many aspects of both the pathogenesis and the treatment still need to be clarified. Future studies should investigate the impact of long-term cyclical intravenous nutrition on bone-regulating hormones as well as the optimal dosages of vitamin D and minerals. In contrast to the high frequency of the disease, the number of studies addressing the pharmacological therapy (timing, drugs, etc.) has been negligible. The potential role of PTH and intestinotrophic hormones – as well as new bisphosphonates – needs to be assessed by randomized studies.

Summary

Patients on long-term HPN are at risk of developing metabolic bone disease (MBD), with a significant reduction in bone mineral density (BMD) and osteoporosis in about 50% of cases. MBD is often asymptomatic. Bone pain, mainly at the spine and lower joints, has been reported in one-third of patients and bone fractures in one-tenth. In most of these cases, MBD is due to general factors such as ageing and post-menopausal status, or to causes related to the patient's underlying illness (HPN-associated MBD), which are already present before commencement of the HPN programme.

Follow-up studies indicate that long-term HPN is not necessarily

Table 14.2. Prevention and treatment of metabolic bone disease in patients on long-term home parenteral nutrition (HPN).

Intervention	Comments
General and lifestyle	
Encourage regular exercise (home-based, low-impact exercise programme)	
Encourage regular and adequate sunlight exposure	
Maintain normal protein/calorie nutritional status	
Diet rich in dairy food	If not contraindicated by the underlying intestinal functions
Avoid cigarette smoking and limit alcohol intake	
Oestrogen replacement therapy in peri-menopausal and post-menopausal period	No study in terms of HPN
Underlying disease factors	
Treat inflammatory conditions	
Use as low as possible dosage of bone-damaging drugs	Oral calcium and vitamin D supplementation may counteract corticosteroid effects
Maintain acid–base balance	Oral sodium bicarbonate supplementation in chronic diarrhoea Prevention of D-lactic acidosis (bacterial over growth)
Oral calcium supplementation	500–1000 mg twice daily
Oral magnesium supplementation	Magnesium oxide 12–24 mmol daily
Nutrients in the parenteral nutrition solution	
Fluids and sodium	Na: amounts not greater than losses, in order to avoid Na-induced hypercalciuria Fluids: as required to maintain balance; infusion rate: in some patients slowing the infusion rate may reduce hypercalciuria
Minerals	Daily amounts to maintain balance in adult patients are within wide ranges Mg: 4–12 mmol; Ca: 4.5–11 mmol; P: 15–30 mmol; Ca:P ratio: 1 meq Ca:2 mmol P (beware risk of formation of calcium phosphate crystals in the solution)
Acetate	As required to avoid acidosis and to maintain serum bicarbonate in the normal range (160 mmol/day is appropriate for most patients)
Amino acids	Not to exceed the patient's needs, in order to avoid Na-induced hypercalciuria (1.5 g/kg/day is appropriate for most patients)

Continued

Table 14.2. *Continued*

Intervention	Comments
Glucose and glucose:lipid ratio	No data in terms of HPN
Vitamin D	Recommended daily infusion for adults: 200 IU/day HPN infusion < 1 per day: oral, IM or IV vitamin D supplementation to maintain normal serum 1,25-dihydroxyvitamin D and 25-hydroxy-vitamin D concentrations Excess vitamin D: risk of bone demineralization Patients with low BMD, low serum PTH and 1,25-dihydroxyvitamin D concentrations associated with normal 25-hydroxyvitamin D: consider for vitamin D withdrawal
Vitamin K	As required to maintain normal prothrombin time; if required, 1 mg/day including that found in lipid emulsion
Aluminium	< 25 μg/l
Drugs	
Bisphosphonates	Clodronate: 1500 mg IV every 3 months (one RCT study) Pamidronate: 30–60 mg IM/month or 90 mg IV every 3–6 months (anecdotal reports only)
Calcitonin	No study in terms of HPN (anecdotal reports only)
Testosterone	No study in terms of HPN
Anabolic steroids	No study in terms of HPN
PTH	No study in terms of HPN
Fluoride	No study in terms of HPN

associated with a worsening of bone health and in some cases an improvement occurs. Nevertheless, accelerated bone loss may occur during HPN therapy, raising the question of a specific role of HPN in the pathogenesis of MBD (HPN-related MBD).

Hypercalciuria due to the following factors: (i) IV nutrient loads (excess of amino acids, calcium, sodium, glucose; deficiency of phosphate; (ii) non-appropriate Ca:P molar ratio in the PN solution (excessive volumes of fluids); (iii) IV vitamin D poisoning; (iv) micronutrient deficiency or toxicity (vitamin K, vitamin C, zinc, copper, fluoride, boron or silicon deficiency; vitamin A, cadmium, aluminium or strontium toxicity); and (v) HPN-induced impaired PTH secretion/function and/or secretion of pro-inflammatory cytokines are the suggested HPN-related pathogenetic factors.

Diagnosis and monitoring rely on BMD and assessment of biochemical markers of bone turnover; this should be performed when commencing

HPN, then yearly if patients remain in stable condition. The bone turnover should also be evaluated if long-lasting changes in the clinical condition occur.

Prevention and treatment are based on lifestyle and dietary recommendations, active treatment of the underlying disease-related factors and on optimization of the parenteral infusion. A few studies have shown that IV bisphosphonates may prevent further bone demineralization in patients on HPN. No studies with other drugs for osteoporosis have been carried out on these patients.

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15 Metabolic and Other Rare Complications of HPN

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Key points

- Rare complications are reviewed, including: (i) renal dysfunction; (ii) chromium toxicity and deficiency; (iii) aluminium toxicity; and (iv) manganese toxicity.
- The acceptable level for aluminium is < 4–5 μg/kg/day.
- Pathogenesis of hyperoxaluria is discussed and the suggested dose of ascorbic acid was set at 100–200 mg/day.
- Cardiopulmonary complications from precipitated crystals are considered.

Introduction

The administration of home parenteral nutrition (HPN) has long been known to carry the risk for potential side effects or complications. Metabolic bone disease, hepatobiliary dysfunction and catheter-related complications are by far the most commonly seen unwanted consequences of HPN. A body of literature does exist reporting less frequently seen complications, which can still be equally damaging – particularly when not recognized. This chapter shall review these more rare complications of HPN, including renal and other metabolic derangements which are known to occur.

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Renal Dysfunction

Though bone and liver disease are frequently cited complications of long-term HPN therapy, renal dysfunction associated with HPN also presents a challenging problem. HPN-associated nephropathy has been one of the more recently described phenomena seen in patients on longer-term HPN, though progression to end-stage renal disease has not been clearly established. Indeed, in one study the change in glomerular filtration rate, measured as creatinine clearance (CrCl) of 33 long-term HPN patients was evaluated prospectively (Buchman *et al*., 1993). Among the 33 patients, CrCl declined by 3.5% ± 6.3% per year ($P = 0.004$), a greater reduction than would have been expected from increasing age alone.

Furthermore, tubular function, measured by tubular reabsorption of phosphate, was shown in the same study to be abnormal in 52% of the subjects (Buchman *et al*., 1993). This finding, however, was not corroborated by a similar later study in children (Moukarzel *et al*., 1991). Buchman *et al*. went on to note that TPN-associated nephropathy in the adult study was not explained fully by increasing patient age, change in nutritional status, HPN duration, use of nephrotoxic medications, number of bacteraemia/fungaemia episodes, infection rate or intravenous protein load (Buchman *et al*., 1993).

Another study assessed renal function, measured by multiple parameters including glomerular filtration rate (GFR) and excretion of various electrolytes, during the periods before and during nocturnal administration of parenteral nutrition (PN) in 16 patients with short bowel syndrome (SBS). Nine patients had decreased GFR. While a statistically significantly increased level of urinary volume and electrolyte excretion occurred during the nocturnal phase of PN, some patients demonstrated hypercalciuria. This study, however, did not elucidate the mechanism by which renal impairment had occurred in these patients (Boncompain-Gerard *et al*., 2000). Indeed, the exact aetiology for the decline in CrCl and tubular function is still not fully understood, but more than likely is multifactorial in nature.

A particular challenge is presented by the critically ill patient requiring continuous renal replacement therapy (CRRT). While arguments for 'overfeeding' versus 'underfeeding' the acutely critically ill patient continue, it is clear that determination of the nutritional needs for critically ill CRRT patients can be more difficult than initially thought. CRRT adds another variable to an already complicated equation for estimating a patient's caloric needs; dialysis has no ability to continually adjust the ability to filter, concentrate, dilute and absorb.

Scheinkestel *et al*. documented that patients who required continuous renal replacement therapy might exhibit markedly abnormal amino acid profiles (Scheinkestel *et al*., 2003). These investigators found that when such patients were provided with protein loads < 2.5 g/kg/day, their amino acid profiles remained markedly abnormal. These profiles subsequently normalized with an increase of protein loads to at least 2.5 g/kg/day, and

nitrogen balances became positive at even higher protein loads. Increased protein intake, however, has been associated with hypercalciuria, which may increase the risk for development of metabolic bone disease (Bengoa *et al.*, 1983)

Toxicities of Heavy Metals and other Electrolytes

Other potential factors in HPN-associated nephropathy include the possible role of heavy metal contamination of HPN solutions. Theoretically, heavy metals found in HPN solutions could deposit in various organs, including the liver, brain and kidneys.

Chromium

In a rat TPN model, significant chromium deposition occurred in the kidney, and histologic abnormalities were also noted (Buchman *et al.*, 2001). These findings appeared to confirm prior investigations which suggested that intravenously administered chromium was deposited primarily in the kidneys and liver (Tsapakos *et al.*, 1983).

Despite correlation between the level of contamination and histologic abnormalities, there was no clear relationship with changes in creatinine. Measurements of changes in serum creatinine alone, however, may not be a sensitive indicator for changes in renal function. Although one prior study did not show that excessive chromium infusion in adults was associated with diminished renal function (Buchman *et al.*, 1992, 1993), other studies in children have shown a significant negative relationship between the amount of chromium infusion, serum chromium concentration and a decline in GFR. Furthermore, these findings may be irreversible as GFR did not improve when chromium was removed from the TPN (Moukarzel *et al.*, 1992).

Chromium is primarily found in a trivalent or hexavalent form, and these are the two forms most likely to be associated with histological derangements of the kidney or liver (Baines, 1965; Tandon *et al.*, 1978). During chromium toxicity, the proximal tubules and glomeruli are most commonly damaged, and the degree of injury appears to be proportional to the level of chromium deposition (Buchman *et al.*, 2001). Indeed, prior investigations have shown significantly elevated serum chromium concentrations in patients found to have long-term, HPN-associated nephropathy (Moukarzel *et al.*, 1991, 1992).

The possibility of chromium deficiency during long-term TPN has also been raised. Several case reports describe neurologic deficits confirmed by nerve conduction studies that appeared to be associated with chromium deficiency and resolved with chromium supplementation (Jeejeebhoy *et al.*, 1977). Another case report described similar neurologic deficits in the setting of long-term HPN, as well as glucose intolerance. This patient had

normal serum chromium concentrations, but he experienced normalization of his symptoms and nerve conduction studies following a 2-week course of daily infusions of 250 μg of trivalent chromium (Verhage *et al*., 1996)

It has recently become apparent that chromium can play a significant role in the maintenance of euglycaemia, particularly in diabetic patients (Morris *et al*., 1999). Normal insulin function depends, in part, on the trivalent form of chromium. Additionally, it has been shown that high serum glucose levels can lead to increased urinary chromium excretion (Ravina *et al*., 1999). Wongseelashote *et al.* recently reported a small case series of patients with normal renal function receiving HPN as their sole nutrition who all required > 20 units of insulin to maintain euglycaemia. They found that insulin requirements could be reduced in some patients by chromium supplementation (Wongseelashote *et al*., 2004). The requirement of chromium in HPN, however, has not been clearly established.

Oxalate

Hyperoxaluria is another long-known phenomenon associated with the administration of HPN. In general, hyperoxaluria results from one of two possible mechanisms: (i) increased enteral absorption secondary to intestinal disease and increased permeability (perhaps related to colonic absorption); or (ii) synthesis of oxalate from increased levels of a precursor (Swartz *et al*., 1984). With respect to the latter, if ileal absorption of bile salts conjugated with glycine occurs, colonic bacteria may deconjugate them and liberate the glycine. Conversion of glycine to glyoxalate occurs, which is then absorbed and oxidized to oxalic acid in the liver (Hockaday *et al*., 1965) Another potential precursor is ascorbic acid, to be discussed later in this chapter.

Oxalate is usually bound to calcium in the diet and is excreted unabsorbed in the stool. Parenteral administration of ascorbic acid in HPN can lead to hyperoxaluria and renal insufficiency (Swartz *et al*., 1984). The mechanism by which renal dysfunction may occur in this setting probably relates to calcium oxalate deposition. Furthermore, there may be a role for increased endogenous production of oxalate in patients receiving long-term HPN.

Previously, it was believed that hyperoxaluria would not occur in patients with ileal resections and an ileostomy or proximal colostomy. It has since been shown that some short-bowel patients with an ileostomy but on long-term HPN developed hyperoxaluria, suggesting the possibility of an increased endogenous oxalate production (Buchman *et al*., 1995). Ascorbic acid can be aerobically oxidized to oxalate via dehydroascorbate. Ascorbic acid is also believed to degrade to oxalate following exposure to light, which functions as a potent free radical initiator (Smith *et al*., 1988).

Although oxalate itself, however, can further degrade under ultraviolet

light exposure to carbon dioxide and formic acid (Gupta *et al*., 1971), Rockwell *et al*. reported detectable concentrations of oxalate, presumably from endogenous production, in neonatal TPN solutions (Rockwell *et al*., 1998). In addition, these investigators found the presence of increased amino acid concentration appeared to confer a protective effect against the conversion of ascorbic acid to oxalate.

The role of ascorbic acid in hyperoxaluria has recently come under more scrutiny. The Food and Drug Administration has raised the recommended level of ascorbic acid in IV multivitamin preparations from 100 mg/day to 200 mg/day (USFDA, 2000a). Recently, the levels of urinary oxalate excretion at both doses were investigated in patients on long-term HPN. A statistically significant increase in urinary oxalate excretion was seen in patients on the higher dose, suggesting that a possible increased risk of nephrolithiasis may exist for such patients (Pena de la Vega *et al*., 2004). In all likelihood, very large doses of ascorbic acid are required to cause true hyperoxaluria (Binder, 1974).

Finally, treatment with conjugated bile acid supplementation in patients with suspected hyperoxaluria can be effective in the prevention of nephrolithiasis by reducing fat malabsorption, decreasing intraluminal fat concentration and decreasing calcium soap formation, thereby allowing oxalate to precipitate as its insoluble calcium salt rather than be absorbed in the colon (Emmett *et al*., 2003).

Aluminium

Aluminium carries potential toxic risks when accumulated at abnormally high levels during long-term HPN use. Particularly at risk are infants and patients with abnormal renal function. The primary sequela of aluminium toxicity associated with HPN appears to be osteomalacia. The mechanisms of bone toxicity relate primarily to impaired calcium bone fixation or altered conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (Vargas *et al*., 1988).

Other derangements that can occur include the following: (i) encephalopathy; (ii) motor abnormalities affecting speech; (iii) seizures; (iv) dementia; (v) myoclonus; and (vi) pathologic fractures. Indeed, increased aluminium levels in the brain have been found in HPN-treated premature infants (Bishop *et al*., 1989). Renal insufficiency may also predispose patients to the development of aluminium toxicity, as the kidneys act as the main route of excretion.

Aluminium is generally found as a contaminant in intravenous products, and the USFDA has investigated this phenomenon in order to determine safe levels. This ultimately led the USFDA in 2000 to issue a report outlining standards for acceptable levels of aluminium in large- and small-volume parenterals (USFDA, 2000a). In this report, the FDA determined that the 'acceptable' level of aluminium intake for parenteral administration is approximately < 4–5 μg/kg/day. New labelling regulations

have been published. These include labelling requirements for the package inserts of intravenous products, cautioning that the product contains aluminium at concentrations < 25 μg/l. In addition, the USFDA mandated that producers of large- and small-volume parenterals must demonstrate they use validated assay methods for measurement of aluminium contamination in their parenterals.

Manganese

Manganese is another trace element that, in patients on long-term HPN, may accumulate to levels capable of causing toxic side effects. Acting both as an important coenzyme as well as playing a significant role in bone, cartilage and connective tissue formation, manganese is excreted normally in the biliary system. Toxic effects were first described in 1837 in Chilean manganese miners who developed *locura manganica*, or manganese madness.

It is thought that patients who suffer from cholestatic liver disease or biliary obstruction may be most vulnerable to developing toxicity due to impaired clearance (Hambridge *et al*., 1989). An elevated serum manganese concentration, however, does not necessarily correlate with toxicity (Siepler *et al*., 2003). A recent study demonstrated that patients receiving HPN, when compared with chronic liver disease or control subjects, had elevated serum and whole blood manganese concentrations. None of these HPN patients, however, demonstrated any signs of manganese toxicity (Wardle *et al*., 1999).

Manganese toxicity most commonly manifests as neurological symptoms, with reports in the literature suggesting Parkinsonian symptoms (typical gait, tremor and muscle rigidity) and neuropsychiatric symptoms (headache, somnolence, confusion) (Fitzgerald *et al*., 1999; Nagatomo *et al*., 1999). As mentioned earlier, manganese miners were first described as having a symptom complex attributed to manganese toxicity. Among the symptoms were an initial maniac stage, insomnia, depression and delusions. These symptoms might have been followed by anorexia, apathy, arthralgias, asthenia or headaches. Finally, later stages might have manifested as gait and balance abnormalities, with a Parkinsonian tremor and rigidity.

Radiologically, manganese toxicity can manifest as deposits seen in the basal ganglia – primarily on MRI – which may correlate with the development of Parkinsonian traits (Takagi *et al*., 2001). It appears that many of the neurologic symptoms will reverse with the withdrawal of manganese from the HPN, as may the MRI findings in the basal ganglia (Mirowitz and Westrich, 1992).

The role of manganese in liver toxicity is not clearly established. There is no strong evidence as yet to support the theory that manganese actually causes cholestasis. A recent study randomized children receiving PN to high or low manganese supplementation. While there were no statistically

significant differences in manganese or serum bilirubin levels, sub-group analysis of children receiving at least 75% of their daily fluid intake from HPN demonstrated that those randomized to higher manganese supplementation had a significantly higher serum direct bilirubin and higher peak direct bilirubin compared with the low-manganese group (Fok *et al*., 2001).

In liver disease, and especially cholestasis, however, manganese excretion is impaired (Messing *et al*., 1983). Furthermore, since bile flow is decreased during TPN infusion, it is more likely that the elevated manganese concentration in such patients is a sequela of liver disease rather than a direct cause.

Finally, manganese deficiency has been reported as potentially resulting in bone abnormalities. A case report, described as a preliminary communication, described bone calcification irregularities and bone demineralization in a TPN-dependent neonate who was found to have a profoundly low serum manganese concentration (Norose *et al*., 1992)

Rare Cardiopulmonary Complications

The cardiopulmonary system certainly can be the site of deleterious effects of HPN. Pulmonary embolus is a rare but potentially devastating complication of HPN; generally speaking, most cases can be attributed to in-dwelling central venous catheter use, which is discussed in a later chapter.

Several case reports in the literature have suggested precipitated crystals as another potential source of microvascular pulmonary emboli. In particular, calcium phosphate precipitation has been well studied as an adverse interaction in HPN solutions. Calcium phosphate crystals generally form as dibasic molecules, which are less soluble than monobasic. Among the apparent risk factors for precipitation of calcium phosphate crystals are: (i) high molar concentrations of calcium and phosphate in the TPN solution; (ii) prolonged standing time; (iii) increased infusion rate; (iv) increased solution pH; (v) increased environmental temperatures; (vi) calcium use as a chloride salt; and (vii) elevated serum magnesium concentrations (Reedy *et al*., 1999).

Clinically, patients with calcium phosphate emboli present with symptoms typical for pulmonary embolus including fever, cough and shortness of breath. High-resolution CT usually reveals pulmonary nodules, and one recent case report cited the potential value of lung biopsy in confirming the diagnosis (McNearney *et al*., 2003). Discontinuation of the HPN in some of the reported cases appeared to have led to resolution of symptoms.

After several case reports – including deaths – attributed to precipitates from HPN, the USFDA issued a safety alert in 1994 containing guidelines for minimization of the risk of calcium phosphate precipitation. Recommendations included: (i) the use of in-line filters; (ii) avoidance of the use of three-in-one admixtures when possible; and (iii) prescribing practices for calcium and phosphate in PN solutions (USFDA, 1994).

Lipid emulsion three-in-one admixtures can obscure precipitates. If a lipid emulsion is needed, the USFDA recommended using a two-in-one with lipid infusion separately, or if three-in-one is medically necessary, adding calcium before the lipid emulsion. The USFDA also recommended calculating the solubility of the calcium from the volume at the time calcium is added, not based upon the final volume of the admixture. All home care personnel administering HPN should visually inspect the solution for the presence of precipitates before and during the infusion. If symptoms of acute respiratory distress, pulmonary embolus or interstitial pneumonitis develop, the PN should be stopped and checked for precipitate, and appropriate medical management of the patient's symptoms should be undertaken.

Summary

The literature on the effects of HPN on the kidneys and cardiopulmonary system – as well as toxicities from heavy metals and other elements – continues to grow. Many mechanisms remain poorly understood, including the decline in both creatinine clearance and renal tubular function. We also continue to learn more about the important role of the trace elements found in HPN. These important components of nutritional support may sometimes, though rarely, carry serious toxicities if their clinical manifestations go unrecognized. Particularly for patients on long-term HPN support, these potential toxicities should always be considered in certain clinical scenarios, as early recognition can clearly be vital to the treatment of these adverse events.

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16 Catheter-related Complications

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Key points

1. Catheter insertion and position

- Sterile conditions when inserting catheters to reduce infectious complications.
- A physician well educated for the task.
- Lower rate of complication at subclavian < jugular < femoral veins.
- Ultrasound my help to guide when inserting into jugular veins.
- Avoid using femoral veins due to high risk of complications.
- Catheter tip at junction of caval vein and atrium results in fewer malfunctions.

2. Catheter-related infection and thrombosis

- Nutrition support team is of paramount importance for patient education and rate of infectious complications.
- General barrier precautions and education of patients is of paramount importance.
- Infections with fungi always require a line shift.
- Repeated line infections may be reduced by the use of an antibiotic lock.
- Catheter-related venous thrombosis may be associated with severe complications.
- If only a single venous access is left, consider referring for intestinal transplant.

 Home Parenteral Nutrition (eds F. Bozzetti, M. Staun and A. Van Gossum)

Introduction

Parenteral nutrition is required when patients are unable to maintain an adequate nutritional status, fluid or electrolyte balance due to insufficient function of the gastrointestinal tract. The most common causes of intestinal failure are: (i) resection of the small bowel due to a catastrophic event such as mesenteric thrombosis; (ii) small-intestinal disorders that cause malabsorption; (iii) conditions with pseudo-obstruction; and (iv) malignant disease with ensuing intestinal complications or a general need for nutritional support.

Home Parenteral Nutrition (HPN) requires a well-functioning central venous line, but the use of this is frequently associated with complications, some of which are serious for the patient, requiring admission to hospital and concomitant increases in the cost of the treatment. This chapter will focus on the most frequent complications related to venous access. Regarding the choice of type of catheter, insertion and care, please refer to Chapter 23, this volume.

Complications Related to Insertion of Catheter

To prevent bacterial contamination and subsequent sepsis, catheter insertion should be carried out using the highest possible sterile barrier precautions, and this includes wearing a mask, a cap, a sterile gown and gloves. Such precautions have been shown to reduce the rate of infection (Raad *et al*., 1994). The experience of the physician performing the procedure is important for the outcome. A previous study by Sznajder *et al*. (l986) has shown that the risk of mechanical complications is significantly less if someone who has performed more than 50 insertions performs the procedure. Regarding the choice of central vein, the data for long-term catheter use are scarce.

Studies in the intensive care setting have shown that subclavian puncture is associated with a lower frequency of catheter-related infections compared to that with jugular insertion (McGee and Gould, 2003). A further advantage of subclavian cannulation is that the exit site of the tunnelled catheter can be placed readily available, allowing the patient self-management of parenteral nutrition and this is obviously important for patients on HPN.

Complications in relation to insertion include the following:

- Local infection or haematoma.
- Bleeding from the subcutaneous tunnel or the puncture site.
- Arterial puncture.
- Haemothorax.
- Pneumothorax.
- Haemopericardium and cardiac tamponade.
- Cardiac arrhythmias.
- Misplacement and migration of the catheter.
- Venous thrombosis.
- Air embolism.

These can be reduced using imaging techniques such as ultrasound for jugular insertion, but this does not apply to the preferred subclavian site (Randolph *et al*., 1996). In the case of previous complications and suspicion of thrombosis, venography can provide essential information for guiding insertion at the subclavian site. Generally, femoral vein catherization should be avoided due to a much higher risk of mechanical complications and thrombosis, which is about ten times the rate for subclavian access (McGee and Gould, 2003).

The position of the distal tip of the central venous catheter is important for increasing longevity and minimizing adverse events in patients on HPN. Thus, immediately after insertion, verification of the position of the tip, using radiography or fluoroscopy, is recommended. In a retrospective study of 141 central venous lines, catheter tip location was the only factor that was statistically predictive of malfunction (Petersen *et al*., 1999). A significant increase in malfunction was observed in cases where the catheter tip was located more than 4 cm superior to the junction of the right atrium and the superior caval vein. Malfunctions were minimized in those cases where the catheter tip was located in the right atrium.

Catheter-related infections

Pathogenesis, definitions and symptoms

Infectious complications are the most serious event related to vascular access devices. In patients on HPN, infections of this kind add significantly to the morbidity and mortality.

The pathogenesis is generally bacterial or fungal growth colonizing the catheter, with both the luminal and outer surfaces becoming contaminated. From there, pathogens can reach the bloodstream and clinical signs of infection may become evident. The hub, a broken line or the use of the catheter for non-nutritional purposes are probably the most common endo-luminal causes of infection. If micro-organisms migrate along the catheter or are introduced during the insertion the infection is of extra-luminal origin.

When performing clinical studies or quality assurance work, a stricter definition of catheter-related infection may be useful and this has previously been presented by Pearson (1996). Here, catheter colonization is defined as: 'growth of more than 15 colony-forming units at semi-quantitative culture or more than 10^3 colony-forming units (quantitative culture) from a proximal or distal catheter segment in the absence of accompanying clinical symptoms'. Local catheter-related infection is based on the same criteria, but with the presence of inflammation (erythema, warmth, swelling or tenderness) at the device site. An exit-site infection presents with erythema, tenderness, induration or purulence within 2 cm of the skin at the exit site of the catheter, and tunnel infection is characterized by erythema, tenderness and induration of the tissue overlying the catheter, with a distance of > 2 cm from the exit site. If the patient uses an implantable

device a pocket infection may occur, when the clinical findings are erythema and necrosis of the skin over the reservoir.

Catheter-related bloodstream infection in a patient with clinical symptoms of bloodstream infection and no other apparent source of infection is defined as: 'isolation of the same organism (identical species and antibiograms) from cultures from catheter segments and blood cultures from a peripheral vein'. If catheter removal is undesirable, indirect diagnosis relies on blood cultures of paired blood samples obtained from the catheter and from a peripheral vein.

Probable systemic catheter-related sepsis is characterized by a colonized catheter associated with clinical signs suggesting septicaemia, despite the lack of positive peripheral blood culture.

From a clinical point of view it is important to recognize both the local and the systemic manifestations of a catheter-related infection. The local signs of infection at the exit site of the catheter include redness of the skin, local pain and discharge of pus from the tunnel, which may appear elevated due the inflammation. It is important to keep in mind that the signs of a systemic infection cover a broad range of symptoms; typically the patient will complain of fever and chills that may appear immediately or hours after the infusion of parenteral nutrition is commenced. However, the symptoms can be very unspecific and patients on HPN who present with new complaints should always be suspected of having a catheter-related infection. Some of the non-specific signs that may appear include cardiopulmonary symptoms with dyspnoea and arrhythmias, gastrointestinal complaints and renal symptoms.

Diagnosis and treatment

In any patient who has a central venous catheter, symptoms and signs of infection without another confirmed source should raise concerns that the catheter may be the source.

Once a catheter-associated infection is suspected, blood cultures should be taken to evaluate the possibility of bacteraemia. Cultures of blood from both central and peripheral sites should be evaluated, since it is difficult to determine whether a positive culture of blood from a central line indicates contamination of the hub, colonization of the catheter or catheter-related bloodstream infection. If a line infection is suspected, initiation of broad-spectrum antibiotic treatment is the response of the clinician after blood cultures have been performed.

In patients on HPN, longevity of lines should be as high as possible since repeated line insertion carries the risk of complications and loss of vascular access. However, if the patient has clinical signs of septic shock the catheter should be removed immediately. Generally, the use of the line in patients with suspected catheter-related bloodstream infection should be very restricted due to the risk of infusing bacteria or bacterial products into the bloodstream.

In a study investigating the difference in bacteriology between colonized catheters and bloodstream infection in 354 HPN patients, 249 catheter tips of a total of 600 catheters were cultured. Sixty tips cultured positive. There

were significant differences between the microbiology of those who were judged to have catheter-related sepsis and those who had only a colonized catheter. If fungi were found this indicated true catheter infection; in contrast, the finding of Gram-positive cultures rather indicated colonization (Lin *et al*., 2003). This is in accordance with clinical experience that if patients present with fungal infections it is always necessary to remove the line, but in the case of a bacterial infection the line can generally be saved in about 30% of cases with bloodstream infection (Jeppesen *et al.*, 1998).

The catheter infection rates reported from various HPN centres are around 0.3 episodes per patient per year (Buchman *et al*., 1994; Jeppesen *et al.*, 1998; Pironi *et al*., 2003; Freshwater *et al*., 2004).

If patients on long-term HPN encounter repeated line infections, intervention – apart from changing the line – may be appropriate. Re-education in all necessary procedures should be carried out in all patients with line sepsis. Other measures that have been applied are the use of line lock with antibiotics, urokinase to lyse a thrombus and possibly alcohol to dissolve debris (Metcalf *et al.*, 2004). No controlled studies on the use of the lock technique in patients on HPN have been reported.

A randomized double-blind trial of antibiotic lock for prevention of endoluminal catheter-related infection with vancomycin compared to heparin was carried out in 127 patients with haematological malignancies, using non-tunnelled catheters. The primary and secondary end points were colonization of the catheter hub and catheter-related bacteraemia, respectively. The antibiotic lock with vancomycin significantly prevented catheter hub colonization with Gram-positive bacteria (Carratala *et al*., 1999). The study strongly indicates that this technique is an effective preventive measure, but it is as yet unproven if the results can be translated to patients on HPN.

In a recent study, Jurewitsch and Jeejeebhoy (2005) applied daily antimicrobial chemotherapeutic treatment with taurolidine, an antibiotic, as a catheter lock in seven HPN patients. The pre-treatment infection rate of 10.8 line infections per 1000 catheter days dropped to 0.8. More studies on this approach are warranted.

Risk factors

The ESPEN-HAN group performed a survey reporting the experience of 12 centres – a total 447 patients and an impressive total number of catheter days of 110,869. Complications occurred in about 25% of patients and in about 50% of cases this was an infection, requiring removal of the catheter in about 12% of patients. Implantable ports and a daily need for nutrition could be identified as risk factors. Interestingly, the use of catheters for other than nutritional purposes reduced the risk of infection, probably reflecting the fact that thorough care of the line, as well as careful administration of parenteral nutrition, is very important (Bozzetti *et al*., 2002).

In another study, Jeppesen *et al.* (1998) demonstrated that the presence of a stoma and the more aged patient were both associated with a higher risk of catheter-related bloodstream infection. However, a retrospective study

demonstrated a reduced risk of infection in patients having a central line for intravenous nutrition when cared for by a nutrition team (Dimick *et al*., 2003).

In a prospective cohort study of 827 patients receiving home infusion therapy due to a variety of diseases, including infections (67%), cancer (24%), nutritional and digestive disease (17%), transplants and HIV (18%), 69 catheter-related bloodstream infections were diagnosed during a total of 69,532 catheter days (Tokars *et al*., 1999). In a Cox regression model the authors identified independent risk factors for infection. These were: (i) a recent bone marrow transplant; (ii) receipt of total parenteral nutrition regardless of whether lipids were included; (iii) treatment outside the home, including an outpatient clinic; (iv) the use of multi-luminal catheters; and (v) a previous bloodstream infection.

Educational intervention generally reduces complications if patients use the information they have been taught, and in particular if the education is interactive. This has also been applied in HPN patients in a randomized controlled trial to test interactive, video-based intervention. Patients in the active group had a significantly lower frequency of line infection at 6 and 18 months (and of admissions for this) (Smith *et al*., 2003). Patients in the active group also proved better at defined problem solving, had less depression and scored better on quality-of-life measures. Many centres will use some kind of instruction, handout material and hands-on exercises – and in some cases video-based programmes or other teaching methods – but very few have been validated.

Catheter obstruction

Catheter tip occlusion during catheter dwell is a common complication, causing difficulty with infusion therapy. It is usually unpredictable and may occur at any time, but can be associated with the lifespan of the catheter, the type of catheter used, handling procedures and repeated events of blood flushing back – and possibly also the type of intravenous nutrition used. If the catheter has been used for a significant period of time it is advisable to replace it rather than attempting to restore function. Case reports on the use of alcohol, saline, heparin and thrombolytic agents have been published. In a double-blind randomized study, Ponec *et al*. (2001) used recombinant tissue plasminogen activator for restoring catheter function with success in 74% of cases compared to 17% in the placebo group; the central venous device had been in use for a median time of 35 days. More studies on long-term patients are warranted.

Catheter-related thrombosis

Thrombosis of the vein associated with the central line is a common finding. If investigated by ultrasound imaging it is present in 30–50% of cases (Hirsch *et al*., 1995), but in the HPN population this complication is more rarely

diagnosed, with 0.05 episodes per catheter year (Jeppesen *et al.*, 1998; Pironi *et al.*, 2003). The pathogenesis is probably multifactorial and includes: (i) vessel injury caused by the procedure of insertion; (ii) venous stasis due to indwelling of the device and damage to the endothelium caused by infusion of parenteral nutrition with a high osmolality; or (iii) by mechanical rubbing of the catheter against the vessel wall. Hypercoagulability related to cancer or other underlying disease may also contribute to the risk.

Catheter-related infection might also contribute to the pathogenesis of thromboembolic complications (Wechsler *et al.*, 1993). In many cases a thrombotic event of the upper extremities will be asymptomatic, but very often the first sign will be malfunction of the catheter. Swelling of the neck and arm, appearance of superficial veins on the anterior chest, fever and signs of pulmonary embolism may ensue. The diagnosis is based on the clinical picture and can in many cases be confirmed by imaging technique with ultrasound, CT-scans or venography. Removal of the line is not always required and a decision about this must be based on the clinical setting, symptoms, catheter function and the possibility of obtaining an alternative intravenous route. If associated with bacteraemia, removal of the catheter is usually required.

The treatment of choice for catheter-related thrombosis is anticoagulant therapy with heparin and vitamin K antagonists. Heparin should be continued for 5–7 days and oral or intravenous anticoagulants should be administered, but the duration of this therapy is unknown, since no studies have been performed and many centres will continue treatment as long as the patient has a central line. In patients with benign disease more aggressive therapeutic options include systemic thrombolysis and thrombectomy, but no randomized studies comparing thrombolytic agents to heparin treatment or placebo are available from HPN patients, so at present thrombolytic treatment cannot be generally recommended.

Prevention is important and can be obtained by careful selection of insertion site and control of the position of the catheter tip (see above). Patients who are at particular risk of thrombosis can be offered prophylactic warfarin treatment (Klerk *et al.,* 2003).

Loss of vascular access

Patients maintained on HPN for many years may encounter repeated line complications, where thrombosis and loss of vascular access may eventually be the result. The upper body venous access sites will usually be occluded first. Attempts to recanalize can be performed with endovascular intervention. If unsuccessful the femoral veins may be accessed, but bear in mind that the general rate of complications with use of this route is significantly higher.

Trans-lumbar venous access has been reported (Denny *et al.*, 1989) in six patients. Case reports of access by direct puncture of the right atrium or by cannulation of the hepatic veins have also been reported (Miyamoto *et al.*, 2002). The use of an external arteriovenous graft for intravenous nutritional support may also be an unconventional option (Turner *et al.*,

2003). With the advancement in the results of intestinal transplantation the clinician should consider the possibility of this procedure. Preferably, this should be done at the latest when one vascular access route remains open, since this is what the patient will need for the nutritional and intensive care support if a transplant is performed.

Summary

This chapter describes the most frequent complications related to venous access, including those related to insertion and placement, catheter-related infections, catheter obstruction and venous thrombosis. Management and preventive measures are also discussed.

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17 Disease-related Complications

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This chapter describes the survival rate, prognostic factors and HPN-induced mortality in adult patients with benign intestinal failure.

Key points

- HPN patients die of causes attributable to the progress of the underlying disease that cannot be prevented by intestinal transplantation.
- Only a minority of those die from HPN-related complications such as sepsis and venous thrombosis.
- At present, HPN-induced liver failure is the main indication for intestinal transplantation in this group of patients.

Epidemiology

Data regarding HPN survival rates, prognostic factors and HPN-induced mortality have been reported from various centres (Jeejeebhoy *et al*., 1976; Howard *et al*., 1991; Messing *et al*., 1995; Jeppesen *et al*., 1998; Scolapio *et al*., 1999; Van Gossum *et al*., 2001; Ugur *et al*., 2006). Table 17.1 gives an overview of the survival rates in some of the largest studies. Patients with Crohn's disease, ischaemic bowel disease, motility disorders, radiation enteritis and congenital bowel disorders all have rather benign causes and long-term prognosis, whereas patients with active cancer have a much more serious cause and a more pessimistic prognosis. Within the patients with benign causes, the mean age of the patients varied in the disease

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Table 17.1. Studies on HPN survival rates.

Author	Overall	Sub-group	1-year survival (%)	3-year survival (%)	5-year survival (%)
Messing *et al.*, 1995 (*n*, 217)	Non-malignant chronic intestinal failure		91	70	62
		Crohn's			82
		Ischaemia			56
		Radiation			52
Scolapio *et al.*, 1999 (*n*, 225)		Crohn's			92
		Ischaemia			60
		Radiation			54
		Motility			48
		Cancer			38
Howard *et al.*, 1991 (*n*, 4350)		Crohn's	96	87	
		Ischaemia	87	84	
		Congenital	94	80	
		Motility	87	62	
		Radiation	87	58	
		Chronic Obstruction	83	40	
		Cancer	20	–	
Toronto[4]	Chronic				75
	Acute				42
OASIS[5]		Crohn's disease and congenital		80	
		Motility		72	
		Ischaemic		70	
		Radiation		65	
ESPEN 1997[6] (*n*, 284)		Crohn's	96		
		Ischaemic	87		
		Radiation	79		
		Cancer	26		
Jeppesen *et al.*, 1998 (1991–1996)	Non-malignant intestinal failure				75
Ugur *et al.*, 2006 (1996–2001)	Non-malignant intestinal failure				75

categories, and it may be hypothesized that age difference is the main explanation for the effect of primary diagnosis on survival.

Other factors affecting the survival of HPN patients are aspects of bowel anatomy, HPN complications and the clinical supervision and education of the patients. With the emerging improvement of the results of intestinal transplantation, attempts are often made to compare patient survival on HPN and after transplantation. Currently, such comparisons are unjustified, since transplants are offered only to patients who cannot be maintained on HPN and subsequently would have died if transplantation had not been performed.

The overall probability of survival will vary between centres according to both the characteristics of the cohort and the experience of the HPN centre. As illustrated in Table 17.1, most centres report a 1-year survival of approximately 90%, whereas the 5-year survival is around 60%. In general, patients with Crohn's disease perform best, whereas HPN patients with intestinal failure due to ischaemia, radiation enteritis and dysmotility disorders perform worst. Independent of the primary diagnosis, certain aspects of bowel anatomy can influence survival. It has been shown that there is a risk of fatality for HPN patients with a bowel obstruction which is 2.6 times higher than that of patients without obstruction.

It has also been demonstrated that short-bowel patients with an end-jejunostomy run a significantly higher risk of death than patients with a similar bowel length but a colon-in-continuity (Messing *et al*., 2001). However, the probability of death was not dependent on the length of small bowel and survival was similar for patients with or without short bowel syndrome, even in those with < 50 cm of residual gut. Children and adolescents with Crohn's, ischaemic bowel or a motility disorder have a better prognosis than middle-aged or geriatric patients with similar diagnoses. This age difference is not explained by differences in expected mortality between similar age groups in the general population. That suggests that older individuals have less ability to withstand medical insults (Howard, 2002).

Finally, the experiences of the HPN centre, the education of the patients and the clinical supervision may all influence patient survival. Messing *et al*. (2001) found that patients who had started HPN before 1984 had a risk of death that was 5.6 times higher than patients who had started since 1987. Since the personnel among managing physicians had been relatively stable, the explanation of this difference is by the steep learning curve of those physicians managing long-term HPN patients.

Across centres it is a uniform finding that the number of patients who die from HPN complications such as sepsis, extensive thrombosis of the superior vena cava with pulmonary emboli, or liver failure is low. Messing *et al*. found that death related to HPN occurred in 8 of 217 patients (4%), representing 11% of deaths (Messing *et al*., 1995). Jeppesen *et al*. (1998) and Ugur *et al*. (2006) have reported similar findings. In two 5-year surveys conducted between 1991 and 2001 only 3% of HPN patients died of causes related to HPN.

Summary

The majority of HPN patients thus die of causes attributable to the progress of the underlying disease that cannot be prevented by intestinal transplantation. Only a minority die from HPN-related complications. However, it is impossible to foresee which of the HPN patients will eventually die from sepsis, thrombosis or emboli, at present leaving only HPN patients with progressive liver insufficiency as being suitable for eventual transplantation. Eventually, results from bowel transplantation are likely to improve significantly. By then, quality of life issues will also determine the treatment strategy of short-bowel patients with intestinal failure.

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Part IV
Practical Issues

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18 Adult Nutritional Requirements

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Key points

- Nutritional requirements should include disease-specific needs, and factors to be considered include medical condition, nutritional status, activity level, fluid restrictions and organ function.
- The electrolyte composition of the home parenteral nutrition (HPN) regimen should reflect fluid losses and the losses that might result from drug therapy.
- The estimated amount of total calories should fall within 20–35 kcal/kg/day, and rarely more than 40 kcal/kg/day.
- The non-protein energy requirement can be calculated as being 100–150 kcal for every 1 g of nitrogen in the parenteral nutrition bag. The recommended ratio of glucose to lipid is approximately 70–85:15–30.
- The unstressed adult patient with normal organ function will require 0.8 g protein/kg/day.
- There is usually a need to add trace elements and vitamins for patients who need long-term parenteral nutrition, particularly in malabsorption states and if no oral diet is taken.

Introduction

The levels of specific nutrients provided for the adult receiving home parenteral nutrition (HPN) should be based on a formal nutritional assessment. Nutritional requirements should include disease-specific needs, and factors to be considered include medical condition, nutritional status, activity level, fluid restrictions and organ function.

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The prescription is decided upon prior to the discharge of the patient and then reviewed shortly after discharge to make sure that it is still appropriate. The prescribed regimen should supply the complete nutrient range if required, and should be easily managed at home with regard to the number of nights of the week to be fed and the length of infusion time. Figures for requirements of macronutrients are generally prescribed on the basis of the actual weight of the patient and altered according to weight changes.

Requirements for Nutrients

Fluid

It is important to assess the patient's fluid status as part of their general assessment when considering parenteral nutrition and fluids. This will help determine the volume that should be provided to the patient on a daily basis. Disturbances of water and salt have a more profound effect on health than nutrients, and imbalances result in dehydration or fluid overload. The electrolyte composition of the HPN regimen should reflect fluid losses and the losses that might result from drug therapy. Table 18.1 estimates the fluid requirements according to clinical condition.

Electrolytes

The standard prescribing ranges for electrolytes assume normal organ function, without abnormal losses. Additional sodium and potassium may be required if serum levels are low. Table 18.2 illustrates the requirements for electrolytes in parenteral feeding (Micklewright and Todorovic, 1997).

Table 18.1. Estimation of fluid requirements (National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition, 1998).

Clinical status	Baseline requirement
Maintenance requirements	
18–60 years of age	35 ml/kg body weight
> 60 years of age	30 ml/kg body weight
Replacement of ongoing fluid losses	
Fever with loss of body fluids	Add 2.0–2.5 ml/kg/day for each 1°C rise in body temperature above 37°C per 24 h period of pyrexia; these individuals must be assessed on a daily basis

Energy

Determining energy requirements should be on individual patient assessment. Predictive equations such as the Schofield Equation (Schofield, 1985) to estimate energy requirements in adults may be useful but care should be taken not to provide excess energy. The estimated amount of total calories should fall within 20–35 kcal/kg/day, and rarely more than 40 kcal/kg/day (Koea *et al*., 1995).

Energy sources

Carbohydrates and lipids are used as the energy sources in parenteral nutrition. As a simple rule of thumb, the non-protein energy requirement can be calculated as being 100–150 kcal for every 1 g of nitrogen in the parenteral nutrition bag. The recommended ratio of glucose to lipid is approximately 70–85:15–30. Contributions from oral intake should be considered and, if possible, parenteral requirements provided over 5 to 6 days or nights rather than 7, to improve quality of life. Monitoring the patient's weight will provide evidence of the need for alteration of fluid/energy prescription.

Carbohydrates

Glucose is the carbohydrate source of choice and, in order to avoid acute and long-term complications, it is recommended that glucose should be administered at the level of 3–6 g/kg/day (Kris-Etherton *et al*., 2000).

Lipids

Almost all patients should be provided with lipid (Jeppesen and Mortensen, 1998), particularly if there is no oral intake of fat. Total fat should not exceed 1.0–1.5 g/kg/day (Kris-Etherton *et al*., 2000). Between 1 and 2% of daily energy requirements should come from linoleic acid (ω-6) and about 0.5% from α-linolenic acid to prevent essential fatty acid deficiency. If patients take some of their oral diet in the form of fat, this should not present a specific problem. In 5-year follow-up of 90 HPN patients, Cavicchi *et al*. (2000) described chronic cholestasis and liver disease when 20% intravenous lipid was provided at a level of > 1 g/kg/body weight/day.

Table 18.2. Estimation of electrolyte requirements (Micklewright and Todorovic, 1997).

Electrolyte	Requirement (mmol/kg/day)
Sodium	1.0–1.5
Potassium	1.0–1.5
Magnesium	0.1–0.2
Calcium	0.1–0.15
Chloride	1.0–1.5
Phosphate	0.5–0.7

Essential fatty acid deficiency (EFAD) will develop in 2–6 months with an intravenous, fat-free regimen. This can be normalized by providing 1.2–2.4% of ω-6 twice weekly. Patients who have an existing serological essential fatty acid deficiency may require up to 2.4 g/kg twice weekly to correct it (Mascioli *et al.*, 1996).

Nitrogen

Adequate energy substrate must be provided to optimize nitrogen utilization. The unstressed adult patient with normal organ function will require 0.8 g/kg/day (see Table 18.3). However, more will be required in the stressed or catabolic patient and this figure may rise to 2.0 g/kg/day. For obese individuals with a BMI of 30–40 kg/m^2, approximately 75% of the value estimated from body weight should be given. For those with a BMI of > 50 kg/m^2, approximately 65% of the value estimated from body weight is recommended (Micklewright and Todorovic, 1997).

Micronutrients

Vitamins and trace elements act as the cofactors and coenzymes involved in metabolism. There is usually a need to add trace elements and vitamins for patients who need long-term parenteral nutrition, particularly in malabsorption states and if no oral diet is taken. These commercial preparations of trace elements and vitamins for use in parenteral nutrition generally provide amounts in excess of basal requirements, as they are intended for patients who are either already nutritionally depleted or who have increased losses. The prescription guidelines should therefore be considered as an approximation of requirements. Tables 18.4 and 18.5 show the recommended parenteral intakes and the levels provided by proprietary sources for parenteral use (American Medical Association Department for Foods and Nutrition 1979a, b; Shenkin, 1987).

Table 18.3. Daily nitrogen requirements for adults (assuming normal organ function).

	Nitrogen (g/kg/day)
Maintenance	0.8–1.0
Catabolic	1.2–2.0

To calculate protein requirements from nitrogen:
protein (g/day) = nitrogen (g/day) x 6.25.

Table 18.4. Daily requirements and sources for parenteral micronutrients.

Trace elements	Daily requirement	Additrace® (μmol/10 ml)	Decan® (μmol/40 ml)
Zinc	38–100	100	153
Copper	8–24	20	7.5
Selenium	0.4	0.4	0.9
Iron	20	20	18
Manganese	3–15	5	3.6
Chromium	0.2–0.3	0.2	0.3
Molybdenum	0.2	0.2	0.26
Cobalt		–	0.025
Iodine	1.0	1.0	0.01
Fluoride	50	50	76

Additrace®, Fresenius Kabi, Sweden; Decan®, Baxter, France.

Table 18.5. Requirements and sources for parenteral vitamins.

	Daily requirement	Vitlipid Adult®	Cernevit®
Fat-soluble vitamins			
Vitamin A (μg)	1000	990	1000
Vitamin E (μg)	10	9.1	10.2
Vitamin K (μg)	150	150	0
Vitamin D (μg)	5	5	5
Water-soluble vitamins			
Vitamin B_1 (μg)	3.0	3.1	3.5
Vitamin B_2 (μg)	3.6	4.9	4.1
Vitamin B_6 (μg)	4.0	4.9	5.5
Niacin (μg)	40	40	46
Folic acid (μg)	400	400	414
Vitamin B_{12} (μg)	5.0	5.0	6.0
Biotin (μg)	60	60	69
Vitamin C (μg)	100	113	125

Vitlipid N Adult®, Fresenius Kabi, Sweden; Cernevit®, Baxter, UK.

Summary

Energy and nitrogen requirements vary depending on age, sex, clinical condition and activity. It is difficult to estimate the available nutrition from oral diet, particularly in those patients with short bowel and malabsorption. All patients receiving home parenteral nutrition should have their nutritional requirements reviewed regularly. This should take into account changes in bowel function (including adaptation), body weight and composition, activity levels and supporting laboratory results.

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19 Carbohydrates

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Key point

- Carbohydrate delivery during home parenteral nutrition (HPN) must avoid hyperglycemia and de novo lipogenesis

Dietary Carbohydrates

Carbohydrate intake accounts for 45–55% of total dietary energy intake in most industrialized countries, and can be even considerably larger in rural areas of Asia and Africa. Digestible carbohydrates can be ingested as: (i) starch, which represents the bulk of total carbohydrates in the diet; (ii) disaccharides; or (iii) simple sugars. Starch and disaccharides require digestion to simple sugars by saliva and pancreatic amylases, and by disaccharidases present in the brush border of the small intestine, before being absorbed as simple sugars through carrier-mediated facilitated transport through the enterocytes.

Recommended dietary intakes of carbohydrates are 55% total energy, with < 20% as disaccharides (present in sweets, bakery produce and dairy produce) and simple sugars (glucose and fructose, present not only in fruit but also in artificially sweetened beverages) (Food and Nutrition Information Center, http://www.nal.usda.gov/fric/etext/000105.htln). Due to the large consumption of sweetened carbonated beverages in industrialized countries and to the use of high-fructose corn syrup as a sweetening agent, fructose consumption has increased markedly over recent decades, and has become a major public health concern because of its potentially deleterious metabolic effects (Bray *et al.*, 2004).

Besides digestible carbohydrates, foods of plant origin also contain undigestible complex carbohydrates, i.e. soluble and unsoluble fibres which do not deliver quantitative amounts of energy to the organism, but

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play an important role in maintaining gut microbial flora and gut function (Asp, 1995).

In total parenteral nutrition (TPN), starch and disaccharides which require digestion into simple sugars cannot be administered and carbohydrates are, therefore, provided exclusively as simple sugars (essentially glucose, since fructose is no longer used in parenteral nutrition due to its potentially serious adverse effects (Bode *et al.*, 1973). In home parenteral nutrition (HPN), a variable proportion of total energy is provided by oral feeding, and includes starch, simple sugars and fibres. This oral feeding is complemented with parenteral nutrition in order to meet energy requirements. Ingested carbohydrate complemented by intravenous glucose means that the proportion of simple sugars is increased in HPN.

The Role of Glucose in Intermediary Metabolism

Glucose is *the* carbohydrate of the human body and can be used by virtually all cell types and all organs of the body as a source of energy. Dietary starch and some disaccharides are absorbed from the gut as glucose through a secondary, active, sodium glucose transport at the apical membrane and a facilitated glucose transport mediated by a glucose transporter, GLUT2, at the baso-lateral aspect of enterocytes (Bizeau and Pagliassotti, 2005).

Fructose from either sucrose digestion or fructose intake is absorbed through a facilitated transport mediated by a transporter, GLUT5, at the apical aspect of enterocytes. Its absorption is slower and more easily saturated than that of glucose, and many individuals present with significant malabsorption after ingestion of large amounts of fructose (Olson and Pessin, 1996). Once absorbed, fructose is rapidly taken up by liver cells, where it is degraded into triose-phosphate and/or converted into glucose. As a result of this hepatic metabolism, fructose concentration in the systemic circulation remains very low, and extra-hepatic tissues mostly metabolize fructose-derived glucose and lactate.

Most tissues of the human body can switch between glucose and lipid as energy sources. The brain, kidney medulla and red blood cells, however, lack the enzymatic machinery required for fat metabolism and rely exclusively on glucose metabolism under normal conditions. Given the central role of the brain in controlling the activities of the various constituents of the body, it is not surprising that strong regulatory mechanisms have evolved to ensure a constant plasma glucose concentration and a constant glucose supply to the brain. The main pathways involving glucose metabolism are illustrated in Fig. 19.1.

Glucoregulation

In normal individuals, plasma glucose is tightly regulated to remain between 4.0 and 5.5 mmol/l even when no food intake occurs over several

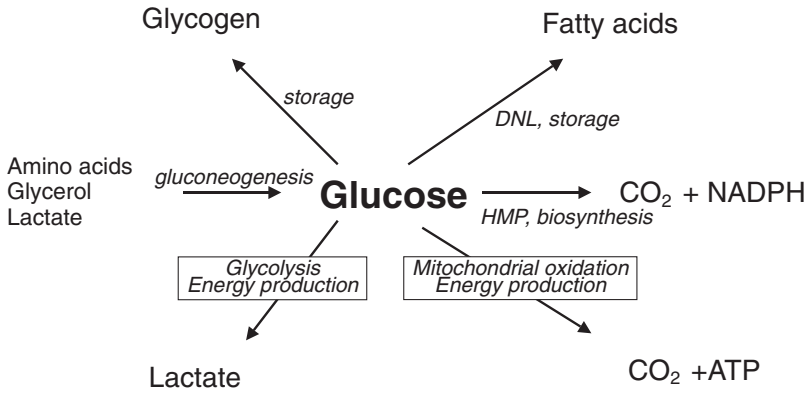

Fig. 19.1. Metabolic pathways for glucose disposal. DNL = de novo lipogenes. HMP = hexose monophosphate pathway.

hours. Under such conditions, glucose utilization by the brain and other tissues amounts to about 2 mg/kg/min, and is balanced by the production of glucose, essentially from the liver, with a minor contribution from the kidneys. Glucose production is made possible by the presence of glucose stored as limited amounts of glycogen (about 70–100 g after an overnight fast) in the liver, which can be reconverted into glucose through glycogenolysis and released into the circulation. In addition, glucose can be synthesized from lactate, glycerol or the carbon skeleton of amino acids through the process of gluconeogenesis.

Both glycogenolysis and gluconeogenesis are reciprocally regulated, by insulin on the one hand and a group of catabolic or stress hormones – including epinephrine, glucagon, cortisol and human growth hormone – on the other. Insulin inhibits both glycogenolysis and gluconeogenesis, whereas stress hormones are potent activators of these processes. The balance between insulin secretion (which is low in fasting conditions) and stress hormones allows for the fine tuning of glucose production required to maintain constant, fasting plasma glucose (Gerich, 1993; Tappy, 1995). Additional intra-hepatic mechanisms, however, known as 'hepatic autoregulation', occur in parallel with this process (Cherrington, 1999).

The efficiency with which these processes allow the maintenance of normoglycaemia is illustrated by the metabolic adaptations to physical exercise. During exercise, the energy and glucose consumption of skeletal muscle increase markedly, and total glucose utilization increases several-fold. Physical exercise, however, leads to an only small drop in glycaemia because it decreases insulin concentration and increases stress hormone release, allowing the stimulation of glucose production in proportion to the enhanced muscle glucose utilization (Kjaer, 1998).

In fasting conditions, glucose utilization occurs mainly in the brain, kidney medulla and red blood cells (RBCs), which are obligatory glucose consumers. In RBCs, glucose is degraded into pyruvate which cannot be further metabolized due to the absence of the RBCs' mitochondria.

Pyruvate is then converted into lactate and released as such into the systemic circulation to be reconverted into glucose in the liver. This cycling (glucose→lactate→glucose) occurs not only in RBCs but also in skeletal muscle and inflammatory cells (Cori cycle).

Glucose utilization by adipose tissue, resting skeletal muscle, fibroblasts, etc. is low in fasting conditions due to the low insulin concentration, and these tissues rely mostly on fat as energy substrates. After carbohydrate ingestion or IV glucose administration, the rise in glycaemia elicits a stimulation of insulin release which acutely increases glucose uptake, oxidation and, if in excess of oxidative capacities, storage as glycogen. This process occurs in all insulin-sensitive tissues, but is quantitatively most important in skeletal muscle (Gerich, 1993; Tappy, 1995).

Interestingly, it has now been documented that a portion of the glucose may be oxidized through the actions of so-called 'lactate shuttles'. In this process, glucose is converted into lactate by one cell type, to be transferred to another adjacent cell where it is oxidized to CO_2. This has been described in glycolytic-oxidative skeletal muscle fibres or in astrocytes (Brooks, 2002). Although the functional significance of these shuttles remains incompletely understood, it is likely that lactate may work as a regulatory signal molecule under some circumstances.

Besides oxidation to CO_2 (in all tissues) and glycogen storage (in liver cells and skeletal muscle, essentially), small amounts of glucose can be metabolized by the hexose-monophosphate pathway, a process which allows synthesis of NADPH to be used in various biosynthetic processes (lipogenesis) and in the defence against oxidants (gluthathione reductase). This pathway also produces ribose-5-P, which is used for the synthesis of nucleic acids. Glucose can also be converted into lipids – essentially in liver cells, but also in adipocytes – although this pathway is quantitatively minor in normal conditions (Hellerstein, 1996; Minehira *et al*., 2003). The essential components of these interactions are illustrated in Fig. 19.2.

Energetics of glucose oxidation

Complete glucose oxidation to CO_2 releases a total of 38 moles ATP/mole glucose, which will subsequently be used for the energy-requiring processes of the organism (transmembrane ion transports, biosynthetic processes, etc.). However, hydrolysis of a few moles ATP is also required for glucose absorption in order to metabolize glucose to fructose 1,6 di-phosphate, or to convert glucose into glycogen or lipids. As a result, the net ATP yield of complete glucose oxidation is less than 38 mole ATP/mole glucose and varies according to the metabolic pathways used for glucose metabolism.

As a consequence of this extra ATP hydrolysis required for glucose metabolism, resting energy expenditure increases after glucose administration, a process known as glucose-induced thermogenesis. It usually corresponds to an energy expenditure equal to 5–10% of the glucose energy available. Besides the obligatory use of ATP for glucose metabolism, a

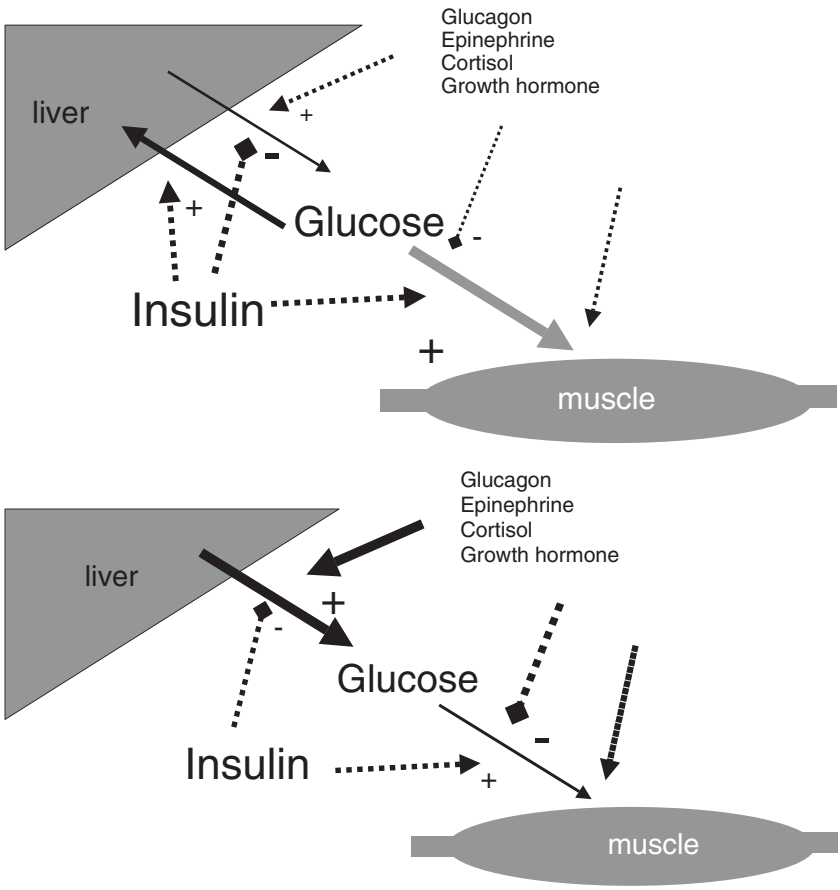

Fig. 19.2. Regulation of glucose metabolism by insulin and stress hormones (glucagon, epinephrine, cortisol and growth hormone) in normal postprandial patients (a) and in critically ill patients during continuous nutrition (b).

glucose/insulin-induced stimulation of the sympathetic nervous system also occurs and may contribute to this thermic effect (Tappy and Jéquier, 1993).

Effects of nutrition on glucose metabolism

Healthy individuals may have a wide range of fuel mix in their diet. Several studies have shown that whole body glucose oxidation rapidly adapts to changes in glucose or carbohydrates intakes. Such an adaptation appears essential, since the amount of glucose which can be stored as glycogen is very limited (about 100 g in the liver and up to ~1 kg in skeletal muscle under extreme conditions), and conversion of massive amounts of glucose into lipid is an energetically very inefficient process. Thus, when a subject is switched from a low- to a high-carbohydrate diet, net glucose storage

(glycogen synthesis) will occur initially. However, over the next few days there is a marked stimulation of glucose oxidation, allowing the restoration of an even carbohydrate balance (Elwyn and Bursztein, 1993).

If carbohydrate intake is in excess of energy requirements, alternative pathways for glucose disposal have to take place. This occurs through a stimulation of *de novo* lipogenesis, which takes place under these extremely unusual circumstances in extra-hepatic tissues (most probably adipose tissue) (Acheson *et al*., 1988; Aarsland *et al*., 1997; Minehira *et al*., 2003).

In contrast, an acute reduction of carbohydrate intake leads, over a few days, to the reverse adaptation, i.e. a decrease in glucose oxidation. If glucose intake drops below a minimal daily intake (corresponding to minimal brain and other obligatory glucose-user organs), additional adaptations have to occur. This is what occurs during starvation, when no carbohydrate is taken up for several consecutive days (Owen *et al*., 1990).

During the initial days of starvation, hepatic glycogenolysis and gluconeogenesis increase in order to ensure sufficient amounts of glucose for the brain. After about 36 h, hepatic glycogen stores are depleted and glucose production relies exclusively on gluconeogenesis, essentially from amino acids. The consequence of this is a substantial catabolism of protein (about 2 g protein required for the synthesis of 1 g glucose). In healthy individuals, however, hepatic ketogenesis is stimulated and increases progressively after 3–4 days of starvation while the brain adapts to use ketone bodies as energy fuels. This coordinated liver–brain metabolic adaptation allows the sparing of endogenous proteins and extends survival time. These two scenarios are illustrated diagrammatically in Fig. 19.3.

Glucose metabolism in critically ill patients

Patients requiring HPN have a nutrition pattern which differs markedly from normal physiological food intake. First, based on a mixed oral/parenteral nutrition, with parenteral carbohydrate being exclusively glucose, they receive a higher proportion of total calories as simple sugars than that provided by a normal diet. Secondly, due to night-time infusion of nutrients, they often have a near-continuous nutrition compared to the essentially episodic food intake of normal individuals. Thirdly, patients submitting to home parenteral nutrition have underlying disorders which may, by themselves, alter energy and substrate metabolism. No study has specifically evaluated glucose utilization in HPN patients, but observations performed in critically ill patients with total parenteral or enteral nutrition may still be relevant.

Acute illnesses produce well-characterized alterations of glucose and energy metabolism (Wolfe *et al*., 1987; Wilmore and Robinson, 1993) which include :

- an increase in total energy expenditure;
- an increased production of glucose which can be attributed to increases in stress hormones; and

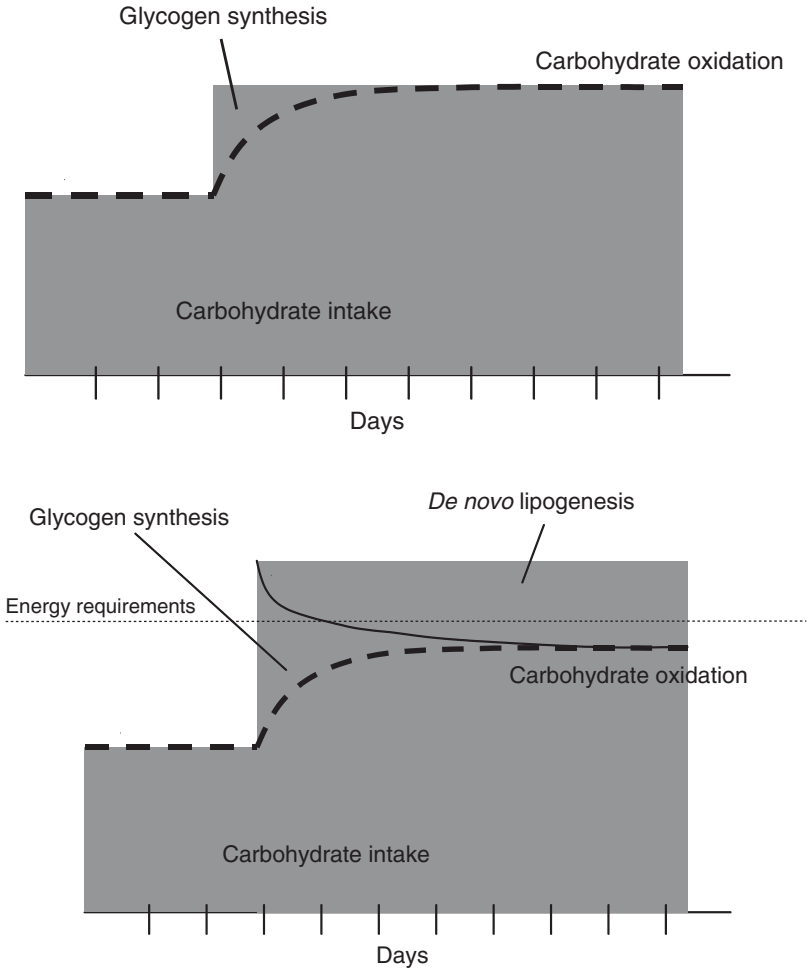

Fig. 19.3. Evolution of carbohydrate oxidation and *de novo* lipogenesis when carbohydrate supply is suddenly altered: (a) modest increase in carbohydrate intake, glucose, oxidation increases to match intake, restoring carbohydrate balance; (b) large increase exceeding energy requirements stimulates *de novo* lipogenesis

- a decreased insulin sensitivity which can be attributed to both stress hormones and inflammatory cytokines.

As a result of these metabolic changes, plasma glucose increases and its rise appears proportional to the severity of the underlying disorder. Furthermore, the subsequently raised glycaemia appears to have deleterious effects, presumably by production of reactive oxygen species and oxidative damages. In support of this deleterious effect of hyperglycaemia, it has been repeatedly observed that aggressive treatment of hyperglycaemia in critically ill patients improves the outcome and decreases mortality. Although these data were collected in intensive care patients, it appears reasonable to extend

these concepts to less acutely ill patients and to avoid hyperglycaemia until further information is available (Van den Berghe *et al*., 2001).

Besides hyperglycaemia, stimulation of glucose production and energy expenditure, critically ill patients also exhibit hyperinsulinaemia, which prevents ketone body synthesis during starvation. This leaves patients exposed to inadequate adaptation to starvation and accelerated protein breakdown if glucose administration is insufficient.

It has been observed that critically ill patients retain the capacity to adapt to changes in carbohydrate intake and to maintain an even carbohydrate balance. This has been observed both during total parenteral nutrition and during continuous enteral nutrition (Tappy *et al*., 1998; Schwarz *et al*., 2000). However, high carbohydrate intakes were associated with stimulation of hepatic *de novo* lipogenesis. Such stimulation of hepatic *de novo* lipogenesis is also observed in healthy individuals submitted to an isocaloric diet rich in simple sugars but low in complex carbohydrates (Hudgins *et al*., 1998).

It would appear, therefore, that both the proportion and nature of carbohydrate in the diet play an important role in this process. Furthermore, in critically ill patients, both the mode of carbohydrate administration (i.e. continuous vs. episodical) and critical illness *per se* may be additional factors which stimulate *de novo* lipogenesis (Minehira *et al*., 2002). In the long term, there is concern that increased *de novo* lipogenesis may favour either the development of non-alcoholic fatty liver disease or lead to hypertriglyceridaemia, with possible adverse vascular effects.

Summary

Due to technical constraints, carbohydrate delivery during HPN differs from a normal feeding pattern by: (i) a near continuous glucose delivery; and (ii) a higher glucose: total carbohydrate ratio. Risks secondary to this feeding pattern (with possible additional aggravating factors due to underlying illness) are hyperglycaemia and stimulation of *de novo* lipogenesis, which can be prevented by avoiding excess glucose administration.

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20 Lipids

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Key points

- Today, a consensus has been reached concerning the advantage of including fat emulsions as a regular component of nutritional provision in Home Parenteral Nutrition (HPN) patients.
- The physicochemical stability of lipid emulsions incorporated in HPN admixtures represents an important issue, with possible deleterious clinical implications.
- In adult patients, minimal fat supply should be about 1 g/kg/week in order to avoid essential fatty acid deficiency, and should not exceed 1 g/kg/day in order to prevent severe HPN-associated liver disease.
- Adequate vitamin E supply must be provided to limit lipid peroxidation in HPN patients.
- Fat emulsions containing LCTs or a mixture of MCTs/LCTs have been successfully used as an essential part of HPN. The safety of newer lipid emulsions (olive-oil based and structured lipids) has recently been demonstrated in adults as well as in children.

Introduction

The limited capacity of an organism under parenteral nutrition to oxidize glucose has led to the development of lipid emulsions. Lipids provide a concentrated and rapidly usable energy supply (they represent a dense caloric source: 9 kcal/g of metabolized fatty acids), cover the requirements for essential fatty acids (EFAs: linoleic acid and alpha-linolenic acid) and

 Home Parenteral Nutrition (eds F. Bozzetti, M. Staun and A. Van Gossum)

provide fat-soluble vitamins. Besides having direct nutritional effects, lipids also modify cell membranes' phospholipid composition, thereby influencing numerous key regulatory functions, e.g. membrane receptor activities, eicosanoid metabolism, cytokine production and gene expression (Yaqoob, 2003).

Today, a consensus has been reached concerning the advantages in including fat emulsions as a regular component of nutritional provision in home parenteral nutrition (HPN) patients. Currently available lipid emulsions include:

- 10, 20 or 30% emulsions of soybean oil (composed of 100% long-chain triacylglycerols (LCTs), including more than 50% of the PUFA linoleic acid (18:2n-6));
- 10 and 20% medium-chain triacylglycerols (MCTs)/LCTs (1:1 wt:wt) emulsions (MEDIALIPIDE® or LIPOFUNDIN®MCT, B. Braun, Melsungen AG, Germany);
- 20% structured-lipid emulsions (STRUCTOLIPID®, Fresenius Kabi AG, Germany); and
- an olive oil-based lipid emulsion (80% olive oil, i.e. mono-unsaturated oleic acid/20% soybean oil; CLINOLEIC®, Baxter SA, France).

In addition, over recent years more specific and/or complex lipid emulsions have been developed (but are not yet available in all countries) which may be used either as ready-for-use emulsions (e.g. (i) SMOFLIPID® (Fresenius Kabi), a physical mixture of soybean oil, MCTs, olive oil, fish oil and additional α-tocopherol; and (ii) LIPIDEM® (B. Braun), composed of MCTs/LCTs/n-3 fatty acids in a 5:4:1 (wt/wt/wt) proportion) (Schlotzer and Kanning, 2004; Ton *et al*., 2005) or as a proportion of the infused lipids (n-3 fatty acids: OMEGAVEN®, Fresenius Kabi).

This growing diversity of lipids available for IV administration in human nutrition and/or therapeutics opens a large research avenue for clinicians interested in the optimization of fat emulsion use both in short-term parenteral nutrition and in patients on HPN (Deckelbaum *et al*., 2004).

General Composition and Stability Issues

Composition and stability of parenteral nutrition admixtures are key points to consider before their administration. Stability problems may occur during preparation, storage and use of complex parenteral nutrition formulations. They can result from the intrinsic composition of the used lipid emulsions but, more frequently, from chemical instabilities arising from incompatibility with other components of the parenteral nutrition admixture. Systematically checking the composition of all parenteral nutrition formulations before use in human therapeutics is crucial, as the administration of an unstable or incompatible admixture may have serious clinical consequences (Food and Drug administration, 1994).

Structure and composition of lipid emulsions

The aim of using intravenously administered lipids is to mimic the flow of chylomicrons which, when delivered into the blood via the intestinal lymph, provide newly absorbed lipids to normally fed subjects. In parenteral nutrition, lipids have necessarily to be administered in the form of an emulsion, i.e. a dispersion of fine oil particles in a vector constituted by a continuous aqueous phase, usually containing glycerol. In addition to these two phases a stabilizing/emulsifying agent is indispensable both for the dispersion of the oil and for the stability of the resulting emulsion.

The first phase is formed by triacylglycerol-rich particles (TGRPs) modelled on the endogenous natural chylomicron. This phase is stabilized in the liquid hydrophilic phase by a surface layer composed mainly of phospholipids (Ferezou and Bach, 1999). In the case of lipid emulsions for parenteral use in humans, lecithins from animal (usually egg yolk) or vegetable sources (usually soybean) are commonly used (Davis, 1983). They contain up to six phospholipids, and provide both mechanical/physical and electrically charged barriers to prevent coalescence of TGRPs.

With lipid emulsions, compared to the amount strictly required for stabilization of the triacylglycerol content, the emulsifier is present in relative excess, leading to the formation of liposome-like, phospholipid-rich particles. When present in large amounts, these particular emulsion particles can impede the lipid and lipoprotein metabolism and modify cell membrane lipid composition (Haumont *et al.*, 1989, 1992; Kalfarentzos *et al.*, 1998). Therefore, because phospholipid excess is particularly noticeable in 10% emulsions, the use of 20 or 30% preparations (providing a more limited phospholipid:triacylglycerol ratio) is recommended (Carpentier and Dupont, 2000).

Stability of intravenous lipid emulsions

A very large number of chemical and physicochemical interactions can potentially occur between lipid emulsions and the other components of the parenteral nutrition admixture. In particular, this can be the case in HPN, based not only on the use of personalized, all-in-one (AIO) admixtures varying widely in composition from one patient to another, but also in the same patient from time to time depending on his/her specific nutritional requirements. Therefore, it is of outstanding importance that pharmacists and/or manufacturers involved in AIO bag preparation systematically ascertain the compatibility of the prescribed nutrients and/or drugs, as well as the final stability of the admixture.

In the case of lipid emulsions, several basic factors can interfere with stability, such as pH, glucose load, amino acids or electrolyte concentrations. Instability may result in a cracked, creamed or an aggregated lipid emulsion, depending on the factor(s) interfering with its stability. For example, after autoclaving, sterilized glucose solutions have a

pH that can range from 3.5 to 6.5, this varying between manufacturers and even within batches from the same manufacturer. This occurs as a result of glucose decomposition, first forming 5-(hydroxymethyl)-2-furanaldehyde and then formic and levulinic acids during the heating process.

The resultant drop in pH may result in a decrease in charge and repulsive forces to droplet aggregation. These aggregates have a combined size greater than the majority of droplets, and their natural Brownian motion is minimized such that they will rise to the surface of the emulsion to form a 'cream' layer.

A similar effect can be observed with cationic electrolytes if the 'critical aggregation concentration/number' – as defined by Davis (1983) – is inadequate. A large amount of cationic electrolytes, which exhibit an opposite charge to that of the surface charge of lipid droplets, will also reduce the surface potential on the droplets and, as a consequence, the repulsive forces between the droplets, leading to aggregation and coalescence. For all these reasons, physicochemical stability of lipid emulsions incorporated in HPN admixtures represents an important issue, with possible deleterious clinical implications (Driscoll, 2005).

Metabolism of Intravenous Lipid Emulsions

The infusion of the fat emulsion leads to the appearance of exogenous lipids in the bloodstream and produces a transitory increase in triacylglycerol and phospholipid concentrations. The metabolic pathways involved in intravascular metabolism of lipid emulsion TGRPs are complex, simultaneously involving several processes: (i) exchange and transfer of lipids and proteins; (ii) enzymatic hydrolysis of triacylglycerols and phospholipids; (iii) uptake of hydrolysis products; and (iv) internalization of several particles by different tissues. Schematically, these metabolic pathways are comparable to those of chylomicrons (Olivecrona and Olivecrona, 1998; Ferezou and Bach, 1999).

However, in contrast to endogenous chylomicrons, artificial emulsion particles contain no apoproteins. As soon as they enter the circulation, TGRPs rapidly acquire several endogenous apolipoproteins, in particular apo C-I, C-II, C-III, apo E and, probably, apo A-IV, derived essentially from the high-density lipoproteins (HDL) (Richelle *et al.*, 1986), but also transferred from the very low-density lipoproteins (VLDL) (Robinson and Quarfordt, 1979). This acquisition is influenced by the physical properties of the TGRP surface layer, depending on the composition of both emulsion triacylglycerols and phospholipids, and will therefore vary from one emulsion to another (Saito *et al.*, 1997; Arimoto *et al.*, 1998; Martins *et al.*, 1998).

In addition, plasma apolipoprotein content may vary according to health status, often being markedly altered in disease and susceptible to modifications with the effectiveness of inflammatory and immune responses

(Chenaud *et al.*, 2004). Therefore, apolipoprotein content of TGRPs provided by lipid emulsions in patients receiving parenteral nutrition may vary considerably depending on the clinical situation; whether these variations may have a critical impact on lipid emulsion efficacy and/or tolerance in the long-term setting remains to be determined. Nevertheless, apolipoprotein acquisition is an essential step as the binding of TGRPs to lipoprotein lipase (LPL) depends on apo C-II and apo C-III, and as cellular uptake of particles is modulated by apo C-III and apo E (Dupont and Carpentier, 1999; Ferezou and Bach, 1999).

After binding, a substantial proportion of core triacylglycerols are hydrolyzed, and the resulting free fatty acids are either taken up by the adjacent tissues or released into the circulation. This process, as well as the transfer of another fraction of triacylglycerols from TGRPs to HDL and low-density lipoproteins (LPL) in the exchange of cholesteryl ester (a process mediated by the cholesteryl ester transfer protein), reduce strongly the particle size and lead to the formation of remnant particles enriched with cholesteryl ester and depleted of triacylglycerols (Dupont and Carpentier, 1999; Ferezou and Bach, 1999). These are largely taken up by the liver (Cooper, 1997; Havel, 1998; Lambert *et al.*, 2001) and to a lesser extent by several other tissues such as muscle and adipose tissues (Karpe *et al.* 1997) or endothelial cells, and possibly by intestinal cells (Van Aerde *et al.*, 1997).

As mentioned earlier, differences in the composition of lipid emulsions clearly modulate selected metabolic steps (Hyltander *et al.*, 1995; Dupont and Carpentier, 1999; Carpentier and Dupont, 2000; Qi *et al.*, 2002; Schlotzer and Kanning, 2004; Simoens *et al.*, 2005; Ton *et al.*, 2005). Nevertheless, whether this may influence the efficacy and safety of lipid emulsions in HPN patients remains largely unexplored.

Lipid Requirements in Adults

The daily lipid requirement in healthy adults on oral diet has been set at 1.0–1.5 g/kg/day. This amount covers non-protein, non-carbohydrate energy requirements and prevents essential fatty acid (i.e. linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3)) deficiency (EFAD). An average daily provision of 3.0–4.5% of total calories as fat appears to prevent EFAD (Burr *et al.*, 1981). In HPN patients a balance has to be found between requirements and potential toxicity, in particular HPN-associated liver disease (see below).

Therefore, although no standard lipid requirements have been defined for these patients, the amount of administered lipid emulsion is lower (in all cases it should be no higher than 1 g/kg/day in long-term use (schematically an administration for more than 3 months) in order to prevent hepatic toxicity (see below; Cavicchi *et al.*, 2000) than in short-term parenteral nutrition (patients on parenteral nutrition for several weeks to < 3 months), enteral nutrition or in healthy or diseased subjects on oral diet. Usually, it varies between 0.3 and 0.9 g/kg/day (Reimund *et al.*, 1999, 2005; Pironi *et al.*, 2003; Chambrier *et al.*, 2004; Vahedi *et al.*, 2005).

In advanced cancer patients on HPN, where the mean length of survival was about 4 months, a lipid/glucose calories ratio of 1:1 was well tolerated for a total overall regimen of 25–30 non-protein kcal/kg/day, every day (Bozzetti *et al*., 1999, 2002). Whether the increase in lipid provision in these patients (alone or in combination with specific pharmacologic interventions), compared to patients receiving HPN for non-malignant diseases, modulates tumour growth has still to be investigated in future clinical studies in humans (Bozzetti *et al*., 1996, 2004).

Intravenous Administration of Lipids in HPN: Efficacy and Safety

Home parenteral nutrition efficacy depends on numerous factors related not only to the composition of parenteral nutrition admixtures but also to patient-related factors, e.g. underlying disease (Howard *et al*., 1991; Messing *et al*., 1995) or the experience and logistics of HPN centres (Messing *et al*., 1995; Smith *et al*., 2002; Reimund, 2003; Freshwater *et al*., 2005; Jonkers-Schuitema *et al*., 2005), etc. Numerous authors have investigated HPN efficacy in single or multiple centres (Messing *et al*., 1995, 1998; Reimund *et al*., 1999; Van Gossum *et al*., 2001; Ireton-Jones and DeLegge, 2005; Violante *et al*., 2006).

In the particular case of lipid provision, efficacy is closely related to safety. Unduly low amounts of lipids may lead to EFAD and its biological and clinical consequences, and too much fat provision may induce side effects which could limit HPN nutritional efficacy and, as a consequence, the patient's quality of life and rehabilitation status.

Essential fatty acid deficiency

Essential fatty acid deficiency is an important concern with HPN patients. Normally, there are large stores of EFAs in the body. However, in patients on fat-free total parenteral nutrition or in HPN patients receiving a too-low fat/too-high glucose admixture for a prolonged time, the induction of hyper-insulinaemia suppresses the mobilization of EFAs from fat stores and induces EFAD which can clinically be characterized by dermatitis (Sinclair, 1956, 1990; Jeppesen *et al*., 1997), hair loss, increased susceptibility to infection (Cederholm *et al*., 1994) or impaired wound healing (Hulsey *et al*., 1977). The following haematological abnormalities have also been described: (i) haemolytic anaemia; (ii) thrombocytopenia or diminished platelet aggregation; (iii) liver fatty infiltration; (iv) increase in hepatic enzyme activity; (v) impaired chylomicron synthesis; and (vi) impaired fat absorption (Jeppesen *et al*., 1997).

It is important to note that biochemical evidence of EFAD appears significantly earlier than clinical symptoms and signs. Usually, it can be diagnosed before clinical manifestations appear by assessing the Holman index or triene:tetraene ratio, i.e. the ratio of eicosatrienoic acid (20:3n-9)

to arachidonic acid (20:4n-6) in patients at risk. Initially, an index of > 0.4 has been considered as indicating EFAD, even in patients with no clinical signs (Collins *et al*., 1971). With improvement of methods of analysis for fatty acids, work by Holman *et al*. (1979) suggested values of > 0.2 as being more appropriate. Later, a value > 0.025 has been proposed as being diagnostic when healthy, free-living reference controls were compared to patients with intestinal fat malabsorption and suspected EFAD (Siguel *et al*., 1987).

Several groups have assessed the EFA status of HPN patients (Abushufa *et al*., 1995; Mascioli *et al*., 1996; Chambrier *et al*., 1998; Jeppesen *et al*., 1998; Reimund *et al*., 1998). Their results can be schematically summarized as follows: (i) EFAD depends on the considered cut-off value. For example, we found a mean Holman index of 0.031 ± 0.017 in 21 HPN patients, which suggested EFAD in several patients as we had defined EFAD as being at a level of > 0.025 (Siguel *et al*., 1987; Reimund *et al*., 1998). However, regarding Holman's definition (Holman *et al*., 1979), no patient will be considered as having subclinical EFAD; (ii) an amount of 1 g/kg/week is sufficient to avoid EFAD in HPN patients according to Holman *et al*. (1979); and (iii) given these data, one can conclude, as Jeppesen *et al*. (1998) did, that 'recommendations regarding lipid dosages in parenteral supplements depend on the degree of correction of plasma fatty acids in the phospholipids one aims at. Lipid dosage adjustments may be performed according to repeated blood tests in individual patients'.

Abnormalities of lipid metabolism

Intravenous fat administration can induce several abnormalities in lipid metabolism such as: (i) hypercholesterolaemia and lipoprotein-X formation; (ii) hypertriglyceridaemia; or (iii) exceptionally, the fat overloading syndrome (Wesson *et al*., 1984; Dahlstrom *et al*., 1988; Haber *et al*., 1988).

Hypercholesterolaemia and lipoprotein-X formation

Hypercholesterolaemia represents the most common alteration of serum lipids in parenteral nutrition patients. The administration of fat emulsions can result in an increase of plasma total cholesterol and phospholipid concentrations and a decrease in HDL-cholesterol, while the abnormal lipoprotein-X is formed. Some authors have suggested that hypercholesterolaemia is caused by excessive phospholipid provision which mobilizes the movement of free cholesterol from extravascular tissue to the vascular compartment (Untracht, 1982).

The phospholipid:triacylglycerol ratio is considered to be an important factor affecting these abnormalities; in fact, these changes are more frequent with 10% emulsions, whereas administration of 20 or 30% emulsions is associated with minor changes only (Rigaud *et al*., 1984; Haumont *et al*., 1989; Meguid *et al*., 1989; Hajri *et al*., 1990; Garcia-de-Lorenzo *et al*., 2003).

One study, performed in post-operative, short-term parenteral nutrition, has also suggested that abnormal lipoprotein-X occurred least with MCT/LCT 20% fat-emulsion than with the 20% LCT emulsion, 10% MCT/LCT or LCT emulsions (Hailer *et al*., 1998). However, these effects occur apparently without increasing the atherogenic risk.

Usually, unlike associated patient-related factors, hypercholesterolaemia and lipoprotein-X formation may not be deleterious to HPN patients, especially if lipids were not provided in excess; Carpentier (1993) recommends a rate of triacylglycerol administration not exceeding 0.15 g/kg/h in home patients on cyclic nocturnal parenteral nutrition, while other authors recommend rates as low as 0.03–0.05 g/kg/h (Jensen *et al*., 1990; Miles, 1991) and regular assessment of patients for these potential complications.

Hypertriglyceridaemia

Hypertriglyceridaemia appears when the metabolic capacity to clear infused lipids is exceeded. However, as for hypercholesterolaemia, if hypertriglyceridaemia occurs in a HPN patient, lipid provision should be adjusted and patient-related factors corrected (Llop *et al*., 2003).

Lipid peroxidation in lipid-based home parenteral nutrition

There are two main defence systems in humans against lipid peroxidation: (i) mineral-dependent enzymes (in particular, superoxide dismutase and glutathione peroxidase); and (ii) tocopherols (vitamin E), the most active being α-tocopherol. Vitamin E interacts directly with lipid peroxides to neutralize them in plasma lipoproteins and cell membranes. Lipid peroxides are labile species that can undergo further decomposition to give products such as malondialdehyde (MDA) and volatile carbohydrates (pentane and ethane), which can be measured in the serum (MDA) and on the breath (pentane). Both these measurements are considered to be sensitive methods for assessment of *in vivo* lipid peroxidation in humans.

In adult HPN patients, high breath pentane (Lemoyne *et al*., 1988; Van Gossum *et al*., 1988) and increased MDA concentrations (Pironi *et al*., 1998; Reimund *et al*., 2002) have been reported as being associated with decreased vitamin E concentrations (Lemoyne *et al*., 1988; Van Gossum *et al*., 1988; Pironi *et al*., 1998; Reimund *et al*., 2002) and to the polyunsaturated fatty acid (PUFA) load (Pironi *et al*., 1998). However, increased lipid peroxidation in HPN patients has never been associated with a detectable biologically or clinically deleterious effect.

Nevertheless, as olive oil-based lipid emulsions provided fewer PUFAs and higher vitamin E levels than did traditional LCT or MCT/LCT emulsions, these have been studied in HPN patients: in a double-blind, randomized study conducted in paediatric patients over 60 days, the peroxidation index was significantly lower after the olive oil treatment

(Goulet *et al*., 1999); in stable, adult HPN patients, despite a decrease in MDA concentrations in adults receiving CLINOLEIC® for a 3-month period at the same dosage as their initial lipid emulsion (LCT or MCT/LCT), the difference did not reach statistical significance.

In summary, adequate vitamin E (in particular, α-tocopherol) supply seems to be the best strategy for limiting lipid peroxidation in HPN patients. Whether olive oil-based or newer lipid emulsions induce less lipid peroxidation remains to be definitively proved.

Intravenous lipids and risk of infection

Compared to patients receiving no artificial nutrition (Snydman *et al*., 1982; The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group, 1991) or to patients on standard polymeric enteral nutrition (Moore *et al*., 1992; Bozzetti *et al*., 2001; Marik and Zagola, 2004) or immune-enhancing enteral nutrition (Braga *et al*., 1998), parenteral nutrition seems to be associated with a higher infectious complication rate, despite some studies in selected situations of short-term parenteral nutrition not confirming these results (Pacelli *et al*., 2001).

However, whether lipids in parenteral nutrition, especially in HPN, may be a metabolic bystander of this increased risk still remains a matter of debate. Considering only clinical studies in HPN patients, no definitive conclusion can be drawn. Some data suggest that the type of fat emulsion used (LCT, MCT/LCT, olive oil-based) does not influence the infection rate in this patients group (Reimund *et al*., 2005; Vahedi *et al*., 2005). The impact of newer emulsions has not yet been assessed.

Home parenteral nutrition-related liver disease and lipid emulsions

Soon after the introduction of parenteral nutrition, a spectrum of parenteral nutrition-associated liver dysfunctions and diseases were reported in both juvenile and adult patients at a rate ranging from 15–85% (Sheldon *et al*., 1978; Whitington, 1985; Baker and Rosenberg, 1987; Stanko *et al*., 1987; Sax and Bower, 1988; Clarke *et al*., 1991). Reported hepatic abnormalities during parenteral nutrition included: (i) increase in liver-associated enzyme blood activities; (ii) steatosis; (iii) steatohepatitis; (iv) steatonecrosis; and (v) intra-hepatic cholestasis, fibrosis and cirrhosis. Usually, these changes were not extreme and were reversible after the cessation of parenteral nutrition. However, some patients, especially those requiring long-term parenteral nutrition – i.e. HPN patients – may develop progressive hepatic failure that can lead to death in some cases.

A multifactorial pathogenesis has been proposed and includes both patient-dependent and nutritional factors (Quigley *et al*., 1993). Lipids have long been considered as one of the principal factors responsible for HPN-associated liver disease both in children (Colomb *et al*., 2000) and in

adults (Gerard-Boncompain *et al*., 1992), presumably due (but without any definitive data supporting this hypothesis), at least in part, to the presence of phytosterols in lipid emulsions (Clayton *et al*., 1998; Iyer *et al*., 1998; Ellegård *et al*., 2005). However, the levels of lipids provided should be considered with respect to the provided amount, as Cavicchi *et al*. (2000) from Messing's group clearly found an association between liver disease and a parenteral lipid intake greater than 1 g/kg/day.

In the case of lower levels of lipid provision in HPN patients, these probably do not contribute in any real sense to HPN-associated liver disease, and the following factors should be considered and, if necessary, corrected (Dickerson and Karwoski, 2002; Howard and Ashley, 2003): (i) total calories and intravenous carbohydrate calorie load (Reimund *et al*., 2001; Luman and Shaffer, 2002); (ii) underlying disease (in particular, ongoing inflammation) (McCowen *et al*., 2000; Reimund *et al*., 2001; Forrest *et al*., 2002); or (iii) intestinal bacterial overgrowth and translocation (Gunsar *et al*., 2002) and/or frequent sepsis (catheter-related infection).

Are parenteral nutrition-associated abnormalities related to the composition of lipid emulsions? This question is important but currently unresolved. Some studies suggested that lipid emulsions composed of 50% MCT and 50% LCT or of structured lipids may have less impact on liver function (Baldermann *et al*., 1991; Jaurrieta *et al*., 1991; Rubin *et al*., 2000); however, these data have not reached any consensus.

Preliminary observations also suggested that olive oil-based parenteral nutrition may reduce the impact of lipid emulsions on liver tests, both in short-term (Garcia-de-Lorenzo *et al*., 2005) and in long-term parenteral nutrition (Reimund *et al*., 2004). Nevertheless, these observations have to be confirmed by prospective, large-scale studies.

Conclusion: Some General Recommendations

Fat emulsions containing LCTs or a mixture of MCTs/LCTs have been successfully used as an essential part of HPN. Until recently, HPN has usually been organized in referral centres providing high expertise both in parenteral nutrition management itself and in the treatment of the often severe underlying diseases. Home parenteral nutrition uses, most commonly, AIO bags whose composition depends on patients' requirements. These AIO bags are infused over a 10–14 h cyclic nocturnal period in the majority of patients via central venous access using an infusion pump, and ideally in patients where a minimal oral intake remains possible. The number of AIO bags administered per week may vary from one patient to another according to their specific nutritional needs. Therefore, no standard lipid content can be recommended.

In most patients lipids are present in the ratio of 1:2 or 1:3 AIO bags:week. In adult patients, minimal fat supply may be around 1 g/kg/week, in order to avoid EFAD. Maximal lipid provision should not

exceed 1 g/kg/day in order to prevent severe HPN-associated liver disease. Regular surveillance of clinical nutritional parameters as well as biological markers (serum cholesterol and triglyceride concentrations, Holman index, liver function tests, etc.) may allow the provision for each patient of the optimal amount of lipid emulsions.

Safety of newer lipid emulsions has recently been reported in children (Goulet *et al*., 1999) and in adults (Reimund *et al*., 2005; Vahedi *et al*., 2005) for an olive oil-base lipid emulsion (CLINOLEIC®, Baxter) as well as for structured lipids (STRUCTOLIPID®, Fresenius Kabi). These studies suggest that these emulsions did not increase the risk of complications in patients with chronic intestinal failure on HPN but, at the same time, did not yet report significant advantages despite the following indications: (i) lower lipid peroxidation in one study in paediatric HPN patients with CLINOLEIC® (Goulet *et al*., 1999); (ii) no effect on parameters of immune function in adult HPN patients after 3 months' CLINOLEIC® administration (Reimund *et al*., 2005); and (iii) a suggestion of potentially better hepatic tolerance for both CLINOLEIC® (Reimund *et al*., 2004) and STRUCTOLIPID® (Rubin *et al*., 2000).

In our study, the observed results have been confirmed for a period of more than 2 years, as patients enrolled in the study continue to receive CLINOLEIC® as the lipid source (personal observation). These results have to be confirmed in larger studies on long-term administration. In addition, the potential interest in newer lipid emulsion use in HPN patients has not yet been explored and opens a large research area for physicians and/or scientists interested both in HPN patient management and in metabolism, as well as for the biological, immunological (Yaqoob, 2003) and clinical efficacy and safety of intravenous lipids.

Summary

Fat emulsions containing LCTs or a mixture of MCTs/LCTs have been successfully used as an essential part of HPN. Home parenteral nutrition uses, most commonly, AIO bags whose composition depends on patients' requirements. The number of AIO bags administered per week may vary from one patient to another according to their specific nutritional needs. In adult patients, minimal fat supply may be around 1 g/kg/week, in order to avoid EFAD. Maximal lipid provision should not exceed 1 g/kg/day to prevent severe HPN-associated liver disease.

Regular surveillance of clinical nutritional parameters as well as of biological markers (serum cholesterol and triglyceride concentrations, Holman index, liver function tests, etc.) may allow the provision for each patient of the optimal amount of lipid emulsions. Safety of newer lipid emulsions has recently been reported in children and adults for an olive oil-base lipid emulsion (CLINOLEIC®, Baxter), as well as for structured lipids (STRUCTOLIPID®, Fresenius Kabi).

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21 Amino Acids, Protein and the Intestine

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Key points

- The gut retains ingested protein, leading to a gradual release of constituent amino acids.
- The gut actively mediates the anabolic effects of enteral nutrition.
- The protein-sparing effect of the gut is facilitated by the 'quality' of ingested protein.
- The gut is crucial in intermediary amino acid metabolism, especially in citrulline production.
- Shortage of bowel mass impairs physiological gut functions.
- By administering parenteral nutrition, the protein-sparing function of the gut is bypassed.
- Loss of enterohepatic recycling may underlie taurine deficiency in patients on parenteral nutrition.
- Beneficial effects of glutamine-enriched parenteral and enteral nutrition have been described, but more supportive evidence is required to prove efficacy conclusively.

Introduction

All living organisms, from monocellular to the human species, need preformed amino acids, found in nature. Amino acids characteristically consist of a carbon chain with a carboxyl group and an amino group. Most amino acids are neutral and have an aliphatic or an aromatic carbon chain. Some are, however, diacidic (glutamic acid, aspartic acid) and some dibasic (lysine, arginine, histidine).

Over 20 different amino acids are found in protein (Table 21.1). Of these, eight amino acids are essential (indispensable) because the human body does not have the ability to synthesize them in significant amounts,

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Table 21.1. Specific functions of amino acids and their intermediate products.

Amino acid	Intermediate products	Functions	Supplementation efficacy
Alanine	Pyruvate	Gluconeogenesis Nitrogen transport	Data too limited
Arginine	Nitric oxide Urea Creatine Agmatine	Vasodilatation Immunomodulation Neurotransmission Ammonia detoxification Muscle constituent/fuel Cell signalling Ornithine precursor	Positive effects for use in immunonutrition on morbidity suggested in surgical and trauma patients; further research warranted.
Citrulline	Arginine production		
Ornithine	Polyamines	Cell differentiation Proline precursor	Improves healing of burn wounds (ornithine alpha-keto glutarate)
Proline	Hydroxyproline	Hepatocyte DNA, protein synthesis Collagen synthesis	
Asparagine		Aspartic acid precursor	(Asparaginase-induced asparagine depletion is therapeutic in leukaemia)
Aspartic acid	Oxaloacetate, fumarate	Gluconeogenesis	
Methionine	Creatine	Cysteine precursor (see arginine)	
Cysteine (Cystine)	Glutathione Taurine	Antioxidant Bile acid conjugation, neuronal cell development, regulation of membrane potential, calcium transport, antioxidant	Improves antioxidant status in undernutrition, inflammatory diseases. Reduces contrast-induced nephropathy in renal failure Mucolysis, symptom reduction in COPD
Glutamic acid	Glutamine alpha-ketoglutarate Glutathione Gamma-aminobutyric acid	Ammonia disposal Gluconeogenesis Antioxidant Inhibition of CNS Excitation of CNS (NMDA receptor)	
Glutamine	Ammonia Purines, pyrimidines	Inter-organ nitrogen transport Renal HCO_3 production RNA, DNA synthesis Glutamic acid precursor	Reduces infectious morbidity in trauma, burns and surgical patients

Continued

Table 21.1. *Continued*

Amino acid	Intermediate products	Functions	Supplementation efficacy
Glycine	Glutathione Creatine	Inhibition of CNS (glycine receptor) Excitation of CNS (NMDA receptor) Antioxidant (see arginine) Serine precursor	Adjuvant to antipsychotics, probably reduces negative symptoms of schizophrenia
Serine	D-serine	Excitation of CNS (NMDA receptor) Glycine precursor Cysteine precursor	Adjuvant to antipsychotics, probably reduces negative symptoms of schizophrenia
Threonine	Glycine Serine	Brain development	
Histidine	Histamine	Immunomodulation Gastric acid secretion	
Lysine	Carnitine Glutamate	Mitochondrial oxidation of long-chain fatty acids	Reduces chronic, stress-induced anxiety
Branched-chain amino acids			
Isoleucine			In upper gastrointestinal haemorrhage
Leucine	α-ketoisocaproic acid	Important in regulation of energy and protein metabolism Substrate for glutamine synthesis	Improves protein malnutrition and restores amino acid and neurotransmitter balance in hepatic failure and hepatic encephalopathy.
Valine	α-keto-β-methylvaleric acid α-ketoisovaleric acid		
Aromatic amino acids			
Phenylalanine	Tyrosine precursor		
Tyrosine	L-dopa Dopamine Norepinephrine, epinephrine Triiodothyronine, thyroxine	Dopamine synthesis Movement, mood, pleasure, motivation Activation of sympathetic nervous system (fight-or-flight response) Regulation of basal metabolic rate	Possible slight improvement of cognitive functions after physical or mental exhaustion. Metabolites are powerful pharmacotherapeutic drugs.
Tryptophan	Kynureninic acid Quinolinic acid Serotonin Melatonin	CNS inhibition CNS excitation Mood regulation Sleep regulation Intestinal motility Regulation of circadian rhythms	No known benefits of the amino acid itself.

and therefore has to rely on food ingestion for their supply. The other 11 amino acids can be synthesized from the eight essential ones, but the capacity to do this may be limited under specific conditions. Optimal diets therefore should contain, in addition to the essential amino acids, non-essential amino acids (see below).

There is a growing literature supporting the possibility that in disease conditions the supply of some non-essential amino acids may become limited, so that the normal amino acid composition of the diet may need to be modified to meet requirements (Luiking *et al.*, 2004; Melis *et al.*, 2004). In cases of severe liver failure the capacity of the liver to degrade certain essential or non-essential amino acids may become limited, which has led to the suggestion that the diet should contain diminished amounts of some amino acids that rely for their breakdown on the liver (Cabre and Gassull, 2005). HPN patients often have a short bowel and diminished intestinal mass, which diminishes the capacity for efficient digestion and absorption of a bolus meal; this, in turn, dictates recommendations on meal size and frequency, and will be discussed in a later part of this chapter.

In plant proteins amino acids exist in the D- and in the L- form. In animals only the l-form is used for incorporation in protein. Amino acids with the d- form in the diet therefore are not – or less efficiently – used for this purpose. Only D-methionine and D-phenylalanine can be efficiently used for human protein synthesis, because they can be transformed into the l-form via transamination reactions. Three or four amino acids are produced in the body that are not found in protein but that serve other purposes. Examples are the intermediates of the urea cycle (e.g. citrulline, ornithine) and proline. Taurine is abundantly present in the cell and acts as both a modulator of cellular hydration state and bile acid conjugant, but is not a true amino acid but an imino acid, because it does not contain a carboxyl but a sulphonic group.

Functions of Amino Acids

The major proportion of amino acids is present in proteins such as muscle protein or collagen, for which they function as building stones. Several types of protein can be distinguished (Table 21.2). Structural proteins in cells are quantitatively the most important group (90% of total body protein, 10–20% of body cell mass (Guyton and Hall, 1996)), whereas plasma and tissue proteins like albumin, immunoglobulins, haemoglobin and fibrinogen comprise < 10% of the total protein content of the body (Anderson and Anderson, 2002). A third group consists of highly active proteins such as enzymes, hormones, cytokines, genes, membrane carrier proteins, signalling proteins and others, which comprise < 1% of total body protein but which are important modulators of metabolism.

Free amino acids comprise only a fraction of the total body pool of amino acids, because > 95% are present in protein. The free plasma pool of amino acids in turn is only a small part of all free amino acids. This pool is

Table 21.2. Examples of different proteins in the body.

Type	Examples
Structural proteins	Actin
	Myosin
	Collagen
Extracellular proteins	Albumin
	Haemoglobin
	Fibrinogen
	Cytokines
	Immunoglobulins
	Acute-phase proteins
Intracellular/cell-bound proteins	Enzymes
	Membrane transporters
	Transcription factors
	Heat shock proteins

very similar in concentration to the extracellular extravascular pool of free amino acids. As this compartment is larger than the plasma compartment, its free amino acid quantities will therefore be proportionally larger than that of the plasma pool (Fig. 21.1).

In turn, the intracellular pool is larger than the free extracellular pool (plasma and extravascular), because most intracellular amino acid concentrations are much higher than extracellular concentrations (Guyton and Hall, 1996). This is due to the fact that a large part of the inward transport of amino acids is subject to active transport, which allows a very steep uphill gradient between the intra- and extracellular compartments. Part of these gradients is maintained by sodium-linked transport and, therefore, must be accompanied by increased Na^+- and K^+-ATPase activity to maintain membrane potential.

This is especially true for amino acids such as glutamine, alanine and serine. Na^+- and K^+-ATPase activity increases during metabolic stress (Hsieh *et al.*, 2003) but may fail to maintain membrane potential (Shires *et al.*, 1983). This explains why, when sodium transport fails in states of severe disease with altered membrane potential, both intracellular and extracellular amino acid concentrations change without necessarily reflecting a state of depletion.

From the foregoing it also follows that the free plasma pool forms only a minute part of the total amino acid content of the body. The amount of free amino acids in the body is primarily dependent on their rate of appearance, which in turn is the sum of protein degradation, synthesis and exogenous intake. Other factors, however, such as the activity of transporters, permeability or leakiness of the plasma membrane and degree of induction of rate-limiting degradative enzymes, also influence the concentration within – and concentration gradients between – compartments. Amino acid concentrations in plasma and other compartments should therefore be interpreted with caution.

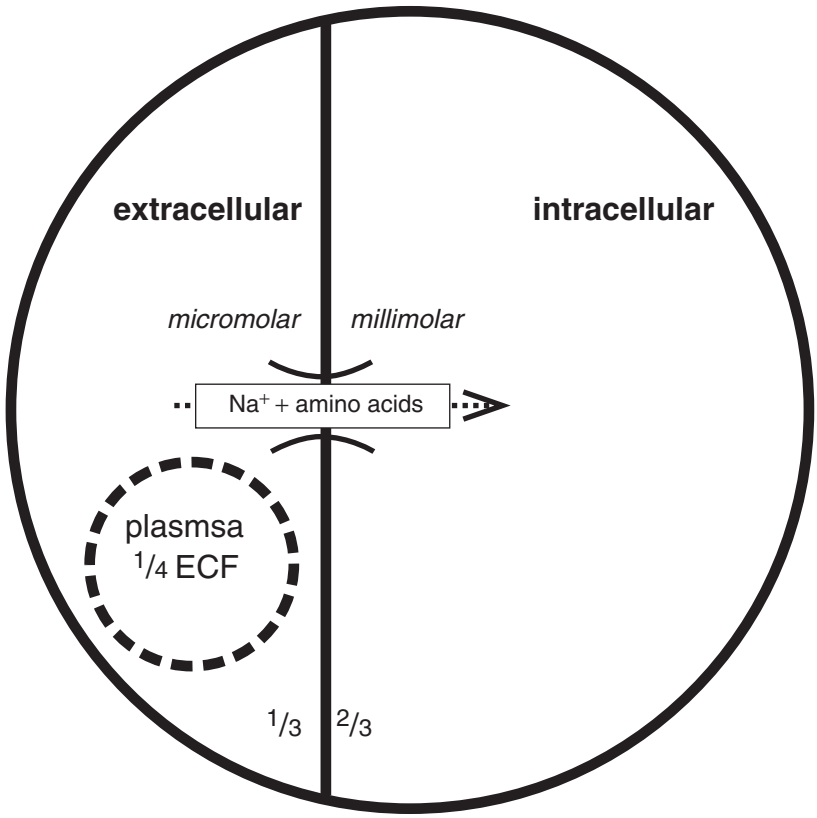

Fig. 21.1. Schematic representation of the distribution and transport of amino acids throughout the intracellular and extracellular compartments.

The availability of a complete precursor pattern of amino acids is crucial for protein synthesis. If one essential amino acid is lacking, peptide chain elongation will stop. In practice this situation is rare. An exception is the situation of bleeding. Haemorrhage presents the organism with substantial amounts of haemoglobin protein which, however, lacks isoleucine, one of the essential branched-chain amino acids. This situation leads to diminished protein synthesis and increased ammonia and urea synthesis (Deutz *et al.*, 1991), which may explain the dismal effects on encephalopathy in patients with liver insufficiency and upper gastrointestinal bleeding (Olde Damink *et al.*, 1999). In the absence of this rare condition and in the absence of an exogenous amino acid supply, protein synthesis will not stop, however, because there is a continuous supply of amino acids from the breakdown of protein. The kinetics of this protein turnover will be discussed in a later part of this chapter.

Specific amino acids may function as precursors of non-protein products playing other roles in human metabolism (Table 21.1). Claims have been made that in specific conditions these amino acids may become

limiting for the synthesis of their non-protein product or for the execution of a specific function. This claim is strongest for glutamine, which is produced in large quantities in burns, trauma and infection and which may become limiting when the disease process is prolonged and severe (Melis *et al.*, 2004). Supplementation may be beneficial in these conditions.

The same claim has been made for arginine, but this claim is not convincingly supported by clinical or experimental data (Luiking *et al.*, 2004). Arginine has been demonstrated to be produced in increased amounts in diseased states due to increased supply by net protein degradation. New formation of arginine by the intestine and kidney contributes no more than 15% of total production. It is therefore unlikely that arginine supply is deficient with regard to the production of NO, polyamines, etc. If there is a beneficial effect of arginine supplementation this may therefore result from its pharmacological action rather than from supplementation of a deficit. At present there is much interest in the potential effects of sulphur-containing amino acids, as they play important roles in the maintenance of redox state during oxidative stress. Efficacy of their supplementation has not been convincingly proved, possibly with the exception of iodine contrast-induced nephrotoxicity (Birck *et al.*, 2003) and acetaminophen poisoning (Brok *et al.,* 2002).

Degradation of Amino Acids

In animal and human metabolism there is continuous and simultaneous synthesis and degradation of protein. Both in health and disease exogenous administration of amino acids (as protein) is required to achieve an optimal balance. In the healthy organism the full quota of amino acids derived from protein degradation cannot be fully reutilized for protein synthesis because of the specific non-protein functions that are served by amino acids leading to non-reversible degradation. This explains why food protein is necessary to cover the deficit. The healthy adult organism is in protein/nitrogen balance when eating well. This implies that the amount of urea and other nitrogenous compounds lost in urine, stools, sweat, hair, nails, etc. equals the amount of food protein absorbed by the intestinal tract. In disease the net loss of protein nitrogen per day is far greater than in health (see below).

The amino acids lost in this manner can be disposed of in several ways, which depend on the metabolic condition of the organism. The amino acid may be wholly or completely used for the production of the specific product, as described in Table 21.1, but as these products are also subject to turnover no net degradation will occur, because the products of their degradation will, in turn, become available, partly as the amino acids that were used for synthesis. After irreversible loss of the amino group of the amino acid the remaining carbon skeleton becomes part of a pool that, without distinction, will deal with that carbon chain. Depending on stress

and fed or starved state the carbon skeletons will be largely oxidized (catabolism, starvation) after transformation to an intermediate of the tricarboxylic acid cycle or, when there is liberal supply, transformed into fat (from acetyl-coA or oxalo-acetyl-coA) or glucose (from pyruvate, lactate).

It is of interest to note that the site of irreversible degradation of amino acids is specific for each amino acid. The group of branched-chain amino acids is largely degraded in peripheral tissues (muscle, adipose tissue), whereas the aromatic amino acids (phenyl-alanine, tyrosine, tryptophan) are largely irreversibly degraded in the liver. It is also of interest that the branched-chain amino acids can be irreversibly degraded in adipose tissue and that the resulting carbon skeleton can be wholly (leucine) or partly (isoleucine) reutilized for triglyceride synthesis in adipose tissue itself.

Protein Metabolism in Starvation and Stress

The differences between starvation and stress metabolism of amino acids are well known. Whereas the body is able to limit protein losses during starvation, this is not the case during stressed states (trauma, infectious states).

In pure starvation all pathways are geared to the preservation of peripheral protein stores, specifically muscle protein. More 'central' organs like the splanchnic tissues lose protein mass (Romijn, 2000). Kinetically, a decrease in protein turnover is found in all organs, with protein synthesis slightly more depressed than protein degradation. In this muscle protein-sparing process the ability of tissues like the central nervous system to burn ketones – which can cross the blood–brain barrier (which fatty acids cannot) – as fuel, is a crucial mechanism. This allows the organism to decrease the production of new glucose (gluconeogenesis), which otherwise would need the carbon skeletons of amino acids. In this manner healthy individuals can decrease their urea production to around 1–2 g of urea nitrogen per day, whereas most of the urinary nitrogen (5–7 g in total) consists of ammonia nitrogen.

On the basis of these findings it has been reasoned (Owen *et al.*, 1969) that the liver produces almost no glucose from amino acid skeletons, whereas most of the glucose produced arises in the kidney because this is paralleled by ammonia production, necessary to buffer the acid urine resulting from the net production of organic acids in starvation. In stressed situations the reverse happens. The protein turnover of central organs such as the liver, spleen and the other components of the immune system is upregulated and net protein synthesis is actually increased in well-resuscitated intensive care patients – and in experimental animals challenged with endotoxin (Bruins *et al.*, 2003). Liver protein mass increases, immune cell proliferation is enhanced and more protein and cells are deposited in the wound. In muscle, protein turnover is also increased in previously well-nourished and resuscitated individuals, but protein degradation is clearly increased faster than protein synthesis,

leading to net muscle protein loss. This protein lost from muscle furnishes the amino acids necessary to build protein accrued in the central tissues. The role that the intestine plays in the re-routing of amino acids will be further discussed below.

Intermediary Amino Acid Metabolism in the Intestine

Glutamine metabolism in the intestine and intestinal integrity

Glutamine is an important substrate for the intestine and plays a central role in intermediary amino acid metabolism in the gut. It serves the following functions: (i) as a fuel; (ii) as precursor of protein, glutathione, polyamines and nucleotide synthesis; and (iii) as a nitrogen carrier. The degradation of glutamine in the gut wall yields, as the main nitrogenous substances, ammonia, alanine, glutamate and citrulline. Enterocytes incubated *in vitro* in a glutamine-containing medium produce glutamic acid, alanine and ammonia in a time- and concentration-dependent manner (Matsutaka *et al.*, 1973).

Windmueller and Spaeth (1974, 1975, 1980) assessed in a large series of semi-*in vivo* experiments on the fate of glutamine-derived nitrogen and the contribution of glutamine to the provision of energy in the intestine. Glutamine was taken up from the intestine in a concentration-dependent manner and was metabolized to other amino acids and ammonia. Glutamine nitrogen was found in the following proportions: 36% in alanine, 7% in proline, 10% in citrulline, 11% in ornithine and 36% in ammonia. Energy coverage was found to be derived in the following proportions: 35% from glutamine carbon, 26% from 3-hydroxybutyrate, 24% from acetoacetate, 7% from glucose and the remainder from lactate and unesterified fatty acids.

Despite these important findings it took another decade before the clinical relevance of these findings was appreciated by clinicians, and before research was initiated to explore the potential benefits of glutamine supplementation through *in vivo* experimentation (Yoshida *et al.*, 1992) or in a clinical setting (Scheltinga *et al.*, 1991; Ziegler *et al.*, 1992).

Glutamine metabolism in the intestine after trauma and in models of sepsis

Souba and Wilmore (Souba and Wilmore, 1983; Souba *et al.*, 1983, 1985 a,b,c, 1987, 1990; Souba, 1993; Sarac *et al.*, 1994) have greatly stimulated research in this area and found that in experimental animals endotoxin was very important in stimulating the uptake of glutamine by both the intestine and liver. We found, in similar experiments in pigs, that both after surgical trauma and after endotoxin challenge net release of glutamine by the hindquarters increased, whereas the net uptake by the intestine decreased (Deutz *et al.*, 1992a; Bruins *et al.*, 2000); uptake by the liver and the spleen increased. In these two organs the metabolism of glutamine changed from a

modest net release in the control, non-stressed situation to net uptake after trauma or endotoxin challenge (Deutz *et al*., 1992a).

This increased net flux of glutamine is supported by the finding that after trauma and sepsis the A-V difference across the hindquarters or forearm increases (Clowes *et al*., 1980; Carli *et al*., 1990; Fong *et al*., 1990; Mjaaland *et al*., 1993; Brown *et al*., 1994). This must imply that the glutamine released by the hindquarters is taken up by central organs such as the liver and spleen, as found in our experiments (Deutz *et al*., 1992a). Rather unexpectedly, whole body tracer data do not indicate a substantial increase in the turnover of glutamine after trauma or during sepsis (Gore and Jahoor, 1994; Jackson *et al*., 1999; van van Acker *et al*., 2000). This probably implies that the increased net flux of glutamine from peripheral tissues to central tissues is not generated by increased production in muscle and increased uptake in central tissues, but rather by decreased uptake in muscle and decreased production in central organs.We found, in contradistinction to the findings of Souba and Wilmore (Souba and Wilmore, 1983; Souba *et al*., 1985 a,b, 1987), that peripheral – predominantly muscle – tissue produces glutamine that is subsequently taken up by the splanchnic tissues but not by the gut. Our data show that the intestine itself is in this process a rather passive organ that takes up less glutamine in the fasted or traumatized state, whereas the liver and the spleen take up more glutamine even in the presence of lower plasma levels (Deutz *et al*., 1992a; Bruins *et al*., 2000). In the semi-*in vivo* setting, plasma glutamine level has been suggested as being an important factor determining uptake of glutamine by the intestine (Windmueller and Spaeth, 1974, 1975, 1980).

A-V differences across the jejunum and ileum in humans during abdominal operations were found to correlate with plasma glutamine levels (van der Hulst *et al*., 1997). The fractional extraction of glutamine was by far the highest (30%) in the jejunum. This was paralleled by the A-V differences of the main products of glutamine degradation: ammonia, citrulline, proline, ornithine and alanine (van der Hulst *et al*., 1997). The release of these degradation products of glutamine was much larger in the jejunum than in the ileum.

A-V differences across the colon showed some uptake of glutamine and a modest release of glutamic acid and ammonia in the venous effluent of the colon in a non-concentration-dependent manner. It is possible that ammonia release in the colon is effectuated by a modest degradation of glutamine in the colonocyte and by bacterial degradation of urea, and probably amino acids.These findings indicate that uptake of glutamine by the small intestine is concentration-dependent (van der Hulst *et al*., 1997). Furthermore, the negative effects of starvation on intestinal integrity have been demonstrated to be counteracted by infusion of glutamine (van der Hulst *et al*., 1993). This raises the question as to which factors determine glutamine levels.

In the past, we have claimed that the depleted state causes plasma glutamine levels to drop. Most clinical patients that have lost weight and are considered to be depleted also exhibit symptoms of chronic inflammation. It is therefore often difficult to separate the influences of chronic inflammation

and depletion. To separate the influences of these two factors we reviewed our data, and found that patients exhibiting signs of inflammatory activity had low plasma glutamine levels and increased permeability of the bowel. In this subgroup of patients glutamine supplementation appears to reduce intestinal permeability (Hulsewe *et al*., 2004).

Glutamine uptake in solid tumours of the colon

Studies in cancer cell lines have shown that some cell types degrade large quantities of glutamine (Bode *et al*., 2002). It has been suggested that some cancer types may therefore act as a 'sink' for glutamine. In the same experiment in surgical patients, in which we studied A-V concentration differences in different parts of the intestine, we also assessed A-V differences across parts of the colon containing malignant tumours. In accordance with observations by Holm's group (Holm *et al*., 1995), we found that there was no preferential uptake of glutamine by these tumours (van der Hulst *et al*., 1997). For coverage of their energy requirements colonic cancers appeared to rely on glycolysis, because there was a substantially increased uptake of glucose and stoichiometric release of lactate compared to that in healthy parts of the colon.

The role of the intestine in the routing of nitrogen and carbon

Disease and trauma need to be overcome by the body by an adequate host response, which requires substrate. In these stress conditions the organism is generally starving. The substrate therefore has to be delivered predominantly by peripheral tissues, released into the circulation and taken up by the central and crucial organs such as the liver, immune system and site of trauma, in which this host response occurs. The transport needs to be non-toxic and the waste products arising from these substrates need to be presented to the organs involved in their clearance. The two main categories of substrates necessary to sustain a host response consist of: (i) appropriate fuel; and (ii) amino acids necessary for synthesis of proteins that play important roles in the host response. Glutamine carbon is an important fuel for white cells in the liver, spleen and the remainder of the immune system (Newsholme, 1988; Murphy and Newsholme, 1998). Glutamine is released by peripheral (muscle) tissues and is derived from three sources: (i) the free intracellular pool; (ii) protein breakdown; and (iii) new formation. The free tissue pool can furnish this glutamine only to a very limited degree, because it is small compared to the flux taken up in the splanchnic area.

Also, the amount of glutamine derived from protein degradation is modest because glutamine constitutes only 5% of human muscle protein and the amount of amino acid-containing nitrogen exported from muscle consists of 30% glutamine. A substantial part of glutamine release is therefore derived from new formation of glutamine in the periphery,

where ammonia taken up is bound to glutamic acid, which in turn arises from transamination of branched-chain amino acids to α-ketoglutarate, largely resulting from the degradation of glucose. The branched-chain amino acids serve as fuel for muscle tissue after their transamination.

Therefore, the catabolic process in muscle furnishes: (i) amino acids that function as building blocks for protein synthesis in the liver, site of trauma and immune system; and (ii) glutamine that serves as fuel for the white cells in the liver, spleen, trauma site and immune system. Glutamine is ideally suited for this purpose, because its concentration and flux can vary without toxic side-effects. The carbon skeleton of glutamine can easily be oxidized to generate energy and the sites where it is degraded are ideally located, so that the ammonia resulting from the first step in its breakdown is presented to the liver and the kidney. These organs can adequately deal with this ammonia by its transformation to urea or by its excretion in the urine, respectively.

The role of the intestine in the routing of amino acid-derived carbon skeletons

The role of the intestine in the routing of amino acid-derived carbon is not completely elucidated. Part of the glutamine skeleton is oxidized, part is degraded to yield alanine and citrulline. Ubiquitously, ^{14}C-labelled glutamine carbon was shown to be metabolized by the intestine to the following: CO_2 (55%), lactate (8–15%), citrate (2%), other organic acids (1%), citrulline (5%), proline (4%), alanine (4%) and glucose (4%) in an *ex vivo* experimental set-up (Windmueller, 1982).

The formation of alanine in muscle can be considered as part of the Cori cycle, in that it is released into the circulation and subsequently serves as a precursor for gluconeogenesis in the liver or kidney. Peripheral tissues take up the glucose thus produced in the liver, where it can yield anaplerotic substrate for the Krebs cycle or where it serves in glycolysis.

Pyruvate resulting from glycolysis in turn can be transaminated with branched-chain acids to yield alanine, which is released into the circulation and, in turn, can participate in renewed Cori cycling. Badly perfused tissues with low mitochondrial metabolism and deficient fatty acid utilization during sepsis or severe illness apparently require increased glycolytic flux, which provides energy in compromised tissues but needs to be fuelled in organs that still have preserved Krebs cycle activity. The main organ performing this function is the liver.

The role of the intestine in the production of specific amino acids

Citrulline and arginine

The intestine is the only site where substantial amounts of citrulline are produced by way of the enzymes glutaminase, ornithine-oxoacid amino-

transferase and ornithine transcarbamylase, which degrade glutamine to citrulline via glutamate and ornithine. The production of citrulline is crucial as an intermediate step in the urea cycle, but it also has been claimed to be crucial because it can be released into the circulation then taken up by the kidney, where arginine can be produced via argininosuccinate synthetase (ASS) and argininosuccinate lyase (ASL).

Arginine plays an important role in protein synthesis and NO production and its deficiency has been implicated in numerous diseases (Wu and Morris, 1998). The relevance of intestinal citrulline production for arginine synthesis is underlined by the fact that the length of the remaining small bowel in short bowel syndrome has been demonstrated to correlate with low arquinine levels (Osowsha *et al.* 2004).

In case reports, hyperammonaemic encephalopathy has been described in the presence of healthy liver but short bowel (Yokoyama *et al.*, 1996), and has been ascribed to a limited supply of urea cycle intermediates. Similarly, focal tubulo-interstitial nephritis has been suggested as resulting from short bowel and low citrulline – and consequently arginine – levels (Hebiguchi *et al.*, 2002). This suggestion was supported by the observation that supplementation with arginine was effective in reversing the renal pathology.

We found in surgical patients a consistently negative arterial-portal concentration difference for arginine (van der Hulst *et al.*, 1997). This arginine is newly formed in the intestines by ASS and ASL, which are modestly expressed in the adult gut and did not arise from net negative protein balance or from residual absorption from the gut lumen, because no net production by the gut was found for other (conditionally) essential amino acids.

The liver takes up arginine and, therefore, in the fasted state intestinal arginine production does not lead to net splanchnic release and does not contribute to the systemic free arginine pool. It must be noted, however, that the hepatic fractional extraction of arginine is only 25%. This indicates that increasing arginine flux in the portal vein may lead to splanchnic arginine production and explains why systemic arginine levels can be stimulated by enteral arginine supplementation.

Cynober (1994) has suggested that, at times of high arginine intake, arginine is taken up from the gut and released into the portal vein. On the other hand, when omnivorous mammals are kept on a low-arginine diet, the intestinal enzymatic machinery adapts and converts most of enterally administered arginine to citrulline (Cynober *et al.*, 1995). It has been suggested that this change represents an adaptation aimed at prohibiting hepatic nitrogen loss, since it has been suggested that the liver does not take up citrulline in contrast to arginine (Windmueller and Spaeth, 1981). However, the view that the liver cannot take up citrulline is not consistently supported by *in vivo* data in laboratory animals (Remesy *et al.*, 1978; Deutz *et al.*, 1992b) and in humans (M.C.G. van de Poll *et al.*, unpublished data). In fact, these recent studies suggest that citrulline extraction may be in the same range as hepatic arginine extraction.

Whether arginine production in the kidney is really crucial at times of dietary shortage is questionable, because in such situations whole body protein catabolism will furnish quantities of arginine that are several-fold larger than those from renal production (Castillo *et al.*, 1993).

Taurine and glycine

We found unexpectedly high concentration differences across the jejunum and ileum of glycine and taurine in surgical patients who had been starved for at least 12 h (van der Hulst *et al.*, 1997). The release of taurine into the venous effluent of the ileum reached levels of a similar order of magnitude to the uptake of glutamine and the release of alanine. An obvious explanation is that in the process of re-absorption of conjugated bile acids in the small bowel these conjugates are de-conjugated and released into the portal vein as bile acids and free glycine and taurine. It demonstrates that enterohepatic cycling of bile salts is not restricted to the bile acid part but also applies to these amino acids.

The consequences of bile acid malabsorption and the coincident loss of glycine – and especially taurine – have not received much attention in the literature, but at least one case report suggests that these findings may be clinically relevant.

It has been shown that children receiving parenteral nutrition without supplemental taurine developed low taurine plasma levels and neuronal (especially retinal) dysfunction, which could be counteracted by addition of taurine to the feed (Geggel *et al.*, 1985). The indispensability of taurine in this condition has been ascribed to low expression of taurine biosynthetic enzymes, which can account for only a very low renewal of the total body pool of taurine. Taurine may, therefore, only be dispensable when it can rely on adequate and almost complete conservation of the taurine pool via enterohepatic cycling of taurine (van der Hulst *et al.*, 1997). Most children and adults on long-term parenteral nutrition suffer from intestinal malabsorption, which may induce substantial losses of bile acids, glycine and taurine in their stools. As far as we know no data are available on this subject.

Intermediary Protein Metabolism in the Intestine

The biological value of protein

It is well known that after a meal a healthy organism retains protein, which implies that at the whole body level more protein is synthesized than is degraded. This retention is balanced after 24 h by net protein loss during the fasting state during the night. It has been suggested (Waterlow, 1995) – and evidence has been provided – that the splanchnic area, and specifically

the intestine itself (Volpi *et al.*, 1996; Mariotti *et al.*, 2000; Dangin *et al.*, 2001; Soeters *et al.*, 2001; van Der Schoor *et al.*, 2002), accumulates protein after a meal and releases amino acids from this protein in the post-absorptive period.

The distinction between intestinal and hepatic utilization of meal-derived protein is difficult, for methodological reasons. In addition, the assessment of protein kinetics by the gut is hampered by the fact that metabolizable amino acids are derived both from the intestinal lumen and from the arterial inflow of amino acids. Also, the intestine stores, synthesizes and releases protein both in the gut lumen and in the gut wall. All these factors complicate the precise assessment of what happens with meal-derived protein.

The quality of a protein is generally believed to be dependent on two factors: (i) the digestibility/absorption; and (ii) the composition of the protein. In recent years it has become apparent that a third factor, too, decisively contributes to protein quality. The previous view considered the rapid appearance of amino acids in the portal vein after a bolus meal as evidence for the quality of the protein. At that time it was not appreciated that this rapid appearance coincided with increased ureagenesis and gluconeogenesis.

A more modern view is that the appearance of amino acids after a bolus meal should be slow and prolonged, in order to make amino acids available to the organism over a protracted period of time and at a slow rate (Pacy 1994; Quevedo 1994; Volpi 1996; Mariotti 2000; Dangin 2001; Soeters 2001). This increases the efficiency of utilization of these amino acids for protein synthesis and decreases their net breakdown. The mechanism operative in this protein-sparing effect is that amino acids derived from the digestion of a bolus meal are, to some degree, retained in the intestinal region (Mahe 1996; Boirie 1997; Gaudichon 1999; van Goudoever 2000; van der Schoor 2001) and do not immediately appear in the portal vein.

There must be a pool of amino acids in the intestine that can enlarge in size after the meal, and that in the post-absorptive state decreases in size and slowly releases amino acids into the portal vein – and subsequently into the systemic circulation (Soeters 2001). The nature of this pool most probably consists of rapidly synthesized or more slowly degraded protein.

Support for this mechanism consists of the fact that bolus meals – with a composition suitable for protein synthesis – decrease and prolong the appearance of amino acids in the portal vein. If a protein is supplied in the bolus meal lacking one essential amino acid and thus disfavouring protein synthesis, amino acids appear more rapidly in the portal vein and induce more ureagenesis (Soeters 2001). This also happens when the bolus meal consists only of protein and does not contain calories such as carbohydrates or fat (Soeters 2001). When a tapered release of amino acids derived from degradation of the protein in the meal, and the resulting low production of

urea, is considered as evidence for the biological value of the protein in question, casein protein clearly has a better quality than either soy (Deutz 1998) or whey proteins (Boirie 1997).

The Regulation of Protein Accretion in the Intestine

Many authors have confirmed the presence of a positive protein balance after a meal (Melville *et al.*, 1989; Millward *et al.*, 1991; Pacy *et al.*, 1994; Quevedo *et al.*, 1994). In most reports whole body level protein degradation was diminished whereas protein synthesis decreased or did not exhibit changes (Melville *et al.*, 1989; Pacy *et al*, 1994; Quevedo *et al.*, 1994; Cayol *et al.*, 1995). After a meal containing either casein or soy as a protein we found that feeding self-evidently increased the net appearance of amino acids in the portal vein. Both proteins increased protein degradation to a similar degree, but protein synthesis increased to a greater extent with casein than with soy (Deutz 1998). This difference was not significant, but the difference between appearance (protein degradation) and disappearance (protein synthesis) of phenylalanine was lower in the casein group than in the soy group. This implies that less of the meal-derived protein appears in the portal vein and that therefore more of the casein protein is temporarily retained in the intestine.

Simultaneously, urea production was greatly enhanced in the first few hours after initiating tube feeding in those pigs in the soy group, whereas this was not the case in the casein group. When more protein is administered, more of the protein-derived amino acids will be oxidized (van der Schoor *et al.*, 2001). Other groups reported similar findings (Mahe *et al.*, 1996; Volpi *et al.*, 1996; Gaudichon *et al.*, 1999; van Goudoever *et al.*, 2000; van der Schoor *et al.*, 2002).

Beaufrere's group (Boirie *et al.*, 1997; Arnal *et al.*, 2000) employed a dual tracer technique with one leucine tracer given with the meal intravenously and a different tracer intragastrically, and found the following: (i) more whey protein than casein protein appeared in the first few hours after the meal in the portal vein; (ii) amino acid concentrations were higher in the whey group; and (iii) the protein synthesis rate was higher. After 2 h, however, protein synthesis dropped in the whey group whereas in the casein group synthesis remained higher than in the whey group, and protein degradation remained suppressed longer in the casein group.

All these findings are consistent with the interpretation that, despite the fact that the meals are identical, isocaloric and isonitrogenous, different proteins are utilized differently. The rapid appearance and high level of oxidation of whey proteins has led to the designation 'fast dietary protein', but implies that it has a short-lived anabolic effect whereas a 'slow dietary protein' – like casein – is oxidized to a lesser extent and has a longer lasting anabolic effect, which makes it a protein with a higher biological value.

The Nature of the Labile Protein Pool in the Intestine

The question may be raised: what is the nature of the protein temporarily retained in the gut after a meal? The first possibility includes differences in the rate of digestion and absorption (Dangin *et al.*, 2001). This may apply for casein, which is known to coagulate in the stomach and consequently to be digested at a much slower rate than most other proteins, but this was not found in the studies of Beaufrere and in our studies. In addition, the differences in appearance that occur when circumstances for protein synthesis are not optimal cannot be explained by the poor digestibility of casein.

The explanation for these findings appears to be more complex. After a bolus meal the concerted action of amino acids, glucose, insulin and cholecystokinin stimulates the secretion and synthesis of pancreatic and intestinal digestive enzymes (O'Keefe *et al.*, 1994; Bragado *et al.*, 2000). Part of this complex is already present in the pancreas as zymogen stores, waiting to be released during the meal. Control of this process occurs at the post-translational level (Bragado *et al.*, 2000). This process adds protein contained in enzymes to the total protein and amino acid pool in the intestine, which makes the interpretation of tracer studies during enteral feeding difficult.

However, it does not explain the retention of meal-derived amino acids, because the enzymes released were already present and were not synthesized from amino acids derived from the meal. These considerations do not fully apply to the synthesis and secretion of enzymes by the intestinal mucosa, because at this location amino acids utilized for enzyme protein synthesis may be derived both from the intestinal lumen and from the systemic circulation (Nakshabendi *et al.*, 1995; Bouteloup-Demange *et al.*, 1998). For this to be the case, it must be possible that goblet cells and enterocytes take up amino acids from the intestinal lumen and from the baso-lateral membrane.

Similar considerations apply to the synthesis of mucin in the intestine, pancreas and in bile. The question is whether mucin is directly synthesized from gut-derived substrate or from substrate derived from the systemic circulation.

A second potential store of amino-nitrogen consists of di-/tri-polypeptides or proteins absorbed from the intestinal lumen or synthesized in the intestinal mucosa and released into the portal vein. Claims have been made that part of protein-derived amino-nitrogen is released in this manner, but very little reliable data are available. At present, an estimate of the quantity of protein secreted into the portal vein by the gut cannot be made.

A third, and very likely, factor contributing to retention of meal-derived protein inside the intestine is proliferation of bacteria and bacterial protein during and after the meal, which subsequently is digested and absorbed by the enterocytes.

These three potential forms of acutely produced protein may form part of the labile protein pool that accumulates during and after the meal, and

in the post-absorptive phase is degraded, furnishing amino acids to the organism. The result is that after 24 h a zero protein balance is reached.

The presence of a labile protein pool in the intestine is known to be present in nature. An extreme example is the python, which feeds once every 2 months. After the feed there is enormous hypertrophy of the intestine, but also the meal itself is known to be digested and absorbed very slowly. This has the beneficial effect that it tapers the release of meal-derived amino acids to the liver, which would otherwise rapidly degrade these amino acids, produce large quantities of urea, burn the resulting carbon skeletons or store them as glycogen or fat. This is beneficial at times when food is scarce, and when the organism has to rely on the unforeseen moment that food is available. The ability of the human organism to retain protein in this labile protein pool is very modest, however, compared with other species such as reptiles (Holmberg *et al.*, 2002).

The data reviewed also indicate that for the labile protein pool to expand maximally, a protein with a high biological value should be consumed, combined with calories and other essential nutrients for promotion of maximal protein synthesis. We reported similar findings with regard to casein and soy protein. Soy appeared much faster in the portal vein and stimulated urea production to a much greater extent than casein. These findings have defined casein as a slow protein, and whey and soy protein as fast proteins, and support the claim that casein is a better protein in healthy organisms consuming bolus meals.

Consequences for Patients on HPN

The most important indications for long-term parenteral nutrition are short bowel syndrome (SBS) and intestinal failure. These patients suffer from massive fluid loss and nutrient malabsorption, but also lack the active role the intestine plays in amino acid and protein metabolism.

Intermediary metabolism

Loss of intestinal mass may lead to disturbances in intermediary metabolism, exemplified by the diminished glutamine to citrulline conversion and consequent low citrulline plasma levels. Such changes may induce very specific demands with respect to amino acid composition of the feed and feeding frequency to avoid specific deficiencies and to maintain nitrogen balance. Solid data (especially clinical data) regarding the need of specific amino acid supplementation in patients with SBS are scarce, however.

Glutamine

Much research considering specific problems in amino acid metabolism in patients on HPN focuses on glutamine (partly reviewed above). The

beneficience and the possible working mechanisms of glutamine remain subject to debate (Ockenga *et al.*, 2005). The strongest claims for the beneficience of glutamine supplementation are derived from clinical studies concerning the simultaneous administration of glutamine and growth hormone. This combination is suggested as both augmenting intestinal adaptation and promoting weaning from parenteral nutrition (Byrne *et al.*, 2005). These results, however, have not been consistently reproduced in similar studies (Scolapio, 2004), which probably implies that the potential effect of glutamine (+ growth hormone) – if it exists – is only small.

Citrulline

Loss of bowel length and mass impairs the conversion of glutamine to citrulline, which is accompanied by reduced citrulline levels. It has been suggested that these levels actually represent a citrulline deficiency, and citrulline supplementation restores citrulline and arginine levels in rats with a short bowel (Osowska *et al.*, 2004). Simultaneously the nitrogen balance improved in animals treated with citrulline. Because the concept of citrulline supplementation in intestinal failure is relatively new, no clinical data regarding its effectiveness are at hand.

Taurine and cysteine

Patients (especially children) on total parenteral nutrition are at risk of developing taurine deficiency (Lourenco and Camilo, 2002). Taurine normally is a non-essential amino acid, but it relies on enterohepatic cycling to maintain its total body pool (van der Hulst *et al.*, 1997). Taurine deficiency in children on artificial nutrition is generally ascribed to the incomplete development of enzymes involved in taurine synthesis, but the role of (absent) enterohepatic cycling has received no attention. Taurine is a standard component of virtually all parenteral and enteral feeding solutions.

Cysteine can function as a precursor for taurine and it has been shown that cysteine supplementation can restore taurine levels in children on HPN (Helms *et al.*, 1999). Cysteine may also have beneficial effects on the intestinal mucosa through its antioxidative capacity (Ardite *et al.*, 2000). Clinical data on the potential role of cysteine in parenteral nutrition are lacking, however.

Protein accretion and feeding frequency

During total parenteral nutrition the protein-sparing effects of the intestine, which facilitate gradual release of nutrients after bolus feeding, are obviously absent. In these patients a continuous infusion of nutrients is needed to ensure a gradual nutrient supply to the body and to maintain body cell mass. Evidently, such a continuous infusion limits the mobility of

the patient. To improve mobility in most patients nocturnal enteral (or parenteral) nutrition is instituted through fine-bore feeding tubes. These patients may also benefit from more frequent but smaller enteral meals during the evening and the night.

Feed composition

In cases of severe, chronic, protein-losing enteropathy, it might become necessary to compensate nitrogen losses by liberal administration of amino acids. In severe cases even surgery should be considered. Such extremes, however, can regularly be avoided and in fact electrolyte losses and disorders generally predominate over nitrogen losses in patients with SBS.

There are a number of disease-specific parenteral and enteral feeding solutions with varying amounts of, for example, sulphur amino acids, arginine and branched-chain amino acids. In most cases however, lack of clinical data leaves room for discussion about their clinical efficacy. Large, randomized clinical trials are needed to establish the potential advantages of such disease-specific feeds. Similarly, the quality of the various products for standard HPN from different manufacturers has not been compared in clinical trials, but similarity in protein source and amino acid composition suggests that these differences, if any, are small.

Summary

Amino acids are the building blocks of protein and are involved in numerous specific functions. Adequate amino acid intake is necessary to maintain body cell mass and to support these specific functions. The gut actively regulates the rate at which ingested proteins are degraded and released to the circulation and thereby mediates the anabolic effects of ingested proteins and the duration of the postprandial anabolic phase.

The gut is also a metabolically active organ, for example for the production of citrulline and for the maintenance of the body taurine pool. These specific gut functions may be impaired in patients on parenteral nutrition and/or patients with intestinal failure. A gradual, long-lasting infusion of amino acids in these patients is preferable to bolus administration for improvement in nitrogen homeostasis.

The composition of parenteral or enteral feeding solutions (for example, high glutamine or citrulline levels) has been suggested as influencing nitrogen balance or specific amino acid functions, but the efficacy of these adjusted compositions is still the subject of debate and ongoing studies.

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22 Micronutrients

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Key point

- In patients on home parenteral nutrition (HPN), provision of micronutrients must avoid deficiency and optimize function.

Introduction

Most patients who require home parenteral nutrition will already have been in hospital for a substantial period, and will have been stabilized on a regimen providing amounts of energy and amino acids which meet their requirements. They will no longer be undergoing net catabolism as a result of previous surgery or other therapy, and it is unlikely that there will be an additional requirement for rapid anabolism. Hence, nutritional requirements for all nutrients, including the micronutrients of vitamins and trace elements, will be similar to those of free-living individuals who are consuming a normal oral diet – variations in requirement will largely result from variations in physical activity.

For a minority of patients there may still be issues with regard to regaining tissue mass and function (especially of skeletal muscle), so that requirements will be higher, and for others there may be substantial, ongoing losses – especially of trace elements – for example, through a high-output ileostomy.

This review will cover typical micronutrient requirements during HPN in adult patients, together with some discussion of the requirements of infants and children, how provision of micronutrients may be optimized, some of the risks of excess provision and will suggest a protocol for monitoring safety and adequacy of supply.

Micronutrient Requirements in HPN

All patients requiring HPN are either completely dependent on the provision of their trace element and vitamin requirements from their parenteral nutrition (PN) regimen, or they may have uncertain or variable intake and absorption from any oral diet they consume. Therefore, they need an intravenous (IV) supply of all essential vitamins and trace elements to meet their daily requirements.

The micronutrient preparations for use in PN have been developed to provide more than basal amounts of all micronutrients, to allow particularly for surgical patients who are catabolic, have increased losses or who have commenced PN already in a depleted state. The amount present in each daily dose is therefore more than the amount expected to be absorbed from the Reference Nutrient Intake – the standards used in the UK (Panel of Dietary Reference Values, Department of Health, 1991) or from the US Dietary Reference Intakes (Food and Nutrition Board, 2000, 2002) – and, since these additives are given IV, they should more than meet the requirements for most individuals.

It is interesting to note the differences between the recommended oral and IV intakes, which reflect the efficiency of intestinal absorption of the different micronutrients from an oral diet (Tables 22.1, 22.2 and 22.3). Similar tables for trace element and vitamin requirements in TPN have been developed for infants and children (Tables 22.4 and 22.5) (Greene *et al.*, 1988).

Three factors might still put patients at risk of micronutrient deficiency.

1. A small number of patients may be deliberately deprived of certain micronutrient supplements if they develop particular complications. For example, development of cholestasis and hyperbilirubinaemia may lead to concern that copper and manganese may be retained and become toxic due to reduced excretion in the bile. In one case, this led to copper being withdrawn 8 months after commencing TPN, and 15 months later the patient developed severe pancytopenia, reversed by copper provision (Fuhrman *et al.*, 2000).

2. More commonly, patients may be given their micronutrient supplements only on a limited number of days per week, for example three to five times. This may be because they only require PN on these days to meet the shortfall in oral intake, or there may be practical reasons due to difficulties in the addition of supplements to bags at home. If patients require PN for only a limited number of days per week to maintain body weight and tissue function, it can be assumed that there is sufficient small intestinal function to permit some absorption of macronutrients. It may, therefore, also be assumed that sufficient micronutrients will have been absorbed from the oral diet that has been consumed. This may not be the case, however, since it will depend on the composition of the food and whether there is a suitable balance of all trace elements and vitamins.

Moreover, for those where there are practical difficulties in supply or addition of micronutrients on each day, individuals may receive bags with energy/amino acids/minerals, but without certain trace elements or vitamins. For example, fat emulsions may only be provided once or twice per week, and hence provision of fat-soluble vitamins may be limited. Although preparations exist which provide fat-soluble vitamins in a water-soluble base, some of these are incomplete. Moreover, some preparations lack certain water-soluble vitamins, and use may lead to deficiency, e.g. of biotin (Carlson *et al.*, 1995).

Patients who receive such a reduced supply of micronutrients are at risk from micronutrient depletion and, ultimately, clinical deficiency, but overall there is little evidence of this, probably because of the excess of most micronutrients available from PN on those days when micronutrients are provided.

3. There remains a significant risk of instability of certain micronutrients within the PN mixture. This is probably of most concern for ascorbic acid, which is readily oxidized if oxygen-permeable EVA bags are used. Oxidation is much more rapid if copper is also present in the PN mixture, which would generally be the case (Allwood and Kearney, 1998). Those patients whose bags are prepared with all additives present before delivery to the home are therefore likely to receive an inadequate amount of vitamin C. Degradation of ascorbate is much reduced if multilayered bags, impermeable to oxygen, are used.

Similarly, there is concern about the stability of thiamine and riboflavin in ultraviolet light (Gibbons *et al.*, 2001). Thiamine is also sensitive to degradation by bisulphite, which is present in some amino acid preparations as a preservative (Smith *et al.*, 1988). Vitamin A is also sensitive to ultraviolet radiation, but this is unlikely to be a problem with normal room lighting.

Certain of the trace elements may also undergo chemical change and hence become less bioavailable, e.g. zinc may complex with some amino acids, copper may react with hydrogen sulphide which is generated by sterilization of cysteine (Bates *et al.*, 1984) or selenite may be reduced to the non-available elemental selenium (Ganther and Kraus, 1989). The extent to which this is a real risk leading to impaired clinical status has not yet been established, but on theoretical grounds it would seem safer, and more effective, to make all additions of micronutrients immediately before infusion**.**

Adequacy of Provision of Trace Elements and Vitamins

In the early days of HPN, patients often received incomplete or unbalanced preparations of trace elements and vitamins, leading to a variety of well-documented deficiency states in both adults (Jeejeebhoy *et al.*, 1977; Takagi *et al.*, 1977; Johnson *et al.*, 1981) and children (Dunlap *et al.*, 1974; Weber *et al.*, 1981; Vinton *et al.*, 1987). With the development of modern, more complete, parenteral micronutrient preparations, recent

studies of trace element and vitamin status have largely confirmed that providing patients receive a regular supply of these supplements, biochemical measurements in plasma will be within 'normal' limits (Davis *et al*., 1987; Malone *et al*., 1989).

Some studies have shown that biochemical status may not be optimal (Reimund *et al*., 2000a, 2002), especially if micronutrients are pre-added to bags and stored in this way for up to 30 days (Baines *et al*., 2001). However, provided the regimen is reviewed to ensure regular provision of all essential vitamins and trace elements, it should now be a rare event indeed for a patient to develop clinical signs of deficiency. None the less, for certain micronutrients there continues to be particular concern about the adequacy of input.

Iron

Iron-deficiency anaemia is still a frequent problem in HPN, one study finding that approximately 30% of patients developed this complication (Forbes and Forbes, 1997), mainly because preparations of trace elements for TPN contain low amounts of iron, or sometimes no iron, due to concerns about incompatibilities in the PN mixture. Anaemia can be readily treated by provision of small daily doses of iron or by whole body iron-dextran infusions (Khaodhiar *et al*., 2002). In a study of four HPN patients on whom autopsy samples were available, tissue iron concentrations were found to be similar to control values, whereas zinc, copper and manganese were more variable (Howard *et al*., 2003). This suggests that the availability of sensitive functional tests for iron status permits fairly accurate provision of adequate amounts, in contrast to those elements where such functional indices are less available.

Selenium

The Reference Nutrient Intake (United Kingdom) or Recommended Dietary Intake (USA) for selenium is about 0.7–1.0 μmol/day (55–75 μg/day) in the oral diet (Panel of Dietary Reference Values; Department of Health, 1991; Food and Nutrition Board, 2000). Since selenium is efficiently absorbed from the small intestine, this is the amount that should be provided IV. In a unique study of autopsy material from patients who had died whilst receiving HPN, a supply of 1.1 μmol/day (600μg/week) was found to maintain an adequate intracellular selenium concentration in most tissues examined (Howard *et al*., 2005).

One extensively used preparation provides only 0.4 μmol/day, and studies have shown that although this may be adequate in maintaining selenium status in many patients, it will not be sufficient to correct depleted selenium status, nor to maintain the status in those with greater needs (Malone *et al*., 1989). This issue is compounded by ongoing concern about the adequacy of selenium intake in the oral diet, with most countries in Europe having low dietary selenium (Rayman, 2002). So, even if

patients are consuming a reasonable oral intake, it is unlikely that this will compensate for a low IV intake. Patients receiving a low daily IV intake may therefore require additional supplements of selenium, possibly in the form of sodium selenite alone.

Vitamin K

A long-standing recommendation from the Nutritional Advisory Group of the American Medical Association was that patients should not receive daily vitamin K supplements if they were on anticoagulant therapy (Nutrition Advisory Group, 1979). Certain fat-soluble vitamin preparations for PN therefore do not contain vitamin K (Table 22.2). Patients may receive some intake of vitamin K from soybean oil emulsions (Lennon *et al*., 1993), but this may not be sufficient and, if not given further vitamin K, patients receiving PN have prolonged prothrombin times (Dalton *et al*., 1984).

The Food and Drug Administration therefore now recommends inclusion of vitamin K in the PN regimen at a level of 150 μg/day (Helphingstine and Bistrian, 2003). This may lead to an increased requirement for warfarin for patients requiring anticoagulation, but

Table 22.1. Daily requirements for trace elements in adult home parenteral nutrition.

Element	RNI	RDA	Additrace®	Decan®
Zn (μmol/mg)	145/9.5	170/11	100/6.5	153/10
Cu (μmol/mg)	19/1.2	14/0.9	20/1.3	7.5/0.5
Se (μmol/μg)	0.75–0.95/60–75	0.7/55	0.4/32	0.9/72
Fe (mmol/mg)	0.17/9.5	0.14/8	0.36/20	0.32/18
Mn (μmol/mg)	26/1.4	42/2.3	5/0.28	3.6/0.2
Cr (μmol/mg)	0.5/26	0.6/30	0.2/10	0.3/15
Mo (μmol/μg)	0.5–4.0/50–400	0.5/50	0.2/19	0.26/25
Co (nmol/μg)	–	–	–	25/1.5
I (μmol/μg)	1.0/127	1.2/150	1.0/127	0.01/1.27
F (μmol/mg)	200/3.8	158/3.0	50/1.0	79/1.5

RNI, reference nutrient intake (UK); RDA, recommended dietary allowance (USA); Additrace®, Fresenius Kabi, Sweden; Decan®, Baxter, France.

Table 22.2. Daily requirements for fat-soluble vitamins in adult home parenteral nutrition.

	RNI	DRI	Vitalipid®	Cemevit®
Vitamin A (μg)	700	1000	1000	1000
Vitamin E (μg)	5.0	10.0	9.1	10.2
Vitamin D (μg)	–	5.0	5.0	5.0
Vitamin K (μg)	70	80	150	0

RNI, reference nutrient intake (UK); DRI, dietary reference intakes (USA); Vitalipid®, Fresenius Kabi, Sweden; Cemevit®, Baxter, UK.

provided clinicians are aware of this likely requirement, the potential benefits of ensuring all patients maintain vitamin K status should be worthwhile. If patients are receiving a preparation that does not include vitamin K, then a separate injection of vitamin K should be given once per week.

Table 22.3. Daily requirements for water-soluble vitamins in adult home parenteral nutrition.

	RNI	DRI	Soluvit N®	Cemevit®
Vitamin B_1 (mg)	0.9	1.5	3.1	3.5
Vitamin B_2 (mg)	1.3	1.7	4.9	4.1
Vitamin B_6 (mg)	1.4	2.0	4.0	4.5
Niacin (mg)	16	19	40	46
Folate (μg) 200	200	200	400	414
Vitamin B_{12} (μg)	1.5	2.0	5.0	6.0
Biotin (μg) 100	100	150	60	69
Vitamin C (mg)	40	60	100	125

RN, reference nutrient intake (UK); DRI, dietary reference intake (USA); Soluvit N®, Fresenius Kabi, Sweden; Cernevit®, Baxter,UK.

Table 22.4. Daily requirements for trace elements during parenteral nutrition in infants (> 3 months) and children (from Greene *et al.*, 1988).

	μmol/kg/day	μg/kg/day
Iron	1.8	100
Zinc	1.5	100
Copper	0.3	20
Selenium	0.025	2.0
Manganese	0.02	1.0
Molybdenum	0.003	0.25
Chromium	0.005	0.2
Iodine	0.008	1.0
Fluoride	1.0	20

Table 22.5. Daily requirements for vitamins during parenteral nutrition in infants (> 3 months) and children (from Greene *et al.*, 1988).

Vitamin A (μg)	700
Vitamin D (IU)	400
Vitamin E (mg)	7.0
Vitamin K (μg)	200
Vitamin B_1 (mg)	1.2
Vitamin B_2 (mg)	1.4
Vitamin B_5 (mg)	5.0
Vitamin B_6 (mg)	1.0
Vitamin B_{12} (μg)	1.0
Vitamin C (mg)	80
Folic acid (μg)	140
Biotin (μg)	20
Niacin (mg)	17

Provision of Micronutrients to Achieve Optimal Tissue Function

Prevention of clinical deficiency is no longer regarded as sufficient evidence of adequacy of provision (Shenkin, 2004). This is especially true for patients receiving HPN, since this may continue for many years, and the main objectives are to ensure the best possible quality of life and freedom from disease over the period of HPN – and beyond that period – if patients adapt to an enteral or oral diet. Micronutrients have a key role in the function of many organs and tissues, including brain, muscle, bone and the immune system. It is widely believed that marginal or subclinical deficiency carries some disadvantage, either at the metabolic level or in terms of non-specific symptoms such as tiredness.

However, demonstrating benefit from preventing or correcting such subclinical deficiency has proved elusive. Despite some early suggestions of benefit on immune function (Chandra, 1992), recent studies have failed to demonstrate any reduction in infections in elderly individuals taking a well-balanced micronutrient supplement (Avenell *et al*., 2005; El Kadiki and Sutton, 2005). And, with a small number of notable exceptions (Clark *et al*., 1996; Hercberg *et al*., 2004) long-term trials of antioxidant vitamins and trace elements have failed to demonstrate a reduction in either coronary artery disease or cancer incidence (Shenkin, 2006). Some evidence exists for improved outcome in critically ill patients with the use of antioxidant micronutrients (Heyland *et al*., 2005), but there have been few long-term studies of micronutrient supply and clinical outcome in patients receiving HPN.

It is now recognized that some changes in tissue function occur as a result of changes in oxidant/antioxidant balance, and that micronutrients play multiple roles in achieving adequate antioxidant status (Evans and Halliwell, 2001). There is special concern in relation to oxidative damage to polyunsaturated fatty acids (PFAs) in lipoproteins, which is a key stage in the development of coronary artery disease. Oxidized fatty acids within cell membranes will also alter the function of membranes and non-specifically impair cell function (Evans and Halliwell, 2001). Moreover, damage to nucleic acids will lead to a reduction in the DNA repair mechanisms or to mutagenesis, which in turn may lead to neoplastic disease. These changes are probably of only minimal concern when considering short-term PN in the acutely ill patient, but they take on more significance when optimizing long-term nutritional care.

In our own studies, we have found that total antioxidant status is frequently poor prior to surgery, and is not corrected by up to 19 days' PN with standard supplements in the post-operative period (Baines and Shenkin, 2002). During HPN, regular provision of standard supplementation maintained plasma concentrations of micronutrients and plasma antioxidant capacity in most patients, but less consistently if the bag had been stored after addition of the micronutrients (Baines *et al*., 2001).

Only a few studies have been reported of antioxidant status in PN. Pironi *et al*. (1998) found an increase in serum malondialdehyde (MDA) in

HPN patients, indicating increased lipid peroxidation, which correlated with the daily PFA load in the lipid emulsion, and also correlated negatively with the plasma tocopherol concentration.

Reimund *et al*. (2000a) have also found increased MDA, which was correlated with a reduced plasma vitamin E concentration. Erythrocyte glutathione peroxidase (GSHPx) and plasma selenium were also reduced. MDA may, therefore, be a sensitive indicator of inadequate/adequate antioxidant status in HPN. In a short-term post-operative TPN study, Linseisen *et al*. (2000) showed that supplementation with an α-tocopherol-enriched MCT/LCT/ω-3 fatty acid emulsion was not associated with evidence of lipid peroxidation, although rather surprisingly this was also the case for an LCT emulsion which was not supplemented with vitamin E.

Taken overall, these studies suggest that increased amounts of tocopherol may be required during HPN, and that care is also required to ensure adequate selenium provision. This should, however, also be balanced by the evidence that high-dose tocopherol supplements (> 150 μg/day) may be associated with increased all-cause mortality (Miller *et al.*, 2005). Hence, much more work is required with accurate clinical outcomes to optimize long-term parenteral intake of the various micronutrients.

Risks of Excess Provision

For most micronutrients, the safety margin between adequacy of provision and toxicity is large, and there is little danger of seriously excessive provision. Moreover, commercial preparations have now been in use in individual patients for many years, and few toxic effects have been observed. None the less, the following continue to be of some concern.

Chromium

Most patients receiving long-term PN have elevated plasma levels of chromium (Malone *et al*., 1989; Moukarzel *et al.*, 1992). This results from the deliberate provision of chromium to ensure prevention of chromium deficiency states, together with the variable contamination of chromium in PN solutions, especially amino acid preparations. It is not clear whether this high level of chromium is directly harmful, although in children on long-term PN serum chromium was inversely correlated with glomerular filtration rate, and renal function was not improved after stopping chromium supplementation in the PN (Moukarzel *et al*., 1992).

Manganese

Manganese toxicity is of greater concern, since a number of patients have now been identified with high blood manganese concentrations and

associated clinical toxicity. High serum or whole blood manganese may result from excess provision, or from reduced excretion in bile as a result of cholestatic disease (Hambidge *et al.*, 1989). Cholestasis is likely to be less important than excess provision (Wardle *et al.*, 1999), although patients with chronic inflammation are more likely to develop hypermanganesaemia, with abnormal biochemical liver function tests (Reimund *et al.*, 2000b).

The main complication of hypermanganesaemia is deposition of manganese in the basal ganglia (Mirowitz and Westrich, 1992), which may be associated with symptoms of Parkinsonism (Ejima *et al.*, 1992; Reynolds *et al.*, 1998). Although withdrawal of manganese provision may reverse deposition in the basal ganglia, as detected by magnetic resonance imaging (Ono *et al.*, 1995), reversal of symptoms is not consistent. Manganese toxicity may also predispose to cholestasis in children (Fell *et al.*, 1996), but other studies have suggested that factors other than manganese are more important in the aetiology of cholestasis in parenterally fed children (Beath *et al.*, 1996).

It seems clear that care must be taken with manganese provision. Over recent years, with better methods of assessing manganese status, recommendations for IV provision have fallen progressively from about 40 μmol/day (Wretlind, 1972) to 3–5 μmol/day (Shenkin, 2001) to 1 μmol/day (Takagi *et al.*, 2002) or less (National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition, 1998). Patients receiving long-term PN should have their manganese status checked, if possible, on a regular basis. Development of unexplained neurological changes or cholestatic disease is an indication for careful assessment of manganese status and provision.

Vitamin D

There is continued uncertainty about how to optimize vitamin D status during HPN. One of the most difficult complications of HPN is a painful metabolic bone disease, with variable histological features and reduced bone mineral density (Jeejeebhoy, 1998). Different studies have suggested the following strategies: (i) overprovision of vitamin D (Verhage *et al.*, 1995); (ii) suppression of normal parathyroid responses (Lipkin, 1998); (iii) a role for excess aluminium provision (Klein *et al.*, 1992); or (iv) an effect of many other dietary components (New, 2003). Firm guidance for optimal vitamin D status cannot, therefore, be given, although it would appear to be good practice to maintain vitamin D concentrations at around the level that maintains a normal plasma parathyroid hormone concentration.

A Protocol for Monitoring Micronutrients during HPN

Based on the discussion above, the following protocol can be proposed for patients on HPN:

- Assess the weekly intake of micronutrients from all sources – IV, plus oral or enteral – making an approximate allowance for the length of small intestine and the likely efficiency of absorption.
- Ensure that the estimated total intake exceeds the recommended intake from an adequate oral diet.
- On starting HPN, and every 3–6 months, check the following criteria: (i) plasma zinc, copper and selenium (with CRP and albumin to assist interpretation); (ii) plasma 25-OH vitamin D and PTH; (iii) plasma vitamin B_{12} and folate; (iv) red blood cell (RBC) folate; (v) RBC or whole blood manganese; (vi) RBC glutathione peroxidase; (vii) haemoglobin, haematocrit and MCV; (viii) urea and electrolytes; and (ix) biochemical liver function tests. The frequency of these checks will vary if there is a change in the patient's condition or if there is a need to change the regimen.
- Certain other measurements of antioxidant status could also be considered, which are mainly used for research purposes – for example total antioxidant capacity (Serafini and Del Rio, 2004) and/or markers of oxidative damage such as malondialdehyde or F_2 isoprostanes (Roth *et al.*, 2004).
- Plasma homocysteine may be helpful in optimizing folate status (Young and Woodside, 2000).

Summary

In patients receiving long-term IV nutrition, the main objectives of provision of micronutrients are prevention of deficiency and optimization of function. In children, there must also be an allowance for growth. These can largely be achieved by meticulous attention to intake relative to requirements of all the micronutrients, together with a careful protocol for laboratory testing. The use of markers of oxidant stress and of oxidative damage, together with physiological markers of tissue function or markers of immune function, will be required in future studies. Attention must also be paid to ensuring that micronutrients are given safely, that incompatibility or degradation does not take place within the IV nutrition bag or mixture, and that patients are not exposed to excess levels of provision. More studies of different levels of provision and long-term outcome are required.

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23 Venous Access Care

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Key points

- *Obtain* venous access, by selecting the most suitable access device and inserting it safely.
- *Maintain* the device effectively; ensuring patency and reducing the risk of sepsis, catheter-related thrombosis and catheter fracture.

Introduction

Successful home parenteral nutrition (HPN) is dependent on reliable, long-term venous access. Loss of access is associated with prolonged periods of hospital care, deterioration in nutritional status, often painful attempts to insert a new device and is feared by patients. However, the care of vascular access devices has to be performed within a range of non-clinical settings, often by patients whose daily lives are complex. The physical, emotional and social consequences of intestinal failure, and dependence on an artificial life support system, may influence attitudes towards the therapy and ability to self-care. Clinical guidelines need to be applied with this understanding.

From interviews with patients using complex medical technologies at home, Lehoux *et al*. (2004) identified feelings of slavery arising from therapy intended to facilitate autonomy. Although the effect of tailoring techniques and equipment, within parameters of safety and efficacy, to the HPN patient's dexterity, aptitude, motivation and domestic circumstances has not been studied, it might ameliorate some of these effects.

While there is an extensive body of evidence to support safe, effective management of vascular access, much of it has emerged from research performed in patients receiving intensive care, cancer chemotherapy or short-term parenteral nutrition. Caution is required when translating this evidence into realistic practice for HPN.

This chapter will address the aspects of vascular access care which are most pertinent to HPN.

Obtaining Venous Access

Vascular access needs to be achieved in such a way that hypertonic fluids can be delivered safely whilst enabling self-management by the patient in any environment, possibly for many years. Problems may occur if the clinician performing the procedure is unfamiliar with the techniques of HPN or of the experience of patients. Collecting and sharing outcome data is particularly important, as a complication resulting from inappropriate vascular access may occur long after insertion of the device, or not be clinically obvious. For example, a badly placed catheter exit site resulting in sepsis due to difficulties with self-care may also add time to daily access management procedures, causing the patient frustration.

Selecting a vascular access device

Skin-tunnelled central venous catheters

In the early 1970s, catheterization of the superior vena cava with a tunnelled, silicone rubber catheter superseded attempts to infuse parenteral nutrition through arteriovenous shunts (Broviac *et al.*, 1973). Hickman *et al.* (1979) modified this catheter by enlarging the internal diameter in order to facilitate marrow transplantation, blood transfusion and sampling. The Broviac and Hickman catheters continue to be commonly used for HPN.

Fixation is achieved through the ingress of adhesions from the subcutaneous tissues into a felt cuff, which is attached to the catheter and positioned within the skin tunnel.

In addition to silicone rubber, catheters manufactured from polyurethane are also available. Both materials have low thrombogenicity (Laidlow *et al.*, 1983; Linder *et al.*, 1984). Antimicrobial-impregnated catheters have recently been shown to reduce the risk of catheter-related sepsis (CRS) in the critical care setting (Maki *et al.*, 1997), but as the effect is very short-term, further development is needed before such interventions are suitable for HPN.

Configuration

There is little evidence to support the use of a large-diameter catheter for HPN, as blood sampling through the device is avoided. The least number

of lumen required to meet therapeutic needs should be selected in order to minimize portals for the entry of organisms. Unfortunately, many HPN patients undergo prolonged periods of hospital care and intravenous (IV) therapy prior to, and sometimes during, the course of HPN, and peripheral vascular access is frequently difficult. These patients might benefit from a multi-lumen catheter, one lumen being dedicated to parenteral nutrition, if frequent blood sampling or other concurrent IV therapies are needed.

Contradictory evidence exists regarding the risks of CRS associated with the use of multi-luminal catheters. However, they may present no greater risk than the use of a single-lumen device, when strict infection control measures are used (Ma *et al.*, 1998). Careful discussion with the patient prior to placement is essential as avoidance of peripheral venous punctures must be balanced against the presence of a more intrusive and work-intensive catheter.

Subcutaneously inserted central venous ports

These are an alternative to catheters with an external segment, and are of particular value when only intermittent therapy is required, although they can be used for daily infusions. The catheter ends in a lightweight, subcutaneous port, incorporating a reservoir chamber covered by a thick silicone septum. Access to the venous system is achieved by inserting a non-coring needle (hypodermic needles damage the silicone) through the skin and septum into the reservoir. One study, comparing outcomes of the two systems, suggests patient choice is an important factor in obtaining low complication rates (Howard *et al.*, 1989).

General considerations, advantages and disadvantages of central venous catheters with external segments and ports are described in Box 23.1.

Peripherally inserted central venous catheters

These are generally suitable for only very short periods of HPN, due to limitations on physical activity and self-management. Polak *et al*. (1998) found that catheter exit sites above the antecubital fossa were more acceptable to patients at home.

Closed distal tip

Groshong® catheters, which have a closed, rounded distal tip incorporating a three-position valve, are a further option. The valve is closed when the catheter is not in use, but opens outward during infusions and inward if blood is withdrawn. This helps to reduce the risk of air embolism and catheter occlusion. As reflux of blood into the catheter tip is avoided, saline – rather than heparin flushes – are recommended in order to maintain patency between infusions. Groshong® catheters are available as a cuffed,

Box 23.1. Aspects of skin-tunnelled central venous catheters with external segment and implanted ports.

Skin-tunnelled catheters secured by felt cuff

General considerations

- May remain in position for many years.
- Fixation of the felt cuff to the skin tunnel is achieved between 7 and 14 days following insertion, during which time the external sutures must remain in position.
- Single, double and triple lumen catheters are available.

Advantages

- Commonly used for a range of home intravenous therapies, therefore hospital and community health professionals are likely to be familiar with insertion, management and problem solving.
- Connecting the infusion to the catheter is painless.
- In the case of fracture can be repaired using a kit specific to the catheter in position.
- There must be a policy for the purchase, location and use of the kits.
- Depending on the causative organism, may be salvaged in the event of sepsis (Messing *et al.*, 1990).

Disadvantages

- Dressings are required over the catheter exit site.
- Alters body image; presents a visible sign of disability.
- Although removal by traction to dislodge the cuff from the subcutaneous tissues has been described, the adhesions which form during months or years of use require surgical dissection.

Totally implanted subcutaneous ports

General considerations

- Immediately following implantation a needle should be inserted and left in position until local swelling subsides. Angled needles in a range of gauges and lengths are available to accommodate ports at different depths.
- Without adequate skin disinfection and aseptic handling, bacteria may be introduced from the skin as the needle is inserted. Local anaesthetic creams may facilitate painless needle insertion, particularly as the patient gains confidence using the device.
- Patients often feel secure inserting the needle at the same point each time. This increases the risk of ulceration and should be avoided.
- In order to avoid distorting the tip of the needle, which would damage the silicone septum and skin during withdrawal, it should be inserted until just touching the metal base of the reservoir.

Advantages

- Minimizes altered body image.
- No dressings are needed and there is unrestricted freedom to bathe and swim when the port is not in use.

Disadvantages

- Not suitable for those with little subcutaneous tissue as tension of skin over the port may result in necrosis.
- The acceptability of inserting a needle through the skin for infusions.
- Very difficult to salvage if sepsis occurs.
- Requires more frequent replacement than a catheter with external segment.
- Removal by surgical dissection.

tunnelled catheter, an implantable port or as a peripherally inserted central catheter.

Inserting the device

Selecting a vein for insertion

The choice between the subclavian, internal jugular or femoral vein as the site for catheterization can be limited by thrombosis, scarring or altered anatomy, as HPN patients frequently undergo repeated central venous catheterization (McIntyre *et al*., 1990). Pre-insertion assessment by physical examination and clinical history are essential, and imaging may also be helpful, in order to identify suitable veins. Central venous catheterization is an important event for the HPN patient and any complication is often remembered in detail, providing helpful guidance to the clinician.

Ultrasound-aided insertion and catheterization by a clinical expert have been identified as key interventions in reducing the risk of procedure-related complications (Sznajder *et al.*, 1986; Randolph *et al.,* 1996).

Conscious sedation or general anaesthesia for the procedure should also be discussed with the patient.

Position of the distal tip

Positioning the distal tip of the catheter at the junction of the superior vena cava and the right atrium has been demonstrated to reduce episodes of catheter malfunction (Petersen *et al*., 1999). Radiography or fluoroscopy are required to confirm the position of the distal tip and any procedure-related complications, such as pneumothorax, prior to commencing parenteral nutrition. A permanent record of the catheter tip position, with the patient in the upright position, should be obtained for the purpose of comparison, should problems occur later.

The catheter exit site

For HPN the catheter exit site needs to be in a position that will avoid interference with physical functions, be visible to and easily handled by the

patient, but can be concealed under clothing. It should be away from areas of high bacterial activity – such as the axilla – and aid catheter care and security by allowing a dressing over the site to be easily maintained.

Maintaining Venous Access

Patients need to be provided with catheter care protocols that minimize the risk of complications; it must be explained how to recognize a problem should it occur and define the action to be taken. This includes the response of health professionals at both the HPN centre and, locally, to the patient's residence.

Equipment must be safe but easy to handle and adapted where necessary. For example, syringes pre-filled with solution for flushing the catheter between infusions can liberate a patient with problems of dexterity, by facilitating self-care.

Catheter care is generally restricted to the patient and a few carers, who all receive detailed training. However, personal and environmental distractions may impair safety during procedures, such as those due to emotional distress, pain or domestic disturbance (Richards *et al.*, 1997). As consistency in practice is a key element in preventing complications, patients at particular risk might benefit from additional nursing support.

Catheter patency

The causes and methods of preventing occlusion are described in Box 23.2.

Preventing complications

Catheter-related sepsis

Rowley and Sinclair (2004) described mapping aseptic procedures to identify the points at which contamination by organisms might occur and evaluated the evidence for preventative interventions. This approach is particularly appropriate for HPN, where factors pertaining to the individual patient and domestic circumstances can be included. The procedures necessary for HPN are listed in Box 23.3.

In a meta-analysis of studies comparing 10% povidone iodine solution with chlorhexidine gluconate for skin disinfection around the catheter exit site, mostly in intensive care patients, Chaiyakunapruk *et al*. (2002) revealed that the use of chlorhexidine reduced the risk of catheter-related bloodstream infection by 49% (risk ratio 0.51 (CI 0.27–0.0.97)). Alcoholic solutions of chlorhexidine produced a statistically significant reduction in risk, but there were few studies which used an aqueous solution.

Box 23.2. Causes and prevention of catheter occlusion.

Malposition

External

- Usually due to the catheter becoming kinked. Prevented by coiling and securing the device.

Internal

- May occur during insertion and commonly evident in relation to arm and neck movements following catheterization. Requires prompt investigation by imaging the catheter and replacing it if necessary.

Occlusion within the catheter

Reflux of blood into the catheter tip

- The catheter should be flushed promptly on completion of an infusion.
- There is conflicting evidence regarding the optimal solution and volume that should be used to flush the catheter.

Heparin

Evidence to support the effectiveness of heparin in preventing the formation of thrombus within the catheter tip is lacking, although a range of doses is used. Heparin at a concentration of 50 units in 5 ml 0.9% sodium chloride is a commonly used solution (Cottee, 1995). However, 0.9% sodium chloride without heparin may be as effective, and further research is needed.

Volume

During insertion, catheters are trimmed to an appropriate length for the patient and the actual fluid capacity of the device is unknown. Brennan (2002) demonstrated that a minimum volume of 5 ml, injected rapidly, was necessary to adequately flush an implanted port with a 1.0 mm internal diameter, 78 cm in length.

Technique

The catheter should be flushed using a non-laminar flow method and a rapid push/pause action, withdrawing the syringe as the last 0.5 ml of fluid is still being injected (Hutton, 1986). Maintaining positive pressure at the end of the flush prevents the reflux of blood into the catheter tip.

Precipitation of drugs and minerals

- Drugs should not be administered through the lumen used for parenteral nutrition, unless there is a specific reason, for example as an antibiotic lock to treat CRS.
- Interaction of calcium/phosphate in paediatric parenteral nutrition is the most common reason for mineral deposits.

Lipid deposits

- Have been reported in association with nutrient mixture, including lipids.
- Flush 10 ml ethanol 20% through the catheter at the end of cyclical infusion of lipid-containing parenteral nutrition to prevent occlusion (Pennington and Pithie, 1987).

Box 23.2. *Continued.*

Occlusion external to the catheter

Extension of fibrin sheath

- Within a few days of placement a thin film of fibrin sheaths the outer surface of vascular access devices. This may extend over the tip of the catheter, acting as a valve.
- No preventative measures have been identified.
- Identified by an ability to infuse/inject, but with increasing resistance, and inability to aspirate blood from the catheter.

Catheter-related venous thrombosis

- Total occlusion of the catheter tip is usually a late sign of venous thrombosis.
- Preventative measures include: (i) the use of catheters manufactured from polyurethane or silicone rubber; (ii) correcting dehydration prior to catheterization and during use of the catheter; (iii) avoiding sepsis; and (iv) prevention of retrograde migration of the catheter tip (infusion of vesicant fluid will cause thrombosis if infused into a tributary vein).

Box 23.3. Aseptic procedures for HPN.

- Changing the dressing over the catheter exit site.
- Making additions to the infusion mixtures.
- Connecting the infusion to a catheter with external segment.
- Connecting an infusion to an implanted port.
- Disconnecting the infusion and flushing the catheter.
- Irrigating an occluded catheter.
- Repairing the catheter.

Rannem *et al*. (1990) found an incidence of catheter-related sepsis of 0.25–0.28 per catheter year in HPN patients with the use of chlorhexidine 0.5% in 70% ethyl alcohol for skin disinfection both at the catheter exit site and at connections in the infusion system, compared to 0.58 when 10% povidone iodine was used.

Patient preference and protection for the catheter from the friction of clothing are important criteria for dressings over the exit site during home care. Gillies *et al*. (2003) review of studies comparing gauze and tape with transparent polyurethane film dressings concluded there was no difference in infectious complications between the two methods. However, the number of studies was small, with low patient numbers. As there is currently no conclusive evidence to guide practice, either type of dressing may be selected, being changed with a frequency that ensures the exit site is kept clean and dry at all times.

Guidelines for preventing catheter-related sepsis are outlined in Box 23.4.

Box 23.4. Guidelines for preventing catheter-related sepsis.

At insertion

- Use sterile gown, mask, gloves and large drapes during catheterization (Raad *et al.*,1994).

Maintenance care during all aseptic interventions

Preparation

- Wash hands with antiseptic handwash, dry well and apply alcohol hand rub before every intervention.
- Prepare the working surface with physical and bacteriological cleaning.

Handling connections

- Minimize the number of connections.
- The catheter hub is an important point for the entry of organisms (Sitges-Serra *et al.*, 1984). Consider attaching a needleless connector to the hub and change at a frequency recommended by manufacturer (Luebke *et al.*, 1998).
- Disinfect the hub or surface of the needleless connector and any other non-sterile area, such as around the administration set port on the nutrient container. Allow time for the disinfectant to take effect before handling.
- Wear sterile gloves, touching only disinfected areas or sterile equipment from opened packaging.
- Avoid physical contact with the inner part of the system, e.g. spike and distal end of administration set.
- Use the same level of asepsis when handling every lumen of a multi-lumen catheter.

The catheter exit site

Observation

Inspect the entry site for redness or discharge. Obtain a swab for microbiological culture and use a gauze rather than transparent film dressing if discharge is present.

Security

Check that the felt cuff is not visible.

Skin cleansing

Wearing sterile gloves, clean around the catheter using gauze soaked with disinfectant; use a circular action, working outwards from the exit site; clean the catheter segment adjacent to the exit site; allow to air dry; do not apply antimicrobial ointment.

Protection

Apply new dressing.

Air embolism

Air will be drawn into the central venous system if either of the following occurs: (i) an unclamped central venous catheter is open to the atmosphere or air is allowed to enter due to failure to prime the administration set prior to connection; or (ii) a fracture in the catheter. All connections should lock securely, but not be over-tightened to avoid damaging the threads and causing leakage of fluid, which might lead to sepsis. Needleless connectors attached to the catheter hub reduce the number of occasions on which the catheter must be opened, and contribute to safety.

Catheter fracture

Damage may be caused by repeatedly clamping the catheter at the same position or the application of excessive pressure, while attempting to flush a partially occluded catheter with a syringe < 10 ml in size (Conn, 1993). Patients should be provided with an additional clamping device, placed between the fracture and the catheter exit site, until the catheter can be repaired.

Summary

HPN maintains the patient's life but complications of the therapy are themselves life-threatening. Care to prevent those complications is most commonly performed on a daily basis by the patient within their own home. The patient is never free and can never usually take a 'break' from therapy.

Health professionals need to translate evidence for good practice into the selection of central venous catheters, associated equipment and protocols for their management, which recognize both the autonomy and vulnerability of the HPN patient.

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24 Teaching Patients Home Parenteral Nutrition

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Key points

- Careful selection of the patient before commencement of training.
- Nutritional support teams and instruction manuals are essential elements in the process.
- Very few studies on the effect of different training regimens or the impact of training on complication rates are at hand.
- Many centres adhere to guidelines, developed locally and not underpinned by quality assurance studies.
- Training patients for home parenteral nutrition (HPN) is carried out by specialized personnel, usually working together in a team.
- Patients are trained in hospital before discharge or in their home.
- Training and educating patients significantly reduces the rate of complications and improves the quality of life with HPN.
- Official guidelines for training are not available and clinical studies of different training regimes are warranted.

Introduction

Home parenteral nutrition is a radical change of conduct of life for the patient, relatives and the carer. In order for it to succeed, each potential candidate for HPN must be assessed on an individual basis using a multidisciplinary team approach, including the expertise of a consultant gastroenterologist/nutrition specialist, a clinical nurse specialist, a dietician and a pharmacist. Within this assessment, several factors must be considered, including patient suitability, home assessment, duration of treatment and who will fund the therapy.

 Home Parenteral Nutrition (eds F. Bozzetti, M. Staun and A. Van Gossum)

HPN is a huge psychosocial strain and involves the patient and relatives 24 hours a day. To make the teaching process a success one needs a specialized team to take care of this very complex task.

Patient suitability

Teaching patients about parenteral nutrition (PN), and training them to become skilled and confident to administer it at home, demands a huge amount of nursing time and commitment from the nurse, the patient and the carer. Although the advantages for most patients include an increased life expectancy for previously fatal intestinal failure and a potentially improved quality of life, the possible disadvantages of HPN have to be discussed, as major lifestyle changes will need to be made. There are many definitions of quality of life, and they may be subjective, therefore discussing lifestyle changes early in the assessment with both the patient and their family is essential. Changes will inevitably have to be made, but HPN should provide more freedom and increased strength to enable the individual to enjoy life.

It is vital that a patient's cognitive and physical abilities are thoroughly assessed before embarking on an HPN training programme, as the patient may have additional skills to master – for example, stoma or enterocutaneous fistula care. Also, there is a little point in commencing training if they are recovering from recent major surgery.

Carers should be encouraged to become involved from the outset, either temporarily – until the patient regains strength, stamina and motivation – or permanently. Like anyone else, people on HPN can suffer minor illness such as influenza, during which time it would be preferable for a carer who has been trained to care for the HPN to prevent mishaps occurring.

Home assessment

The patient's home environment, medical suitability, rehabilitative potential, social and economic factors and reimbursement sources shall be assessed by the physician, nurse, social worker or other designated health care professionals to determine the availability of appropriate resources before the initiation of home nutrition support (ASPEN Board of Directors, Standards for Home Nutrition Support)

Home assessment should be carried out prior to the patient's discharge with HPN, to ensure that PN can be managed safely and effectively within the home environment (Magnay, 2000). Adjustments will undoubtedly need to be made to accommodate HPN supplies, but it cannot be emphasized too strongly that the home should not become akin to a hospital ward.

A nurse should visit the patient's home before discharge to help decide where to store supplies, and to help choose a 'clean area' with hand-washing facilities where sterile procedures will be performed. This should be somewhere peaceful and quiet, with no distractions, and ideally where family pets can be excluded. The nurse will also check that there are sufficient safe and accessible electrical power points for the intravenous pump, and that there is a telephone in or close to the area where the patient will be receiving the PN.

Referrals to the occupational therapist and social services may be necessary if modifications to the home are required.

Patient preparation

Before training commences, it is important that the patient and carer are fully prepared physically, psychologically and emotionally. Many patients will have had a long period of illness and may be experiencing stages of the grieving process, coming to terms with the loss of their health and possibly altered body image (Kubler-Ross, 1969). They must be given time, following the initial meeting with the consultant when HPN is proposed, to consider the facts. It can be beneficial for the patient to meet someone already established on HPN, either from the same centre or via an organization such as Patients on Intraveneus and Nasogastric Nutrition Therapy (PINNT).

In 2001 (Micklewright *et al.*, 2002) the ESPEN-HAN working group gathered information about how patients are taught the necessary procedures to undertake HPN. A questionnaire about HPN teaching practice was circulated to centres in seven European countries. Responses were obtained from 51 centres in those countries. Centres ranged in size from 18 to 203 beds and had between 0 and 95 patients on HPN, 63% of centres having fewer than ten patients. Not all patients with intestinal failure will be able to cope with HPN, and in the survey one or more criteria were used by 62% of centres to exclude patients from their HPN programme. These included intellect (33%), physical disability (24%), social situation (25%), underlying disease (18%) and age (16%).

All centres had a nutrition support team and 96% followed guidelines, usually locally developed. Generally, training was carried in an inpatient setting over 1–2 weeks with one or more patients simultaneously. The personnel involved were hospital nurses/clinical nurse specialists (84%) and/or doctors (39%).

The centres reported that teaching included the following: (i) catheter care (100%); (ii) preventing and recognizing complications (98%); (iii) most common mistakes (92%); (iv) pump care (92%); (v) managing complications (90%); (vi) adding vitamins (55%); (vii) bag preparation (51%); (viii) IV medication (50%); and (ix) compounding (18%).

Quality of care was assured by periodic surveys (47%) and re-checking the teaching process (33%) following the occurrence of complications.

There was no significant variation between the large and small centres for either exclusion criteria or teaching methods.

This survey has highlighted common teaching practice across seven European countries. Local or national guidelines underpinned practice in the majority of centres.

Patient training

From the European study (Micklewright *et al.*, 2002) we know that centres use different methods for training, including instruction manuals with illustrations of the procedures, some centres using videotapes.

Training sessions usually involve more patients, team members and the patient's family, if required. It is important that only key designated members of the nursing staff provide the training and that they use exactly the same procedures for the patient in the teaching programme. No time limits for training should be set for allowing patients to make progress at their individual pace.

This ensures continuity and standards of care (Magnay, 2000), minimizes misunderstanding and increases trust in those involved in the patient's management. Training should start when the central venous access has been obtained, if the patient's condition allows and the programme is calculated to run for at least about 2 weeks, where the patient can do everything by himself by the second week. It will, however, be customized for each individual.

The teaching programme must include:

- Anatomy and physiology of the gastrointestinal canal and the basics of nutrition.
- Managing complications occurring during the treatment.
- Preventing and recognizing complications.
- Sterile procedures.
- Catheter care.
- Most common mistakes.
- Pump care.
- Bag preparation.
- Adding vitamins and medication IV.
- Commencing and discontinuing the HPN.

Prior to commencing training, suitable vascular access must be established.

No time limits for training are set. We all learn at different rates and the learning environment should be quiet and uninterrupted.

The training follows the principles of asepsis and the procedures are taught in a step-by-step fashion, but the overall aim is to enable the patient to understand the rationale behind them. A demonstration is followed by hands-on exercises.

Written, photographic and video information all reinforce the specific

skills taught, and act as a point of reference. The use of handout material is recommended and used in many centres.

A progress chart is useful to confirm practice and proficiency for each individual skill required, from hand washing and donning sterile gloves to heparin-locking the central venous catheter. It is important that the consequences of non-compliance are stressed, and that they can be life threatening.

Once the patient and carer are considered to be competent and feel confident in the overall management of their PN, they remain in hospital for approximately a further week. However, during this time the patient is responsible for commencing and discontinuing their PN unsupervised by their trainers. This allows for potential problems to arise within a sheltered environment where nursing staff are available to assist and offer advice if needed.

During this time the patient can decide on starting and finishing times of feeding to fit in with their individual home routine.

The home care company will be contacted, ancillary lists organized and delivery discharge date confirmed.

The literature on training regimens is scarce. However, in 2002, a case-control study (Smith *et al*., 2002) compared two groups of affiliated patients with non-affiliated controls, who were matched with diagnosis, HPN duration, sex and age. This study was undertaken to evaluate the influence of education and peer support on HPN patient outcomes. Group 1 data were obtained from patients in large HPN medical practice programmes. Group 2 data were obtained from patients in small medical practices with a small number of HPN patients. All participants were evaluated by structured interviews. This study showed that patients affiliated with a specialized HPN team and national organization had a better outcome, regardless of HPN programme size. Specifically, affiliated patients compared with non-affiliated, case-matched controls experienced a significantly higher quality of life, less reactive depression and a lower incidence of catheter-related sepsis. All these outcomes are clinically important.

Prevention plays a fundamental role in the management of central venous catheter (CVC) infections in patients receiving HPN, and the nutritional team – including nursing and local care – can effectively reduce infection rates and security. In 2002 Santarpia *et al*. (2002) showed in a retrospective study that patients (group A) given more detailed written and oral instruction on the aseptic management of CVC and how to avoid and recognize complications had a lower incidence of CVC-related sepsis than did patients (group B) receiving standard information. HPN patients need clear information about infectious complications as well as clear and continuous instructions by a well-trained team on the use of catheters.

Home visits

It is beneficial for one of the trainers to accompany the patient home (Wengler *et al.*, 2006) and it is essential to check that everything that has been ordered arrives, is the correct size and is in good working order.

On discharge it is stressed that the patient is not to be left alone, and that support is only a telephone call away whenever needed. If possible, it is advisable for the patient not to feed on their first night at home, as it can be an emotional time if the family has spent weeks – even months – in hospital.

On the first night it can be arranged for one of their trainers to telephone the patient after the time they have commenced their feed at night, and again in the morning.

Summary

HPN is a complex therapy and should not be embarked upon lightly. Training patients for HPN may take place in hospital or in the home of the patient. In order for it to succeed, patient suitability should be selective and preparation and training must be thorough, using a patient-centred and multidisciplinary approach. Written information should be available to support and reinforce the practical skills taught. It is essential that the patient has open, 24-hour access available from the nutritional support team and from the home care company.

One study suggests that the number of HPN patients is increasing and that specialist centres with experience and back-up facilities are necessary to manage them (Van Gossum *et al.*, 1999). The overall success or failure of the therapy hinges on these factors. Therefore, the experience gained by the HPN team plays a central role confirming that HPN is not a common treatment, and must be performed by particularly well-trained, experienced teams to prevent and treat major complications.

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25 Preparation and Provision of HPN Solutions

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Key points

- The guarantee of adequate technique is based on the strict follow-up of the PN preparation protocol, the validation of the elaboration process and the training of personnel.
- In order to increase PN stability and decrease lipid peroxidation, the use of photo-protection and multi-layer bags is recommended, as well as organic phosphates and low-PUFA lipid emulsions.
- For the sake of security, 1.2-micron filters should be used.
- It is important for patients and caregivers to be aware of conservation requirements.
- Some pharmaceutical companies have 'ready-to-use' bags with pre-defined compositions, the stability of which is guaranteed for longer periods of time.

Introduction

In contrast to most hospitalized patients who require parenteral nutrition (PN) for a few days, home parenteral nutrition (HPN) patients need PN for long periods of time and caloric intake needs to be adjusted to avoid weight loss or overfeeding complications. Some patients need extra fluid or electrolyte supplementation that can be incorporated into the bag or administered separately. Many of these patients are also receiving intravenous (IV) drugs that can sometimes be added to the PN bag to facilitate their administration.

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Preparation

Essential prerequisites include secure venous access and the availability of medical, nursing, dietetic and pharmacy staff skilled in the management of HPN. Most pharmacies in large hospitals have specific units for PN bag preparation where a strict aseptic technique is followed under the supervision of a pharmacist. The guarantee of aseptic technique is based on the following: (i) strict follow-up of the PN preparation protocol; (ii) the use of laminar flow cabins in a specific clean area; (iii) the quality of solutions; (iv) the validation of the elaboration process; (v) the microbiological controls; and (vi) the training of personnel.

Pharmaceutical companies and hospital pharmacies

Although initially, in most of the HPN programmes in Europe, elaboration was performed almost completely by hospital pharmacies, nowadays some pharmaceutical companies have 'ready-to-use' bags with pre-defined composition, the stability of which is guaranteed for longer periods of time. This is very important for HPN patients who, in contrast to hospitalized patients for whom PN can be elaborated almost on a daily basis, cannot collect bags every day; therefore, longer shelf life is essential. On the other hand, hospital-made PN bags have the advantage of providing individualized composition for every patient.

Problems and recommendations

The main problems we encounter in PN preparation are emulsion stability and calcium phosphate precipitation. Some authors have recommended the separate administration of lipids, arguing that we do not know if the emulsion is stable and that we cannot see calcium phosphate precipitations if they occur – because of the opacity of lipids. But, as we shall see later, calcium phosphate precipitation can be avoided by using organic phosphates, and most PN emulsions are stable if we follow preparation protocols. For the sake of security, 1.2-micron filters should be used.

In addition, when lipids are administered separately, two different lines will be needed – or two lumen lines can be used – because if we administer PN and lipids in the same line, simultaneously, we may have also stability problems and, if one is administered before the other, there could be side effects or it could be inconvenient for the patient because they cannot afford to be disconnected for any length of time. 'All-in-one' PN solutions have other important advantages in HPN: (i) they need less line manipulation; (ii) they are less costly; (iii) they need only an administration pump; and (iv) micro-organisms reproduce with more difficulty than in lipids alone.

Emulsion stability

Emulsion stability depends mainly on pH, temperature, amino acid concentration, electrolyte concentration – particularly divalent cations – and type of lipids used. It is also fundamental to follow the right sequence of addition. Adding amino acids first is recommended, because they stabilize the emulsion and counteract the deleterious effects of highly concentrated glucose and electrolytes. With higher amino acid concentration the emulsion is more stable.

It has been also shown that very low lipid concentration can decrease PN stability. Some studies found that olive-based lipid emulsions and MCT/LCT emulsions are more stable than LCT emulsions (Driscoll *et al.*, 2001; Fig. 25.1). In HPN, the use of more stable fat emulsions would be recommended, because these PNs need a more extended expiration time. Filter use is also recommended to increase security.

Calcium phosphate precipitation

High concentrations of calcium and phosphate can cause calcium phosphate precipitation. This depends on calcium and phosphate concentration, pH, amino acid concentration, types of calcium and phosphate salt, ambient temperature, infusion speed and storage time. There are reference curves which indicate calcium and inorganic phosphate compatibility (Poole *et al.*, 1983; Dunham *et al.*, 1991); when inorganic phosphates are used, we have to be very cautious not to exceed calcium and phosphorus concentration limits. Amino acids have a protective effect, forming complexes with calcium or phosphate, diminishing precipitation risk.

Addition order is also very important. Calcium or phosphate can be added at the beginning with amino acids and the other component should

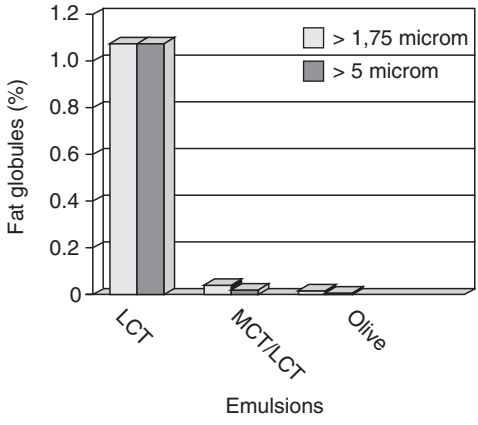

Fig. 25.1. Percentages of fat globules > 1.75 and > 5.0 microns in a PN with different lipid emulsions at 30 hours.

be added at the end, when the final volume is reached. Sometimes, particularly in paediatrics, calcium and inorganic phosphate limits are below patient requirements. Nevertheless, organic phosphates are also stable with PN (Ronchera *et al*., 1995) and their limits are higher than the concentrations usually used (Hanning *et al*., 1989; Raupp *et al*., 1991; Prinzivalli *et al*., 1999). The use of filters is recommended: 0.22-micron filters in no-fat PN and 1.22-micron filters in 'all-in-one' PN.

Vitamin degradation

Long-term PN patients generally need daily administration of vitamins to prevent deficiencies (Mikalunas *et al*., 2001). Many years ago, some studies showed that vitamins could degrade in PN solutions and that trace elements could interact with vitamins, thus diminishing their stability. Because of that, their addition was recommended, just before PN administration and every other day with trace elements.

The most unstable vitamins in PN are thiamine, retinol, riboflavin and ascorbic acid. Thiamine instability is due to its reduction by meta-bisulphites, which was important when amino acid solutions used to contain sulphites, but nowadays most of them are sulphite free. Retinol and riboflavin degradation are mainly due to photodegradation, but 'all-in-one' PN and protection from light diminish this degradation. Ascorbic acid is oxidized in the presence of oxygen and this oxidation is catalysed by copper. This degradation decreases in 'all-in-one' bags and with high cysteine concentration.

In PN hospital preparation there are two main reasons why vitamin C is in contact with oxygen increasing its oxidation: (i) at the preparation site when the bag is filled by gravity or pumps; and (ii) bag permeability. The first can be avoided or diminished by using nitrogen for filling bags or by decreasing both oxygen contact during the filling and residual oxygen inside the bag as much as possible. The second is responsible for vitamin C degradation over time and can be inhibited by using multi-layer bags (Gomis *et al*., 1996; Dupertuis *et al*., 2002, 2005; Fig. 25.2). These bags prevent oxygen from passing and also provide some photo-protection.

Nowadays, using multi-layer and photo-protection bags we can introduce vitamins and trace elements in PN bags with 5-day stability.

Peroxidation

Lipid peroxidation in 'all-in-one' bags seems to be directly related to the PUFA content and inversely related to the alpha-tocopherol:poly-unsaturated fatty acid (PUFA) ratio of the emulsion (Pironi *et al*., 2003). The main factors that influence PN oxidation are: (i) light; (ii) contact with oxygen during the preparation or oxygen bag permeability; (iii) trace elements like iron or copper; and (iv) temperature (Steger *et al*., 2000; Fig. 25.3).

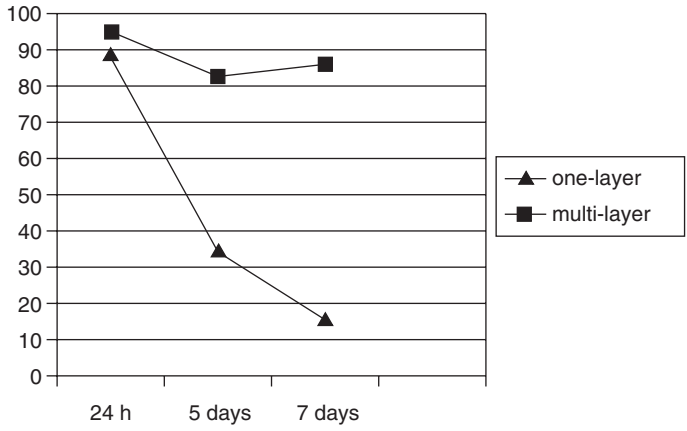

Fig. 25.2. Percentages of initial concentration of vitamin C in uni-layer and multi-layer bags over a period of 7 days.

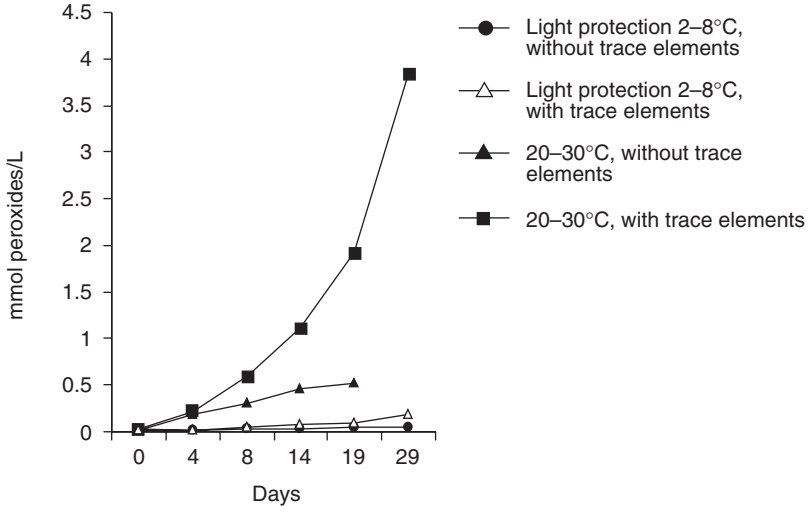

Fig. 25.3. Peroxide generation under different conditions.

In HPN patients there is an increased oxidative stress and inadequate antioxidant status (Massarenti *et al.*, 2004).

In order to avoid peroxide formation, refrigeration of PN throughout storage is recommended, as well as avoidance of high temperatures during administration, protection of PN bags from light and avoiding contact with oxygen. Multi-layer bags significantly reduce hydroperoxide generation (Balet *et al.*, 2004). If one-layer, ethyl vinyl acetate (EVA) bags are used, it is better to utilize low-PUFA lipid emulsions because hydroperoxide content depends on this (Balet *et al.*, 2004; Fig. 25.4).

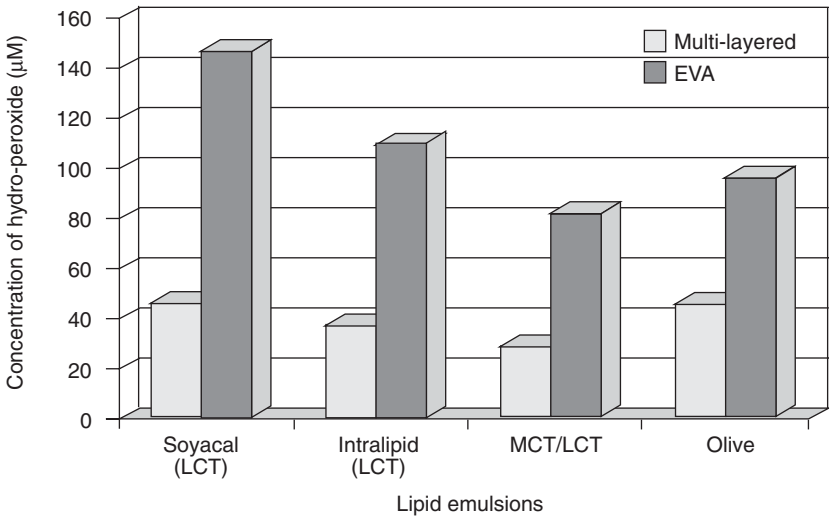

Fig. 25.4. Concentrations of hydro-peroxides (µM) in different all-in-one bags (FOX method after 7 days at 4°C and 48 h at 37°C).

Drug stability

Drugs can only be added to PN solutions or be infused via a Y-site when studies regarding their drug compatibility and emulsion stability have been performed. Some drugs, such as insulin, ranitidine or octreotide, are stable in 'all-in-one' PNs and can be added at the preparation site, avoiding patient or caregiver work and line manipulation.

Elaboration Sheets and Labelling

Home parenteral nutrition orders, in general, do not change frequently. These PNs usually change their composition when patients have had medical revisions or complications. Occasionally they can continue for years without any change in PN formulation. It is very important to avoid re-transcription errors. Sometimes it may be necessary to separate home PN- from hospitalized PN-order transcriptions to avoid daily or weekly copying of PN composition.

It would be good practice with these patients not to change the elaboration sheet unless a new prescription order is sent. It is also very important to have open communication with prescription physicians to avoid prescription or legibility problems. An error in HPN composition can have more serious consequences than with a hospitalized patient, because it can be difficult to detect and the problem can exist for a longer period of time. For instance, forgetting to add vitamins or trace elements is not a problem for 1 or 2 days, but can be damaging for long periods of time.

Computer programs can help when preparation sheets are generated. Labelling is also important, and patients or caregivers should check labels every time they receive their bags and contact the pharmacist if something does not match.

Location of Solution Preparation and Provision

There are many differences between countries – and even between hospitals within the same country. Sometimes preparations have much to do with disposition. There are three main scenarios, the advantages and disadvantages of which are summarized in Table 25.1.

Preparation in hospital

The advantage of this kind of preparation is that patients receive all their needs or almost their needs in one bag. Patient manipulation is minimal. Vitamins and trace elements are included, and also some stable drugs. Although there can be many different individual situations, in most cases patients or their relatives have to pick up the PN bags at pharmacy services, once or twice a week.

Ready-to-use parenteral nutrition

These are multi-chamber bags made by pharmaceutical companies with pre-defined compositions. Almost every day, more different newly registered compositions appear. Companies ensure both emulsion stability and the absence of compatibility problems for long periods of time, while

Table 25.1. Advantages and disadvantages of different types of site preparations.

	Hospital-made PN	Ready-to-use PN (multi-chamber bags)	Individualized pharmaceutical company preparation
Expiration date	5 days (mean)	> 1 year	5–6 days
Composition	Individualized	Standard	Individualized
Vitamins and trace elements	Included	Not included	Included
Drugs	Included if stable	Not included	Included if stable
Disposition to patients	Collect at hospital/delivery to patient's residence[a]	Collect at hospital/delivery to patient's residence[a]	Delivery to patient's residence
Schedule	Once/twice per week	Depends on patient's storage capacity	Daily
Price	++	+++	+++++

[a] If home care services are available.

the chambers are not joined and for 5–8 days after joining. They also guarantee the stability if some electrolytes are introduced. The solutions do not contain vitamins or trace elements, which should be added before administration. When the composition does not match the patient's exact requirements, patients – or their carers – must also add electrolytes and/or administer fluid bags, drugs, etc.

Individualized company preparations

Some companies prepare individualized PN for HPN prescribed in hospitals. Usually, PN orders are sent from pharmacy services by computer and bags are sent to the patient's residence. Vitamins, trace elements and some drugs can be included. The only disadvantage is price.

Delivery

There are different forms of bag delivery, depending on hospitals and availability in each country.

In some countries, there are companies that have homecare services with or without PN compounding. They deliver PN bags, disposable items such as infusion sets and even pumps, refrigerators, etc. Some of them also offer nursing support at home. In some places this is carried out by primary care.

In other cases, patients or caregivers pick up the bags at the hospital and they should be taught that if delivery distance is long, or ambient temperature is high, they need to refrigerate the bags – using ice if necessary – but avoiding the possibility of freezing.

Administration of HPN

It is recommended that 1.2-micron filters be used because they avoid not only precipitates but also the coalescence of oil droplets and other particles from the preparation process (rubber, glass, etc.). These particles can be deposited in the lungs (Walpot *et al*., 1989). Although there are no studies concerning deleterious particle effects in the long-term PN patient, HPN patients will receive a large amount of intravenous fluids over the course of their life. The fewer particles they receive, the fewer side effects they could have. There are filters incorporated in the administration set that provide the advantage of diminishing home line manipulation.

It is important that patient or caregivers, besides being familiar with line care, know about PN integrity and the necessity of storing it under refrigeration. They also need to know that the product should be administered below 25°C and not to remove the photo-protection from the

bag. When infusion is not cyclic, patients have to be aware not to be outside on a day when temperatures are > 28°C (Lee *et al*., 2003).

Future Role of the Pharmacist in HPN

It is important for pharmacists be part of HPN teams, contributing their knowledge of stability, product availability, etc. Their future role depends on the development of HPN. If, as would be desirable, HPN monitoring is concentrated in experienced hospitals, pharmacists should continue to be part of HPN teams, helping design PN compositions in accordance with stability issues and patient necessities. If all patients or caregivers collect bags in the pharmacy, the pharmacist could educate them concerning issues related to PN bag storage and administration. If, on the other hand, HPN could be ordered by any hospital, pharmacists could also have an important role in hospitals where there is no nutritional support unit or team, helping physicians in charge of patients to prescribe PN.

Summary

Home PN preparation can be performed by hospitals or by the pharmaceutical industry, using either long expiration time multi-chamber bags or individualized ones. In order to increase PN stability and decrease lipid peroxidation, the use of photo-protection and multi-layer bags is recommended, as well as organic phosphates and low-PUFA lipid emulsions. The use of filters of 1.2 micron diameter can increase security. Preparation site and distribution depends on the hospital and the available types within the country.

When home care services are available, bags are delivered to the patient's residence, frequently along with materials. Sometimes nursing care is also provided. Depending on the country, these services can be provided by the pharmaceutical industry or by primary care. If these services are not available, patients/care providers must collect the bags once or twice per week. It is important for them to be aware of conservation requirements.

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26 Administration of Home Parenteral Nutrition

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Key points

- In the majority of Home Parenteral Nutrition (HPN) patients, parenteral nutrition is administered on a cyclical nocturnal basis.
- The duration of administration must take into consideration the volume of infusion, the patient's tolerance and the vascular patency.
- Although it has been generally recommended, the benefit of using a heparin lock has not been proved.
- The use of pumps is very variable from one country to another.

Introduction

The administration of parenteral nutrition at home should meet some specific goals: (i) safety; (ii) tolerance; and (iii) the patient's autonomy. Taking into account these parameters, the main objective primarily is to combine an optimal nutritional support with the best quality of life for patients on home parenteral nutrition (HPN).

Administration of HPN must consider various issues:

- The patient's characteristics: (i) age; (ii) indication for HPN and underlying disease: (iii) co-morbidity; (iv) degree of rehabilitation and professional activity; and (v) willingness.
- The type of perfusion: volume, composition, compounding.
- The type of venous access, as well as the patient's vascular patency.

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The HPN Regimen

Timing of infusions

In the majority of HPN patients, PN is administered on a cyclical nocturnal basis (Van Gossum *et al.*, 2001). This regimen has the dual advantage of providing autonomy during the daytime from 6–12 h and of encouraging oral food intake. Nevertheless, the cyclical nocturnal regimen may induce some discomfort, such as sleep disturbance due to frequent urine excretion (Scolapio *et al.*, 2002; Persoon *et al.*, 2005). Moreover, the sleep period can also be disturbed by the control pump alarm.

A small percentage of patients prefer a cyclical diurnal regimen and, more rarely, a continuous daily administration. It is more frequently observed in patients with an advanced cancer, for whom the autonomy is already very limited.

The duration of administration must take into consideration the volume of infusion and the patient's tolerance. The rate of administration should be progressively adapted over time and according to the patient's general level of health. Some factors may limit the rate of administration: (i) the need for a large volume; (ii) the existence of some degree of cardiac failure; and (iii) the vascular patency. Indeed, in patients with previous venous thrombosis and/or superior vena cava syndrome, the rate of administration must be very cautious.

The timing of HPN administration is also dependent on who is doing the IV line connection and disconnection. This is much more flexible for a patient who performs the manipulation by himself than for a patient requiring the assistance of a relative or a community nurse. Another factor that may interfere with the timing of HPN infusion is the volume of intestinal fluid output. Indeed, patients having a high-output jejunostomy may experience fatigue, malaise and thirst only a few hours after stopping the infusion – concomitant with hypovolaemia.

The infusion bag

Usually, HPN is administered as an 'all-in-one' bag. This is more comfortable and requires only one giving set. Moreover, the risk of bacterial contamination is minimal. Individually prepared bags have to be stored in a refrigerator. It is advisable to remove the bag from the fridge some hours before starting the infusion. The commercially available bags can be stored at room temperature and are reconstituted immediately before their administration. For patients receiving commercially prepared bags in the long term, there is a need to add vitamins and trace elements before administration. This has to be performed in sterile conditions.

The home environment

In addition to the sterile handling of giving sets, needles and bags, HPN administration requires a suitable environment. It is recommended that the professional carer visits the home facilities where the manipulations have to be performed, in order to assure a sufficient level of hygiene. A Canadian survey recently showed the following factors as being insignificant in determining line sepsis (Chang *et al.*, 2005): (i) community agency; (ii) socio-economic status; and (iii) educational status. Patients who were in the high-risk category for line sepsis included the following categories: (i) had had medication or blood work performed through the catheter; (ii) had a higher number of dependants or had a trained family member involved in HPN; and (iii) patients who were part-time students or receiving social assistance.

Venous access

The administration of HPN must also consider the venous access and the type of device which is used. In the majority of patients, HPN is administered throughout a central venous catheter. The selection of venous access is based on the following criteria: (i) the vascular anatomy; (ii) the expected duration of HPN; (iii) the patient's activity and willingness; and (iv) the ability of the patient or their caregiver. Further considerations include body image and costs.

It has been shown that the use of a peripherally inserted central catheter (PICC) has a statistically increased risk of catheter infection (De Legge *et al.*, 2005).

In short-bowel fistula and certain other gastrointestinal diseases, salt, water and magnesium balance may remain negative despite oral supplementation, even in patients with adequate nutritional status (Martinez-Riquelme *et al.*, 2005). It has been recently shown that subcutaneous, self-administered fluid infusion (0.5–1.0 l 0.9% saline ± 0.5 l 5% dextrose ± 2–4 mmol $MgSO_4$) at home could be an easily managed, safe and effective method for restoring and maintaining water, salt and magnesium balance. That could be of special interest in the frail or elderly, in whom home parenteral nutrition may be difficult.

There are no guidelines for changing needles when ports are used. Manufacturers recommend changing the needle daily. This is uncomfortable for the patient and extremely expensive. In clinical practice most needles are changed once a week. An analysis of over 100,000 catheter days showed that 36% of the needles were changed every day. A daily puncture of the port was associated with more complications and removals of the device than when punctures were less frequent. An inviolate skin barrier over the port loses its significance if patients are infused every day. The risk of infection increases by daily needle perforation of the skin over the port. Some patients prefer to leave the needle in the site in between intervals of HPN administration to avoid the

discomfort of repeated piercing. Safety can be confirmed by performing a prospective randomized trial.

The use of a heparin lock has been recommended for a long time in patients receiving HPN in order to prevent catheter thrombosis (Lyons *et al.*, 1981). When a heparin lock is employed, a large range of doses can be used (50–500 units in 5 ml sodium chloride 0.9%). Although it was not a randomized trial, the use of a low-dose (50 units in 5 ml saline) heparin block has been recommended.

The analysis of 110,896 days with CVC in patients on HPN by the HAN-Group showed significant disadvantages of heparin flush. There have been significantly more infections, removals and occlusions when heparin flush was used. Heparin has severe adverse effects, e.g. thrombocytopenia, bone disease and loss of hair. In Germany there is no registration for this indication. No randomized prospective study has been performed to show the potential benefit of heparin flush for prevention of catheter thrombosis in long-term HPN patients. Many teams have elected to flush the catheter using a few millilitres of sodium chloride 0.9%.

IV infusion sets

Giving sets for home parenteral nutrition are discarded after each use. Administration sets for separate fat emulsions should be discarded after each unit of fat is infused (Driscoll *et al.*, 1996). Containers and administration sets free of plasticizer – di-2-ethylhexyl-phthalate (DEHP) – should be used in order to prevent DEHP contamination of infusions, especially those containing fat emulsions. Since DEHP is highly lipophilic, fat emulsions are capable of extracting DEHP from the polyvinylchloride (PVC) administration sets. This is important in long-term patients. There may be adverse effects from DEHP related to its potential for neurotoxicity, carcinogenicity and hepatotoxicity in animals. Most of the infusion containers used in Europe are made from EVA.

Infusion pumps

In a clinical setting, intravenous infusion pumps are integral components of parenteral nutrition administration. Use of an electronic infusion pump for safe administration of infusions in hospital is recommended. This is different to the situation in long-term parenteral nutrition in home patients, where infusion time in HPN is regularly between 10 and 14 h. Normally, it is adjusted by the patient and not by physician. There is no difference when infusion time is not exactly as suggested by the physician. The best time is that preferred by the patient, unless there is hyperglycaemia or hyperlipidaemia.

If patients have experience of HPN with and without infusion pumps they refuse the pump, the reason being that the pump involves frequent

alarms, and sleeping is interrupted. If there is no legal requirement, infusion pumps are not necessary for patients on HPN. The use of pumps is very variable from one to another country throughout Europe (Van Gossum *et al.*, 2001). In HPN patients who are not using pumps, the use of flow control devices (Dialaflow) is recommended.

In conclusion, administration of HPN should follow some general guidelines, but may be individually adapted to each patient.

Summary

In the majority of the patients, PN is administered on a cyclical nocturnal basis. This regimen may induce some discomfort such as sleep disturbance. The rate of administration must take into account the volume of infusion, the patient's tolerance and the vascular patency.

Usually, HPN is administered as an 'all-in-one' bag. The selection of venous access is based on several parameters. There are no guidelines for changing needles when ports are used. Although it is largely used, the benefit of a heparin lock has not been proved. The use of pumps is variable from one country to another. Administration of HPN must follow some general guidelines, but may be individually adapted to each patient in order to improve the quality of life.

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27 Monitoring Patients on Home Parenteral Nutrition

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Key points

- Monitoring to be carried out by the specialized team at the hospital, by a home care agency or by the community nurse.
- Intervals between monitoring visits for the stable patient to be 2–3 months.
- Parameters monitored at visits to include biochemical variables, anthropometry; and, every 6 months or yearly, measurements of trace element and vitamin status and bone mineral density.
- Monitoring normally to take place at the discharging hospital with access to the specialized team.
- Monitoring may also be carried out by a home care agency involving the hospital or the general practitioner.
- Intervals between visits may vary, being on average 3 months. Do not forget that the unstable patient may need more attention.
- Assignment of responsibility for monitoring is probably very important for the quality of the process. A questionnaire-based study indicated that, in general, responsibility should be assigned to a specific person most often associated with the specialized hospital team.
- Biochemistry and anthropometry to be measured at all visits; trace elements, vitamins and bone mineral density (BMD) only occasionally; yearly intervals are recommended.
- Official guidelines for monitoring are not available, and prospective studies on the impact of different monitoring regimens on outcome – including the quality of life – of HPN patients are warranted.

Introduction

When patients are sent home with parenteral nutrition (HPN), a plan for monitoring the effect of the treatment must be established. The purpose of

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monitoring is to secure that treatment goals are achieved and that patients obtain the best possible quality of life. Although well trained, patients must be able to recognize and cope with complications, including infections and mechanical problems with the catheter, venous thrombosis as well as metabolic disturbances. Supplying parenteral nutrition is technically demanding, involves considerable costs and may, in some cases, cause serious complications.

A successful clinical outcome requires clinical supervision at regular intervals and careful attendance of the patients. Monitoring should ideally be carried out by a nutrition team, taking into consideration the clinical situation of the patient, his or her individual wishes and the resources of the attending institution (Klein, 1997; Payne-James, 1997; ASPEN, 1999). Being complex and, for many patients, performed daily, HPN may also impact the mood of the patient.

Parameters monitored at visits

No quality assurance studies on the monitoring process of HPN patients are available, so the current monitoring practice of HPN patients is based mainly on experience. The organization usually involves the multidisciplinary nutrition team, and management is in some cases underpinned by guidelines, either national or international, or guidelines provided by the national society of clinical nutrition (Van Gossum *et al.*, 1999). At present no official European guidelines have been presented. The ASPEN guidelines outline the basics of the monitoring practice, but do not provide the details (ASPEN, 1999).

When evaluating how well patients manage at home and which parameters to monitor there are no comparative studies stating the significance in relation to outcome or quality of life. However, we know from a European survey conducted in 2002 (Wengler *et al.*, 2006) how the monitoring of HPN patients is performed.

In this study 42 European HPN centres were asked the questions about the following aspects: (i) the use of written guidelines; (ii) the structure of the department, including the presence of an HPN team responsible for monitoring this specific group of patients after discharge from the hospital; (iii) home visits; (iv) where monitoring took place; (v) the personnel involved; (vi) to whom the responsibility for the monitoring process was assigned; (vii) intervals between monitoring visits; (viii) the clinical parameters evaluated at monitoring visits; and (ix) how handling of complications and monitoring were managed.

The HPN experience of the centres was in the range 2–30 years and ranged in size from 0–125 HPN patients, representing a total of 934, of whom 54% had received HPN for > 2 years. The primary disease was non-malignant in 90% whilst 10% had been diagnosed with active cancer.

Based on the results of this questionnaire-based study, the following scheme (Table 27.1) for monitoring practice can be outlined. This would

Table 27.1. HPN monitoring scheme.

	Once per week	Every 1–3 months	Twice per year	Once every 1–2 years
Body weight	+			
Body temp.	+			
Blood pressure		+		
Hydration		+		
Oral intake		+		
Mood		+		
Quality of life				
Haematology		+		
Liver function		+		
Crea/K/Na		+		
Ca/Mg/P		+		
Glucose		+		
Chol/trig.			+	
Alb.		+		
Trace elements		+		
Vits A, E, D, B_{12}			+	
BMD				+
Urine volume			+	

provide information on the clinical status and response to the nutrition therapy. The intervals between visits and activities carried out must, of course, be individualized since the needs of the individual patient will vary significantly. In particular, shortly after discharge patients may need more advice and attention from those responsible for the treatment.

General quality of life

In the first month after starting HPN, the patient will need special attention and a review of his/her psychosocial status. The patient may develop depression after being in hospital for a long time and then being at home coping with this new situation with relatives, everyday life activities and, for some patients, a job. Assessment of quality of life of the HPN patient can be measured routinely by using the Short Form Health Survey (SF 36) or equivalent to evaluate the impact of the infusion therapy on daily activities. A valuable tool could be specific questionnaires designed for this patient population in order to study quality of life with HPN, but no such studies have yet been reported.

Body weight

Body weight should be monitored once a week. The patients can do it by themselves at home and, if the body weight does not increase as expected, one should consider other causes such as metabolic disturbances, sepsis or the impact of an underlying disease. If, by contrast, the weight increases

very rapidly, the team must consider whether the patient is over-hydrated and appropriate measures should be taken. In the case of severe metabolic disturbance, patients must be admitted to hospital and some centres will routinely assess the HPN treatment during short admissions, or by monitoring electrolyte and water balance in a home care setting.

For patients with significant malabsorption, short bowel syndrome (SBS), measurement of intestinal function may guide the clinician with regard to the needs of parenteral supply (Jeppesen and Mortensen, 2000). The impact of such measures for HPN patients on outcome and quality of life has not been reported.

The European study (Wengler *et al.*, 2006) showed that all HPN centres measured body weight or anthropometry at every visit and 48% of centres also assessed blood pressure and pulse at every visit. Nearly all centres in the study evaluated the state of hydration and 74% of the centres asked patients about oral intake. The mood of the HPN patient was considered in 86% of the centres at every monitoring visit. This, therefore, appears to be a key parameter that majority opinion agrees should be evaluated as a routine.

Biochemical parameters

The following biochemical parameters should be evaluated at every monitoring visit: haematology, biochemical tests for liver function, creatinine and electrolytes, Ca, Mg and phosphate. Intervals between measurements depend on the clinical situation, but for the stable patient 2–3 months are usually sufficient. This is also reflected in the European study (Wengler *et al.*, 2006), since all centres reported that these biochemical parameters were monitored at each visit. Biochemical abnormalities are not uncommon in this patient population, a broad range of changes having been reported regarding haematology and electrolytes, as well as trace element deficiencies (Burnes *et al.*, 1992).

In general, elevated levels of triglycerides are not a problem if manufacturers' guidelines regarding dosing of parenteral lipid are taken into consideration. Many centres will routinely measure levels of triglycerides and, in the European study, about 50% of centres performed such measurements. In this study, 14% of centres measured the levels of vitamins A, E, D, B_{12} and folic acid, but not at every visit, but rather in the case of problems arising.

BMD

Considering that secondary osteoporosis is frequently observed (Pironi *et al.*, 2002; Haderslev *et al.*, 2004), measurement of bone mineral density (BMD) using DEXA scans is recommended at yearly intervals for the majority of patients, and a small group presenting with very low BMD entering treatment protocols may require DEXA scans at 6-month intervals. Regarding monitoring practice, 64% of European centres

measured BMD in all patients 1–2 times per year, the rest less often (Wengler *et al.*, 2006).

The patient/caregiver must be able to: (i) recognize vascular access device complications; (ii) recognize signs and symptoms of fluid imbalance; (iii) perform testing of the urine for glucose; and (iv) recognize signs and symptoms of hyper- or hypoglycaemia (ASPEN, 1999).

Patients sent home with HPN due to an active malignant disease may have problems (pain relief, psychosocial problems; Bozetti, 2003), which differ significantly from those generally seen in benign disorders. Thus, when monitoring, it is important that the nutrition support team work closely together with the palliative unit or the oncologists, in order to solve specific issues.

Location and personnel involved in monitoring the HPN patient

Monitoring usually takes place at the discharging hospital with access to the specialized team. The members of the team include physicians, nutrition nurses, dieticians, pharmacists, psychologists and social workers. The main responsibility for monitoring the patient should be assigned to one specific person (contact person), for example the physician or the nutrition nurse.

Monitoring can also be carried out by a home care agency involving the hospital or the general practitioner. It is important to keep close contact with the patient when starting treatment until the patient/caregiver is confident with the situation. The patient should have at least one nursing visit at home to assess and monitor the initiation of parenteral nutrition in the home. In Europe the stable patient on HPN is monitored at the discharging hospital (73%), at a local hospital (12%), by the General Practitioner (11%) or by a home care agency (4%) (Wengler *et al.*, 2006).

Almost all centres (90%) reported that the main responsibility for monitoring the patient was assigned to one specific person, and this is in line with the framework for guidelines presented by ASPEN (1999). Home visits after discharge for monitoring purposes were carried out by 31 of the centres involving a specialized HPN team, general practitioner and community nurse or home care agency.

Intervals between monitoring visits

Intervals between monitoring visits vary according to the needs of the patient. When starting HPN treatment, visits should be 2 weeks after discharge, but very much depending on how stable the patient's condition is. When the parenteral nutrition is stable and the patient is confident with the treatment, intervals between monitoring visits are normally every 1–3 months. The unstable patient needs more attention.

In cases with problems or complications the patient must contact the

HPN team, outpatient clinic, local hospital, community nurse, general practitioner or home care agency.

Intervals between monitoring visits for the stable HPN patient in Europe were in the range 1–6 months; 52% of patients were seen at intervals of 2–3 months (Wengler, 2006).

Regular checks should be made to ascertain whether parenteral therapy is still required, whether the patient could be weaned off or if nutrition by the enteral route should be increased.

Summary

Monitoring of patients on HPN is essential for the evaluation of treatment effect and management of the complications associated with this treatment. Monitoring is most often carried out at the discharging hospital with access to the specialized nutrition team. Monitoring can also be performed by a home care agency involving the hospital or the general practitioner. Intervals between visits vary, being on average 3 months. The unstable patient may need more attention.

Assignment of responsibility for monitoring is probably very important for the quality of the process. A previous questionnaire-based study indicated that, in general, responsibility was assigned to a specific person most often associated with the specialized hospital team.

Biochemistry and anthropometry should be measured at all visits; trace elements, vitamins and bone mineral density only occasionally – yearly intervals are recommended.

Official guidelines for monitoring are not available, and prospective studies on the impact of different monitoring regimens on outcome – including the quality of life – of HPN patients are warranted.

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28 Dietetics in Home Parenteral Nutrition

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Key points

The main clinical responsibilities of a dietician working within a multidisciplinary team (MDT) in the field of home pareneral nutrition (HPN) are:

- Assessment and monitoring of nutritional status.
- Assessment and monitoring of enteral intake.
- The design of appropriate parenteral nutrition regimens.
- The monitoring of HPN regimens and ensuring that nutritional deficiencies do not occur.
- The provision of advice and evidence-based nutrition education material for patients/carers.
- The participation in audit and research as part of the clinical governance strategy.
- Being a point of contact for patients, providing some psychological support.

Introduction

Over the past 30 years, dietetics has developed significantly in the field of artificial nutrition support. There has been a transition from physically preparing modular tube feeds and diets to an evidence-based, educational role. Howard *et al*. (1999) defined dietetic practice as 'the singular ability to translate complex clinical nutritional concepts into simple everyday language coupled with acceptable strategies for implementing nutritional change'. A dietician should be an integral member of the nutrition support

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team; effective communication with clinicians, nurses, pharmacists, patients and carers is imperative.

Assessment and Monitoring of Nutritional Status

Assessment of nutritional status should include anthropometric and biochemical indices, and take into account intestinal absorption and enteral/parenteral intake.

The goal of parenteral nutrition is to replenish and maintain nutritional and functional status, thereby optimizing body image and, ultimately, quality of life. The ease of this will depend on the clinical condition of the patient (e.g. sepsis). In palliative care, HPN should produce the best balance between quality and length of life.

Anthropometric assessment

There is no universally agreed, single measurement of nutritional status, making the assessment of malnutrition difficult. Body weight is the most widely recognized objective tool used in nutritional assessment, as it is simple and equipment is readily available. Caution is required in patients with precarious fluid balance, such as those with a high-output stoma, oedema or in severely malnourished patients undergoing initial re-feeding, as rapid fluctuations in weight are likely to reflect changes in hydration, rather than in lean body mass.

Weight is often expressed as an index of height to give a measure of body mass index (BMI), where a BMI of 20–25 kg/m^2 is considered desirable. A BMI of < 18.5 kg/m^2 is used as a definition of undernutrition (Roche, 1981). It is generally accepted that a loss of body weight greater than 10% over the preceding 3 months (and not intentional) is considered significant, in terms of clinical outcome (Dewys *et al.*, 1980) and that 20% recent weight loss is evidence of protein energy malnutrition (Kinney, 1988). Patients attending HPN clinics should routinely have weight and BMI measured at every visit.

Weight, BMI and recent weight loss give limited information on body composition.

Body fat reserves and protein status can be estimated from bedside techniques such as triceps skinfold thickness (using skinfold calipers) and mid-arm muscle circumference (MAMC) (Blackburn *et al.*, 1977). Initial measurements of upper arm anthropometry can be compared to standardized tables (Jelliffe, 1966; Frisancho, 1981), but consideration must be given to the demographics of the original populations recruited, the sample size and whether these reference tables apply to an HPN population of today.

Dieticians should be able to demonstrate evidence of health gain and

improved clinical outcomes for patients. The measurement of MAMC is a unique skill that a dietician can offer to the multidisciplinary team (MDT) in order to prospectively monitor HPN patients. It is vital that the same, experienced individual performs all the measurements as these are limited by intra-/inter-observer variability (Hall *et al.*, 1980).

Other techniques such as bioelectrical impedance analysis require further validation before they can be recommended in routine clinical practice, particularly in those patients with extremely low BMI (< 16 kg/m^2) and/or deranged fluid balance (Kyle *et al.*, 2004).

An anthropometric survey of 130 HPN patients was carried out at Hope Hospital, Manchester, UK (Table 28.1).

Biochemical assessment

Biochemical measurements have been frequently included as an element of nutritional assessment tools in research and clinical practice.

Biochemical monitoring, assessed at each HPN clinic, should include the following:

- Full blood count, bone and liver profiles.
- Copper, zinc, selenium and vitamin D status.
- C-reactive protein (CRP).
- Ferritin, folate and vitamin $B_{12.}$
- Coagulation screen.

Changes in nutritional status often occur through non-nutritional factors. Failure to improve nutritional status may be due to sepsis/acute disease state, rather than through the inadequate provision of nutrition. Markers of the inflammatory response, such as CRP, white blood cell count (WCC) and platelets are useful in indicating sepsis and should be regularly monitored.

Albumin levels are considered to reflect disease severity rather than nutritional status, as levels can fall following surgery (Cuthbertson and Tompsett, 1935), with inflammatory markers (Fleck *et al.*, 1985), and can be normal in cases of severe malnutrition, such as anorexia nervosa (McClain *et al.*, 1993).

Table 28.1. Anthropometry data from 130 HPN patients at Hope Hospital, Manchester, UK (from Farrer, 2004, personal communication).

Measurement	Median (range)
Weight (kg)	60 (41.0–94.0)
BMI (kg/m^2)	22.5 (15.0–30.0)
TSF (mm)	11.0 (2.8–22.0)
MAC (cm)	27 (18.0–42.0)
MAMC (cm)	23.6 (17.2–34.0)

HPN is associated with hepatobiliary complications, from mild elevation of liver function tests to hepatic steatosis and intra-hepatic cholestasis. Guglielmi *et al.* (2001) demonstrated that hepatobiliary complications were less frequent when patients received oral feeding, as utilization of the gastrointestinal tract stimulates biliary secretion. Lumen and Shaffer (2002) reported an inverse relationship between raised alkaline phosphatase and remaining length of small bowel, especially in patients with < 100 cm of small bowel. The dietitian should encourage oral intake, unless it is contraindicated, e.g. in bowel perforation with intra-abdominal collections.

Assessment and Monitoring of Enteral Intake/Output

The contribution of oral intake to meeting total nutritional requirements should be assessed, considering both intake and nutrient losses, such as malabsorption. The measurement of habitual dietary intake is fraught with difficulty and requires a detailed dietary assessment. Oral nutritional intake can be estimated from records of actual intake kept at the time of eating, or from retrospective information, which is more common in clinical practice. A diet history should consider food items, frequency of consumption, day-to-day variability, cooking methods and portion sizes.

Dietary intake is associated with many cultural, behavioural, social and psychological factors, as well as being a means of providing the body with macro- and micronutrients. Patients may have experienced many different forms of oral/enteral tube feeding, with limited success. A patient commencing HPN may be filled with apprehension and it is vital to offer psychological support to patients and their families, not only to optimize nutritional status and for social interaction, but also to minimize the potential side effects of hepatobiliary complications, dehydration or malabsorption.

Estimation of nutrient losses

Malabsorption is correlated to the length of small bowel remaining and functional capacity (Hylander *et al.*, 1980; Nightingale *et al.*, 1990) and, depending on anatomy, the composition of dietary intake.

Balance studies are used to assess intestinal absorption, where all oral input is controlled (food, fluid and medication) and output is measured over a defined time period. These techniques are often impractical to perform on all patients in the clinical setting, and since no routine bedside technique is available, the degree of malabsorption is often estimated. Percentage absorption of the total energy intake indigested may vary between 20 and 80% (Woolf *et al.*, 1983; McIntyre *et al.*, 1986; Rodrigues *et al.*, 1989; Messing *et al.*, 1991; Nordgaard *et al.,* 1996*)*, but when interpreting the research studies, consideration must be given to the

diversity of the population (in terms of anatomy and the period elapsed since previous surgical resection).

Dietary Aspects of Specific Conditions

Short bowel: end-jejunostomy

Studies comparing different proportions of fat and carbohydrate have shown no differences in either the amount of energy absorbed (McIntyre *et al.*, 1986), stomal output (Nordgaard *et al.*, 1994) or absorption of sodium and potassium (Ovesen *et al.*, 1983; McIntyre *et al.*, 1986).

A constant proportion of fat is absorbed, so as fat intake increases there is an increased amount of fat in the stoma effluent. This does not seem to be harmful, although increased fat excretion may reduce the absorption of calcium and magnesium (Ovesen *et al.*, 1983). High-fat diets have the benefit of increasing energy intake and palatability.

Studies comparing dietary supplements have also shown no beneficial effects of elemental diets in absorptive capacity (McIntyre *et al.*, 1986). Non-polymeric feeds have the disadvantages of being both hyper-osmolar and of containing a minimal amount of sodium, which will exacerbate stomal water and sodium losses (Newton *et al.*, 1985).

Patients with short bowel syndrome (SBS) frequently have excessive losses of fluid and electrolytes from jejunostomy/fistulae. Whilst additional fluid and electrolytes can be provided via the parenteral nutrition, advice on the management of hydration status – including oral fluid intake – is important. Patients should be educated to recognize the symptoms of dehydration (postural hypotension, dizziness, thirst and reduced urinary output) and given practical day-to-day management guidance. This should include recommendations on a hypotonic fluid restriction (500–1000 ml/day), administration of an oral glucose-electrolyte solution (with a sodium content > 90 mmol/l (Nightingale *et al.*, 1992a), medication to reduce stomal losses and additional intravenous saline, as required.

In contrast to patients with a colon in continuity, requirements for fluid, electrolytes and nutrients are not likely to change over time in those with a jejunostomy (Hill *et al.*, 1974; Nightingale *et al.*, 1990).

Short bowel: colon in continuity

Dietary modification is important in the management of patients with a jejunocolic anastomosis. Energy absorption is significantly greater when high-carbohydrate, low-fat diets are consumed (Nordgaard *et al.*, 1994) and there is increased jejunal absorption of macronutrients, water and electrolytes over time (Weinstein *et al.*, 1969). Fermentation of

carbohydrate to short-chain fatty acids (SCFAs) in the colon may provide up to 1000 kcal/day (Nordgaard *et al.*, 1996). Unabsorbed fatty acids and bile salts reduce water and sodium absorption (Ammon and Philips, 1973), bind calcium and magnesium (high-fat diets increase divalent cation loss, Hessov *et al.*, 1983) and contribute to the formation of calcium oxalate renal stones (Nightingale *et al.*, 1992b). A low-oxalate diet should be recommended, with avoidance of beetroot, rhubarb and spinach (Tomson, 2001).

There needs to be a balance between an ideal dietary composition and palatability/tolerance. High-carbohydrate diets are bulky and increase gas formation. Patients should be encouraged to take sufficient carbohydrate and to find a balance between reducing fat and maintaining palatability/adequate energy.

Intestinal failure without a short bowel length

Pseudo-obstruction/motility disorders and scleroderma account for approximately 10% of HPN patients in the UK (Elia *et al.*, 2003). These patients may have significantly reduced oral intakes. Support should be given to optimize oral nutrition and a modified dietary consistency/composition may be required.

Summary

The dietician, as an integral member of the multidisciplinary team, has an important role to play in the assessment and prospective monitoring of patients receiving HPN. Enteral nutrition has a trophic effect on the gut mucosa and can prevent hepatobiliary complications, whilst positively influencing the quality of life of the patient. A clear understanding of the patient's anatomy is imperative in order to advise the patient on appropriate diet and fluid intake, whilst liaising with the MDT to ensure the nutritional adequacy of the parenteral nutrition regimen.

Key dietetic roles include the assessment of nutritional status with the utilization of appropriate techniques, advising on enteral intake, considering the contribution of oral/enteral intake to total nutritional requirements and avoiding exacerbation of symptoms.

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Part V
Paediatrics

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29 Home Parenteral Nutrition in Children

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Key points

- All children who depend on long-term parenteral nutrition should be discharged on Home Parenteral Nutrition (HPN) if familial criteria are fulfilled.
- Parents or caregivers should undergo a structured teaching and training programme conducted by a nurse from the HPN centre's nutrition support team.
- The patient should be on a stable regimen before being sent home.
- Parenteral nutrition solutions providing macro- and micronutrients for paediatric HPN should be compounded according to individual patient needs.
- Centres caring for infants and children on HPN must have adequate expertise and resources.

Indications and Contraindications

The indications for long-term parenteral nutrition are all situations where oral or enteral nutrition cannot meet nutritional needs.

The main reasons for home parenteral nutrition in children (Vargas *et al.*, 1997; Ament, 1988; ESPGHAN-ESPEN, 2005) are:

1. Primary digestive diseases.

Short bowel syndrome (SBS):

- Inborn gut malformations (excluding gut atresia);
- Mesentery volvulus resulting in gut necrosis;
- Necrotic enterocolitis in neonates;
- Inflammatory bowel disease.

Intestinal wall damage:

- Chronic inflammation, e.g. necrotic enterocolitis in neonates, autoimmune diarrhoea, Crohn's disease;
- Chemotherapy;
- Radiation enteropathy;
- Hereditary untreatable diarrhoea.

Motility disorders:

- Pseudo-obstruction syndrome;
- Extensive gut aganglionosis.

Intestinal fistulas, especially jejunal or ileal.
Protein-losing enteropathy, when enteral nutrition using a MCT-enriched and high-protein diet is insufficient.

2. Primary non-digestive indications, i.e. severe malnutrition caused by:

- Cystic fibrosis;
- Cancerous diseases;
- Hereditary immune deficiency;
- AIDS;
- Chronic organ failure: hepatic, renal, respiratory (especially as a preparation and nutritional state improving prior to transplantation).

European data collected in 2003 showed that the most frequent reasons for HPN in children were: SBS (44%), chronic diarrhoea (autoimmune diarrhoea, hereditary untreatable diarrhoea), pseudo-obstruction syndrome and hereditary immune deficiency (Lyszkowska *et al.*, 2004).

Patients eligible for HPN should be in a stable, safe condition. This includes stability of the underlying disease, fluid and electrolyte requirements and a safe central venous access. Age for safely commencing HPN depends on each individual condition. Most paediatric HPN programmes cater for children < 1 year old and even include babies < 6 months of age (Vargas *et al.*, 1987; Colomb *et al.*, 2003; ESPGHAN-ESPEN, 2005).

The absolute contraindication for HPN – no central venous access – is independent of age. Sometimes the inability of the child's caregivers can create an obstacle to HPN (low mental level, vision defect).

Venous Access

Paediatric HPN usually requires a central venous access. Selection of the most appropriate access device is based on the patient's vascular access history, venous anatomy and the nature of the underlying disease. In the decision-making process of choosing a central venous access device (CVAD), the child's development, social and intellectual skills, activity level,

body-image concerns and family's function need to be assessed (Wheeler and Frey, 1995; Orr, 1999).

Types of CVAD

Partially implanted devices (PIDs) or tunnelled catheters

These catheters are placed percutaneously, under general or regional anaesthesia (more commonly in children), in a central vein and tunnelled from the access site to an exit site usually in the chest area or in the upper abdomen. One or two Dacron cuffs are located on the part of the catheter that will be placed in the subcutaneous tunnel. In 2–4 weeks, tissue adherence to the cuff helps secure the catheter and decreases the incidence of infection because the cuff provides a barrier for bacteria. The most common vessels used for central venous catheterization are the subclavian, internal jugular, external jugular and femoral veins. The characteristics of this type of CVAD are shown in Table 29.1 (Marcoux *et al.*, 1991; Stovroff and Teague, 1998).

Totally implanted devices or implantable access ports

A totally implanted device consists of a catheter connected to a port or reservoir (Miller, 1998). Placement is similar to a tunnelled catheter but, instead of exiting the skin, the catheter is attached to a port which is placed in a subcutaneous pocket usually on the chest. The injection port consists of a durable, hard, protective shell (e.g. titanium, stainless steel or hard plastic) and an overlying Silastic diaphragm. A special side-hole needle (Huber needle) is used to puncture the diaphragm to access the reservoir. Straight or 90°-bent needles are available in several gauges and lengths. The needle does not damage the diaphragm, and the procedure may be repeated up to 2000 times before the system needs replacement. Body image is preserved, a very important advantage in adolescents (Table 29.2).

Other access

When more commonly used veins are not available, other sites for vascular access can be considered, such as the thoracic central veins through a thoracotomy or by means of interventional radiology (Steiger, 2002). Rarely, arteriovenous fistulae can be used for long-term HPN programmes, especially in the case of repeated catheter complications (Ricour *et al.*, 1990). Use of these alternatives requires experience, and should be considered only exceptionally.

Completely implanted small, subcutaneous ports connected to a peripherally inserted central venous catheter have recently been

Table 29.1. Comparison of central venous access devices.

Device	Description	Advantages	Disadvantages
Tunnelled catheters Broviac®, Vygon®, Hickman®, Corcath®, Groshong®, Quinton®, Raff®	Silicone, radiopaque, flexible One or two Dacron® cuffs Single, double, triple lumen	Reduced risk of bacterial migration Easy to use Potential unlimited use Easily removed Able to be repaired Reduced risk of infection	Requires heparin flushes daily Frequent dressing changes Must be clamped May affect body image Susceptible to damage and may be pulled out accidentally Patient/family must learn catheter care
Totally implanted devices Port-a-cath®, Infus-A-port®, MediPort®, Groshong venous Port®, Norport SP®	Totally implantable metal or plastic device Single or double reservoir	Cannot be pulled out No dressing care Flushed monthly No limitations on most physical activity Minor changes in body image	More difficult to access Must puncture the skin each time it is used Hard to manipulate for self-administered infusions Special needle Removal more complex

Table 29.2. Central venous access for home parenteral nutrition in children and adults.

Age	Tunnelled catheters	Ports
< 1 year	2.7–4.2 F, one lumen	Rarely used
1–3 years	3.0–5.0 F, one lumen	Preferably a tunnelled CVC
4–11 years	4.2–7.0 F, one/two lumina	0.6–1.0 mm internal diameter
Adolescents	5.0–12.5 F, one/three lumina	0.8–1.4 mm internal diameter
Adults	7.0–13.0 F, one/three lumina	0.8–1.4 mm internal diameter

developed (PAS Port®, CathLink®) (Walker and Caltone, 1994), but no significant experience in paediatric patients has been reported.

Recommendations for use

No data are available for comparison of the use of implanted ports with Broviac-type catheters in terms of lifespan, complications and quality of life (ESPGHAN-ESPEN, 2005). However, these devices have not been used routinely in young children requiring HPN especially because they require needle puncture for each port access (Chung and Ziegler, 1998).

In those patients previously having had multiple central lines, venous duplex ultrasonography may be used to more accurately assess the degree of thrombosis and/or central vein patency and to safely map sites for CVAD placement (Wiener, 1995). Occasionally, a magnetic resonance imaging study is most useful in mapping potentially patent central veins.

Infusions

Substrates and nutritional requirements

Parenteral nutrition is not merely an energy and protein supply. It is inseparable from fluids and electrolytes, which are vehicles for nutritional ingredients. The supply of water, electrolytes, macro- and microelements, carbohydrates, lipids and amino acids depends on the patient's age, weight, underlying disease or diseases and – related to these – metabolic tolerance, needs and possibilities (Friis-Hansen, 1961; Winters, 1973).

The average intakes of all ingredients used in parenteral nutrition in children are presented in Tables 29.3 and 29.4 (Allison and Walker, 1986; Bresson *et al.*, 1989; Ament, 1998; Bollinger *et al.*, 2003).

Carbohydrates

The only carbohydrate used in parenteral nutrition in children is Dextrose (D-Glucose). One gramme of Dextrose provides 3.4 kcal. It is the main

Table 29.3. Fluid and electrolyte requirements in children.

Age (years)	Water (ml/kg/day)	Na (mmol/kg/day)	K (mmol/kg/day)	Ca (mmol/kg/day)	P (mmol/kg/day)	Mg (mmol/kg/day)
< 1	120–150 (max. 180)	2–3	1–3	1.50–2.25	1.50–2.20	0.24–0.42
1–2	80–120 (max. 150)	1–3	1–3	0.60–1.50	0.60–1.50	0.10–0.24
3–5	80–100	1–3	1–3	0.60–1.50	0.60–1.50	0.10–0.24
6–12	60–80	1–3	1–3	0.60–1.50	0.60–1.50	0.10–0.24
13–18						

Table 29.4. Energy, glucose, lipid and amino acid requirements in children.

Age (years)	Total energy (kcal/kg/day)	Glucose (g/kg/day)	Lipids (g/kg/day)	Amino acids (g/kg/day)
< 1	90–100	12–18	2–3	1.8–2.5
1–7	75–90	8–11	2–3	1.5–1.8
7–12	60–75	8–10	1.5–2.0	1.0–1.5
12–18	30–60	5–7	1.5–2.0	0.8–1.3

source of non-protein energy – about 20–30% of the total kcal delivered parenterally (Ament, 1998). Major attention should be given to the rate of glucose delivery in children on a cyclic PN regimen. Glucose tolerance decreases from birth to adulthood. The rate of glucose delivery should be progressively increased and should not exceed 1.2–1.4 g/kg/h in an infant, 1.0–1.2 g/kg/h in a child 1–10 years old and 0.5–0.8 g/kg/h in an adolescent. Therefore, the total glucose supply should not exceed 400 g/day in an adolescent receiving cyclic 10/24 h or 12/24 h infusion.

Lipids

Lipids are the second most important source of energy (9 kcal/g) and also provide essential fatty acids. Lipid emulsions should provide 30% of non-protein energy. They are used in paediatrics as: (i) long-chain triglycerides (soybean: Intralipid® 20%, Ivelip® 20%, Lipofundin N® 20%, Lipovenoes® 20%; olive oil: ClinOleic® 20%); and (ii) long- and medium-chain triglycerides (Lipofundin MCT/LCT® 20%), using the same nutritional products as for adult patients. Fish oil emulsion could be also used in children as an additive to enrich lipid emulsion with ω-3 fatty acids and to optimize parenteral nutrition in specific clinical situations (Ament, 1998; Bollinger *et al.*, 2003).

Amino acids

Solutions of L-amino acids are the main source of nitrogen. Amino acid requirements in parenteral nutrition have been estimated on the basis of fetal nitrogen accumulation or analysis of breast-fed infant data. Amino acid solutions used in young children should provide the serum amino acids pattern resembling that seen in breast-fed infants (Heird *et al.*, 1987). In infancy there are a larger number of essential amino acids than in adults. Cysteine, taurine, tyrosine, histidine and glutamic and aspartic acids can be ranked amongst the essential amino acids (Ament, 1998; Bollinger *et al.*, 2003). Therefore, the composition of amino acid solutions for infants and young children differs from those used in adult patients or adolescents, e.g. Aminoven Infant®, Primene®, Vaminolact®, Aminopaed®, Aminoplasmal®, Pädamin® and Vamin 9 Glucose®.

The optimal energy:nitrogen ratio in children is approximately 150–250:1 (MacFie *et al.*, 1981).

Vitamins and trace elements

Each PN infusion should provide water-soluble and lipid-soluble vitamins and trace elements according to the patient's age, weight and specific needs. The vitamin requirements for younger children differ from those of adult parenteral nutrition. The major differences concern the lipid-soluble vitamins (Green *et al.*, 1988). The most widely used solutions of vitamins in children up to 11 years of age are Soluvit® (water-soluble vitamins) and Vitalipid Infant® (lipid-soluble vitamins). Those preparations used for children over 11 years of age include Soluvit®, Vitalipid Adult® (lipid-soluble vitamins) and Cernevit® (water- and lipid-soluble vitamins but lacking vitamin K). Vitamin K should be given separately (IV, IM or orally).

Some of the trace elements are routinely provided in parenteral nutrition solution, e.g. Peditrace® (Zn, Cu, Mn, Mn, Se and F) for children weighing up to 15 kg; or Addamel® (Cr, Cu, Fe, Mn, I, F, Mo, Se and Zn) for children weighing over 15 kg.

Iron

Iron supplementation should be provided to patients receiving long-term PN (> 3 weeks). Iron should then be given periodically IV or IM (e.g. once per month). In infants and young children the standard dose of iron is 100 μg/kg/day (3 mg/kg/month). Using this dose in long-term parenteral nutrition, an accumulation of excess iron can be observed in some patients. Therefore, the concentration of ferritin should be monitored in children on long-term HPN. Provision of iron should be decreased at ferritin concentrations of 500 ng/ml, and stopped completely at 1000 ng/ml (Ben Hariz *et al.*, 1993a).

Phosphate

Organic phosphate solutions (Glycophos®, Phocytan®) are more often used than inorganic ones, as in young children a small volume of an admixture may contain a high concentration of ions – especially calcium and phosphate – which can precipitate. This reaction can be prevented by the use of organic phosphate solutions.

Parenteral nutrition has to be adapted for the individual patient's clinical situation. The level should be lower when partial enteral nutrition is possible or, conversely, higher in catabolic patients or in cases of increased fluid, electrolytes and protein losses via the gastrointestinal tract. Parenteral nutrition has to be adapted for the special needs of patients

with kidney, liver or lung failure or of those undergoing specific treatments (e.g. organ transplantation, oncological treatment).

Organisation and Technical Aspects

Organisation

HPN should be based on multidisciplinary hospital nutrition support teams, including the following: physician(s), pharmacist(s), nurse(s), dietician(s) and social worker(s) (ESPGHAN-ESPEN, 2005). They should work as a team supporting the parents. HPN centres should have adequate expertise and resources to ensure a good standard of care. Physicians should be trained and qualified to be responsible for the appropriate use, prescription and follow-up of patients on HPN programmes. Nurses who are responsible for parents' teaching and training should evaluate their capacities to deal with all medical and technical issues related to the child's treatment. Pharmacists should ensure safety of compounding and storage of the PN mixtures.

Cost savings

HPN is an expensive technique. The annual cost of HPN, including nutrients, pump and disposable equipment, has been estimated to be about $60,000 (Bisset *et al.*, 1992) to $80,000 per patient (Richards and Irving, 1996) in the UK, but as much as $100,000 and up to $150,000 per patient in the USA (Elia 1995; Howard *et al.*, 1995). However, cost-benefit studies have demonstrated that HPN is about 65% more cost-effective than hospital treatment for children than for adults (Detsky *et al.*, 1986; Elia 1995; Richards and Irving, 1996). The longer a patient survives on HPN, the more cost-effective home-treatment becomes. A paediatric study showed that HPN led to savings of about $2 million in a single year through the decrease in the incidence of septic episodes, from 1/142 days in hospital to 1/567 days at home (Melville *et al.*, 1997).

Preparation of a HPN paediatric programme

Prior to discharge, parents must undergo structured training in all aspects of care and complications (Ricour *et al.*, 1990; Bisset *et al.*, 1992; Puntis 1995; Phillips, 1999; ESPGHAN-ESPEN, 2005). The teaching programme begins as soon as the decision to proceed with HPN is taken. It is best undertaken during the period when at least one parent or both are resident in the hospital, especially if the family lives far from the HPN centre. The mean duration of the teaching programme is about 2 weeks (Ricour *et al.*, 1990; Bisset *et al.*, 1992), but the duration needs to be

tailored to each family's needs. The structured teaching programme must have a written plan, step by step instructions and a method of recording achievement of competencies.

It comprises theoretical and practical aspects, and written and audio-visual tools may be used. Each session is limited to learning one particular skill, and a new subject has to be introduced only when parents are competent in and confident with the previous one. A written record of progress should be kept. Some teams recommend that the parents spend 1–2 nights with their child in a special 'isolation' room, close to the medical unit but without any help from hospital nurses, in order to simulate home conditions and to assess their autonomy, just before the family returns home (Ricour *et al.*, 1990).

When a teaching nurse goes to the home with the child and family on first discharge, parents are more confident in dealing with all practical problems. When parents cannot be autonomous, especially in the case of a single-parent family, the help of a community nurse is required (Ricour *et al.*, 1990; Puntis 1995).

In some countries, candidates for HPN can be referred to outside service organizations, which employ nurses who sometimes meet the family in the hospital for the first encounter and then visit the patient at home to complete the instruction given at the hospital. Community health professionals should be involved in all aspects of discharge planning and subsequent shared care (Bisset *et al.*, 1992; Meadows 1997; Smith and Daughtrey, 2000). The physician and the teaching nurse from the HPN centre should also inform staff from the referring hospital about emergency guidelines (Bisset *et al.*, 1992). This may be done by holding a discharge planning meeting attended by parents and all professionals involved in the child's care. It is best held at the patient's local hospital. Those attending may include the child (if old enough), parents, members of the specialist nutrition team, a local paediatrician, a nurse from the local hospital, a community nurse and the patient's general practitioner.

Rhythm of infusion

HPN is based on cyclical (10–18/24 h) parenteral infusion of a nutrient formula (Ricour *et al.*, 1990; Bisset *et al.*, 1992). Children, like adults, almost always tolerate a nocturnal infusion over a period of 10–12 h, especially when oral or enteral feeding is possible. Cyclic infusion has metabolic, physical and psychological advantages. In infants, especially when enteral feeding is not tolerated, or in children with major digestive fluid and electrolyte losses, a longer period of infusion is required (14–18 h).

When PN is commenced in the hospital ward, all children are infused continuously 24/24 h before undergoing an adaptation period, during which time the rate of infusion is gradually increased and the infusion period generally decreased from 24/24 to 12/24 – and at most 18/24 hours

in exceptional circumstances. According to the patient's condition, a progressive increase and decrease of infusion rate during the initial and final hours of infusion should be considered in order to avoid hypoglycaemia and hyperglycaemia (Ricour *et al.*, 1990).

Equipment

Pumps

A pump is indispensable for parenteral infusion in children. Pumps for children's HPN should achieve a good compromise between safety and comfort. The main requirements for safety are: (i) volumetric accuracy with a wide range of flow rate; (ii) no risk of sudden discontinuation of infusion (reliable battery); (iii) no risk of free flow; (iv) 'keep vein open' status; (v) audible and written alarms (e.g. for air bubbles in line, empty container, occlusion, change in pressure, dose limit or low battery); and (vi) child-proof (Meadows, 1997; ESPGHAN-ESPEN, 2005).

Other requirements are also important for the quality of life: (i) simplicity in priming the set; (ii) clean ambient air; (iii) preselection of infusion rates; (iv) minimum number of false alarms; (v) minimum motor noise; and (vi) minimum weight and volume, with carrying handle and binding on IV poles. Portable pumps are now more widely available and can have a major impact on improving the quality of life. Any faulty pump should be replaced within a reasonable time span (e.g. 4 h), or a second pump should be available in the home. Pumps should be annually serviced.

The supply of equipment and ancillaries should be delivered to the home. Families should not have to collect equipment from different sources (Meadows, 1997).

Filters

The aim of filtration to reduce the risk of precipitates reaching the patient has been emphasized (Driscoll *et al.*, 1996; Bethune *et al.*, 2001; ESPGHAN-ESPEN, 2005). Filters should be 1.2-micron, air-eliminating filters when an all-in-one, lipid-containing formula is delivered, in contrast to 0.22-micron, air-eliminating filters suitable for non-lipid-containing PN.

Nutrition Mixtures for Paediatric HPN

Binary mixtures including glucose, amino acids, electrolytes, trace elements and vitamins (lipids being administered separately on a Y-line) or all-in-one mixtures are provided to children on HPN. Mixtures may be manufactured and delivered to patients with ancillary equipment weekly,

fortnightly or monthly. Vitamins or drugs added to nutrient mixtures might impair stability but, on the other hand, availability of certain drugs and vitamins might be reduced when introduced into PN mixtures (Ben Hariz *et al.*, 1993b). Thus, depending on these limiting factors, the 'safe' duration of PN bag storage varies from about 8 to (exceptionally) 30 days. Bags should be stored at 4°C, from their production to their delivery to the patient.

Home care companies should provide the families with a refrigerator for PN bag storage. Special mixtures should be prepared according to individual requirements (Ricour *et al.*, 1990). The so-called standard PN mixtures compounded by pharmaceutical companies, suitable only for adult patients on short-term and/or complementary PN, cannot meet children's nutritional requirements and are free of vitamins and trace elements. The use of non-paediatric-standard PN formulas in children on HPN can lead to severe metabolic complications. Currently, a few standard formulas are suitable for children on HPN.

Outcome

Long-term outcome: the role of centralized HPN expert centres

The largest paediatric surveys (Vargas *et al.*, 1987; Ricour *et al.*, 1990; Colomb *et al.*, 2003) have reported a mean HPN duration of about 2 years, with an upper duration longer than 15 years. Children on HPN have better survival rates and greater likelihood of resuming full enteral nutrition after 1 year than do older patients (Howard *et al.*, 1995). About 50% of paediatric patients can be weaned from HPN, the functional prognosis being better for congenital SBS and inflammatory bowel diseases than for other indications (Ricour *et al.*, 1990; Colomb *et al.*, 2003).

In children with chronic intestinal failure who cannot be weaned from PN, small-bowel transplantation might be an alternative to lifelong HPN, depending on each individual situation (complications of long-term PN, tolerance of the family).

Since the first isolated small-bowel transplantations using cyclosporin A, major advances have resulted from use of new immunosuppressive treatments (Goulet *et al.*, 2000). When liver structure and function are impaired by long-term PN, a combined small-bowel and liver transplantation should be considered. However, the timing of referral and criteria for isolated intestinal or combined transplantation is still a matter of debate (Brook 1998; Goulet *et al.*, 2000).

The role of expert, centralized HPN centres is to improve the quality of HPN and thus to decrease the number of transplantations which are due to, or precipitated by, PN-associated complications. Therefore, early referral of patients on long-term PN to specialized HPN centres – and especially before irreversible liver failure occurs – might increase their quality of life and survival times and reduce the cost of care.

Monitoring

Parenteral nutrition in infants and children is always initiated in the hospital setting with careful monitoring. Children discharged on HPN must be psychologically stable, have caregivers who are willing and able to provide care, and have appropriate resources, including a safe home environment (ASPEN Board of Directors, 2002). Once at home, monitoring should be designed to determine the effectiveness and appropriateness of nutritional support: (i) nutritional status and growth; and (ii) risk of complications due to nutritional support. Once discharged from hospital, a regular outpatient follow-up is planned in order to check clinical and biological parameters. Visits are planned according to each individual situation, initially at monthly intervals, more frequently if necessary, especially in infants. A 24-h telephone contact should be provided by the hospital nutrition support team (Ricour *et al.*, 1990; Meadows, 1997; Smith and Daughtry, 2000). Close cooperation with general practitioners and local, non-specialized hospital units is indispensable in an emergency.

Often, nutritional needs must be integrated with other services to promote growth and development. The home care team includes parents or caregivers, paediatricians, nutrition care specialists, sub-specialists, teachers, dieticians, pharmacists and visiting nurses. Speech and occupational therapists, social workers and psychologists may be also involved.

Monitoring of HPN patients varies according to the individual child's condition (Table 29.5). There are no established national standards or evidence-based recommendations, but the ESPGHAN-ESPEN group has provided recommendations, not evidence-based but nevertheless expert advice. However, below there is a suggested protocol:

1. Monitor the clinical status and the response to nutritional therapy.

- Physical examination, weight, height and head circumference (< 2 years old) should be performed on a routine basis and plotted on appropriate growth curves.
- Assessment for clinical signs of nutrient deficiencies or excesses (Jensen and Binkley, 2002).
- Caregivers should monitor fluid status, intake and output on a daily basis, with temperature and urine glucose recordings daily to weekly.
- Evaluation of functional status and performance.

2. Review the appropriateness of the nutrition therapy, therapeutic regimen and route of administration.

- Assessment of the need for continued nutrition support.
- Monitoring of fluid, nutrient and oral intake.
- Checking of venous access.

3. Assess laboratory data.

The ESPGHAN-ESPEN recommendations provide a schedule for biologic

Table 29.5. Laboratory monitoring of paediatric patients on home parenteral nutrition.

Laboratory parameter	Baseline	Optional baseline	Weekly x 2	Monthly x 3	Every 6 months
Complete blood count with differential	+		+	+	+
Electrolytes with pH and venous CO_2	+		+	+	+
Chemistry profile: glucose, blood urea, creatinine, total protein, albumin, triglycerides, calcium, phosphorus, magnesium	+		+	+	+
Liver function tests: total bilirubin, alkaline phosphatase, LDH, SGOT, SGPT, GGT	+		+	+	+
Protein and PTT	+	+	+	+	+
Iron studies					+
Zn, Se		+			+
B_{12}, folate		+			+

monitoring (ESPGHAN-ESPEN, 2005). Although there is not a generalized schedule of biochemical monitoring, the monitoring should include electrolytes, BUN/creatinine, calcium, phosphorus, magnesium, acid–base status, visceral proteins, liver function tests, glucose, triglycerides and complete blood counts, initially weekly (especially at the hospital) to monthly but with the frequency decreasing over time (Ireton-Jones *et al.*, 2003; Vanderhoof and Young, 2003). Trace elements, fat-soluble vitamins, iron, folate/vitamin B_{12} and carnitine assessment every 3–12 months should also be considered, according to the patient's condition. Trace element studies every 2–6 months and fat-soluble vitamin assessment every 6–12 months should also be considered.

4. Identify and clearly monitor patients transitioning from parenteral to enteral/tube feeding.

5. Recognize potential complications.

(i) Complications associated with CVADs
Central catheter lines should be maintained with proper dressing techniques and adherence to sterile technique whenever the line is accessed (La Quaglia, 1992). Special attention should be paid to clinical signs that suggest central venous thrombosis: neck pain, neck swelling, anterior chest vein distension or shortness of breath (Newell, 2003).

(ii) Metabolic complications
PN-based liver disease is a challenging situation for children on HPN. Both PN itself and underlying digestive disease contribute to liver damage.

Many risk factors have been identified and may be avoided or treated (ESPGHAN-ESPEN, 2005). Besides periodically checking liver function tests, a liver ultrasound should be performed every 6–12 months, looking for both gallstones or biliary sludge and changes in liver appearance, especially fatty liver or portal hypertension. Metabolic bone disease is not an unusual complication in adult patients on long-term HPN (Miranda-Sanchez *et al.*, 2004); nevertheless, the incidence in the paediatric population is not known. DEXA should be used both for diagnosis and follow-up of mineral bone density in children.

Monitoring guidelines may be modified and more focused when certain disease states are present, and checking the hydration status and serum electrolytes is essential.

Summary

Long-term parenteral nutrition is required to preserve nutritional status in children when oral or enteral nutrition cannot provide protein and energy needs, especially in diseases with impaired digestive function. When a child does not need hospitalization but depends on long-term PN, HPN is an alternative to prolonged hospitalization and is recognized as the best option for improving the quality of life of these children and their families within the constraints of the disease.

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Part VI

Miscellaneous Aspects of Home Parenteral Nutrition

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30 Quality of Life for Patients on Home Parenteral Nutrition

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Key points

- One of the main aims of HPN is to improve quality of life.
- HPN has an inevitable impact on quality of life, either positive or negative.
- HPN affects both the patient and family or caregiver.
- HPN is difficult to assess as there is no direct measurement of success.

Introduction

Home parenteral nutrition (HPN) is a life-saving treatment that supports those patients whose gastrointestinal tract is unable to absorb sufficient nutrients to sustain life. HPN has revolutionized the treatment of intestinal failure and has enabled patients to leave hospital and, in some cases, to return to work. Although HPN is a complex procedure which puts great demands on patients and impacts on their quality of life (QoL) the alternatives are to die from malnutrition and dehydration, or to be dependent on prolonged hospital care or on multiple hospital admissions for administration of intravenous (IV) nutrition and/or fluids.

Patients commencing HPN are a heterogeneous group, spanning a wide age range and fall into three broad categories:

- Previously fit and well individuals who have suffered a catastrophic event such as mesenteric thrombosis or volvulus.
- Those suffering from chronic disorders such as Crohn's disease or intestinal obstruction which have become unresponsive to treatment, HPN being the last resort.
- (i) Patients with malignancies affected by cancer therapies which result in intestinal failure; (ii) malnourished, hypophagic patients who need

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nutritional support to improve compliance with chemo-/radiotherapy; or (iii) those with advanced disease whose survival is affected by inability to receive nutrition (Cozzaglio *et al.*, 1997).

Generally, patients with a chronic condition have had time to adjust to the limitations imposed by their illness and more readily accept the need for HPN. The impact on those previously in good health is twofold, with the need to come to terms with their illness and the added burden imposed by a complex intervention such as HPN. Initial reactions such as anger, anxiety and depression resulting from inability to eat normally, loss of independence, change in social and work status and loss of control of bodily functions are all experiences encountered on starting HPN. These emotional and psychological responses may pass as the individual adjusts to their altered circumstances (Gulledge *et al.*, 1987).

The aim of HPN therapy is to rehabilitate patients back into the community, thus reducing hospital costs and improving their QoL. To meet these aims patients/carers must be equipped with the knowledge and skills to manage this complex therapy in a safe and competent manner. According to Van Gossum *et al.* (1996), most centres in Europe train patients in hospital, 67% of them using standard protocols. Training was, on average, completed in just over 14 days. Despite this, only 43% of patients were able to self-care.

Patients should also be given an element of choice about aspects of their treatment, e.g. the type of catheter, method of infusion, etc. to ensure as much compatibility as possible with their expected lifestyle. Body image is particularly important to some, and external catheters are a constant reminder of dependence on HPN and disease. Implanted ports are less restrictive in terms of choice of clothing and activities such as swimming. Meeting established patients prior to discharge will dispel some of the fears and anxieties in the short term, and encouragement to join one of the patient groups such as PINNT (UK) or other national patient support groups will provide peer support and empowerment in the long term.

Securing adequate insurance coverage, personal wealth, retaining access sites, avoiding short- and long-term complications such as bone and liver disease, all impact to some extent on the quality of life achieved. However, this depends in the long term on the individual – a helpless or hopeless attitude will negatively affect QoL.

Quality of Life

Quality of life is difficult to define and measure. For Calman (1984), QoL 'Is a reflection of the difference at a given time between the hopes and expectations of an individual and the individual's present experience'.

According to Flanagan (1978) there are five domains that contribute to overall QoL (Table 30.1). All these domains can be affected to a greater or

lesser extent by a person's health status, symptoms and level of physical and social functioning. Illness and/or treatment has a negative impact on the sense of well-being and the ability to perform the normal daily activities required to meet basic needs and fulfil normal roles. Sleep deprivation, fatigue, depression, anxiety and anger may affect functional performance or, conversely, decreased functional status may contribute to a depressed mood.

Hopes and expectations will be different for the terminal cancer patient than for a patient with benign disease and, when measuring QoL in patients on HPN, we need to look at the starting points patients are coming from and compare like with like in order to obtain meaningful data. Only the individual concerned – and close family and friends – can assess how illness and/or treatment has affected their lives and it is of paramount importance that those individuals participate in research activities aimed at gaining an understanding of QoL on HPN.

Measuring quality of life

As part of the UK Health Technology Assessment programme the effectiveness of HPN was assessed by Richards *et al*. (1997), and included a systematic review of QoL evidence. A number of studies using a variety of validated, non-validated and functional questionnaires were identified. Only three studies included patient participation (Detsky *et al*., 1986; Herfindal *et al*., 1989; Carlson *et al*., 1995), one involved the patient plus doctor (Galunduik *et al*., 1990) and two used the doctors' values (Messing *et al*., 1989; O'Hanrahan and Irving, 1992). Only one non-validated questionnaire was designed to be HPN specific (Carlson *et al*., 1995).

Carlson (1995) appears to be the first to have developed a specific HPN questionnaire, which identified problems specific to the HPN

Table 30.1. Flanagan's Domains of Quality of Life.

Physical and material well-being	Material well-being and financial security
	Health and personal safety
Relations with other people	Relations with spouse, parents, siblings and other relatives; having and rearing children
	Relations with friends
Social, community and civic activities	Helping and encouraging others
	Participating in local government affairs
Personal development and fulfilment	Intellectual development; understanding and planning occupational role/career
	Creativity and personal expression
Recreation	Socialising with others; passive and observational recreational activities
	Participating in active recreational activities

population. Later studies continued to use generic, validated questionnaires to compare HPN patients to a healthy population, whilst others used disease-specific instruments to investigate more specific issues.

The current literature is difficult to interpret for a number of reasons:

- A wide variety of instruments have been used and it is difficult to compare findings.
- Some studies do not differentiate between those with benign and malignant disease.
- There is no patient participation in some studies and judgements have been made solely by clinicians.
- Studies have not used the same time point for data collection.
- Technology has moved on and earlier studies may have little relevance to the current situation.
- Little patient participation in developing suitable instrumentation.

Quality of life on HPN: patients with malignancy

In the USA (Howard *et al*., 1991) malignancy is the main indication for HPN, accounting for 46% of patients. However, there is considerable debate about the use of HPN within Europe for patients with incurable cancer. Van Gossum *et al*. (1996) found the prevalence to be as follows: Netherlands (60%), Spain (39%), France (27%), Belgium (23%), Denmark (8%) and the UK (5%). This may be due to differences in national healthcare provision, ethical and or cultural differences.

It is interesting to note that, in an Italian study (Bozzetti *et al*., 2002), only 43% of patients were aware of their diagnosis and < 1% of their prognosis. This is totally opposite to the position in the UK, where diagnosis and prognosis are fully disclosed. The evidence of improved QoL on HPN in advanced cancer is poor and its use probably says more about a country's culture or attitudes to palliation than about medical judgement. The dilemma remains whether to burden the patient/carer with complex technology with the risk of complications and readmittances to hospital to buy extra time – and possibly a small improvement in QoL – or to let the patient die with dignity (McKinlay, 2004).

The duration of HPN for the majority of these patients is short lived. King *et al.* (1993) recorded a median duration of 66.5 days for patients with gynaecological cancers. Other studies have demonstrated a median duration of 4 months (Cozzaglio *et al.*, 1997; Bozzetti *et al.*, 2002). King *et al.* (1993) reported an HPN-related complication rate of 9%, mostly catheter-related sepsis, and there was no HPN-related mortality. In the Cozzaglio study there were 51 readmissions to hospital for a total of 371 days (about 4% of the entire HPN period) – only about one-third of this time was for HPN-related complications. This suggests that HPN is relatively safe and that the number of hospital readmissions is acceptable.

King *et al.* (1993) showed an overall improvement in QoL compared to

that pre-HPN. Morale and social interactions improved as did GI discomfort, nausea, vomiting and fatigue. Sixteen per cent of patients worked outside the home and 6.6% undertook recreational travel. However, this study has a number of flaws in that the QoL assessment was based on the impressions of clinicians who had undertaken a retrospective review of patient case notes using an arbitrary scoring system. Cozzaglio *et al.* (1997) also reported improved QoL for patients who survived for more than 3 months. Again, this was based on clinical judgement rather than on patient participation.

Bozzetti *et al.* (2002), studying 69 Italian patients, measured QoL using the Rotterdam Symptom Checklist (RSCL), a validated cancer-specific tool, at the start of HPN followed by monthly intervals. Fifty per cent of patients complained of worries, tension and desperate feelings about the future. Anorexia, tiredness, lack of energy and decreased sexual interest were evident. Most were unable to do housekeeping, climb stairs, do odd jobs, walk outside and go to work or they needed help to do these activities. Yet, when asked 'how are you today?', 58% answered 'well'. After 1 month on HPN, around 50% of the patients had deteriorated, 40% had improved and the rest remained the same in terms of physical, psychological and activity assessments.

Both Cozzaglio *et al.* (1997) and Bozzetti *et al.* (2002) have demonstrated improved or stabilized QoL for patients surviving longer than 3 months, although this deteriorated during the final 2 months of life. This indicates that, for HPN to impact positively on QoL, a patient needs to survive for at least 3 months. Both studies used the Karnofsky Performance Status score (KPS), a functional scoring instrument (100 normal–10 moribund) to follow the course of a patient's illness. Those with the highest score at the time of tumour diagnosis tended to have the best survival and QoL over the course of their illness. Patients starting HPN with a KPS > 50 survived longer than those with a lower score.

Quality of life on HPN: patients with benign disease

The duration of HPN for the majority of patients is less than 1 year. Between 40 and 70% of those with benign disease will recover and only 25–50% will progress to long-term HPN.

A number of studies have compared HPN patients to the healthy population using validated generic tools such as the Short Form Health Survey (SF-36) and European quality of life (EuroQoL). Patients scored lower than the general population for six out of eight domains: (i) physical functioning (extent to which health limits physical activity); (ii) role functioning (extent to which physical health interferes with work or other daily activities); (iii) body pain; (iv) general health; (v) vitality; and (vi) social functioning.

Mental health and emotional functioning scores were similar to the bottom end of the standard population scores (Richards and Irving, 1997). Reddy and Malone (1998) and Pironi *et al.* (2004) confirmed these results

for five of the same domains. Carlsson *et al*. (2003) compared patients with short bowel syndrome (SBS) who were on HPN to those without HPN. Only vitality and mental health produced equal scores for both groups of patients, patients on HPN scoring lower for the other six domains. Patients addicted to narcotics scored 25% lower.

Richards and Irving (1997) found that younger patients (< 45 years) had scores nearer to the healthy population, whilst those > 55 years had worse scores. This was not confirmed by Pironi *et al*. (2004) who, rather than using the raw SF-36 scores as Richards had done, standardized patient responses for the sex- and age-matched group scores of the healthy population, which may account for the difference. Both studies show no difference between men and women and no difference according to duration of HPN. This latter finding is at odds with both Detzky *et al.* (1986), who reported that QoL scores were poorer in the first year on HPN, but improving as the patient became established, reaching a peak at years 4–5 and Smith (1993), who showed that poorer QoL was associated with duration of HPN.

Pironi *et al*. (2004) repeated his study with 20 patients around 10 months later, and found that the domains had worsened for eight of the patients and were related to decreased body mass index, a greater incidence of intestinal motility disorders, oral liquid diet and an increase in the number of infusions per week. This supports O'Hanrahan and Irving's (1992) findings that certain sub-groups of patients have worse QoL scores (mesenteric vascular disease, pancreatic disease/malabsorption and systemic sclerosis), reflecting the more widespread and extra-intestinal components of these conditions.

On the other hand, patients with Crohn's disease – once established on HPN – had better scores than pre-HPN (Galanduik *et al*., 1990) and did well. Ninety-five per cent were able to look after themselves independently and 75% maintained employment or looked after their families (O'Hanrahan and Irving, 1992).

A high proportion of patients with bowel disease have a stoma. Jeppesen *et al*. (1999) compared two groups of Danish patients with bowel disease, one group on HPN and the other without, using: (i) the Sickness Impact Profile (SIP) – a non-disease-specific behavioural measure of health status; and (ii) the disease-specific Inflammatory Bowel Disease Questionnaire (IBDQ). They showed no difference between non-HPN patients with or without a stoma but found worse scores for HPN patients with a stoma than for HPN patients without a stoma. From these data Jeppesen *et al*. postulated that stomas could be a major detriment to QoL on HPN, an argument not supported by other authors (Richards and Irving, 1997; Carlsson *et al*., 2003).

Jeppesen *et al*. (1999) observed an overall poorer QoL for HPN-dependent patients. Reduced reserves of strength affected ambulation, mobility, body care and movement, limiting activity in connection with home management and employment. Reduced levels of strength were more pronounced in women and those > 45 years. Only 14% were in full-

time work, similar to the rates of 20% in the UK (Richards and Irving, 1997), 19% in the Netherlands (Persoon *et al*., 2005), but much lower than the 65% reported by Van Gossum *et al*. (2001) in a multi-centre European study.

Giving up work for most people is difficult. Unemployment compromises financial security and personal wealth, which in turn affects personal development and fulfilment and reduces self-esteem. HPN therapy, tiredness, pain, diarrhoea or repeated hospital admissions will affect a patient's ability to work, and might in part account for the low levels of employment previously quoted. On the other hand, in countries where comprehensive social security systems exist, for example the Netherlands, UK and Denmark, patients may choose to stop work or work part-time. All but seven of the 49 Danish HPN patients were granted a disability or retirement pension (five of the remaining seven were students).

What effects can be attributed to underlying disease and/or directly to HPN are difficult to detect. Persoon *et al*. (2005), using an HPN-specific questionnaire and structured interviews with Dutch patients, revealed that up to 90% of patients had one or more physical problems: fatigue, diarrhoea, feeling cold, having a dry mouth, cramps in hands and feet, etc., these being attributed primarily to the underlying disease rather than to HPN. Fatigue and diarrhoea had the most impact on daily life. Fatigue may be due to sleeping disturbances, which are reported to be higher than in the general population. This may in part be due to the large infusions of cyclic HPN causing frequent nocturia, or by noisy feeding pumps (Carter *et al*., 1996). One-third of patients reported decreased sexual functioning, either through diminished interest or inability to relax.

When interviewed about the effects of HPN *per se*, patients identified 125 different problems relating to treatment. Nearly 60% of these were of a psychosocial nature, such as negative moods and feelings, lack of freedom, social limitations, being dependent, problems relating to holidays and inability to work. Over 60% of patients had depressive disorders of which 17% were severe, yet only one-third of patients with an indication of severe depression were taking antidepressant drugs. Other causes of concern were: (i) problems with care providers; (ii) connecting the HPN infusion to the bag; (iii) problems related to the pump; and (iv) financial limitations.

Summary

Modern health care mandates that limited resources are used wisely and, although HPN has shown clear benefits for patients in prolonging life, clinicians are expected to demonstrate not only positive health outcomes but also effects on QoL. It is important to identify the additional burden imposed by HPN to better understand the consequences of the treatment, to help inform future patients about the consequences of treatment and, as

more centres offer intestinal transplantation, to aid the decision-making process regarding patient selection.

Studies show that QoL on HPN is poorer than for the normal population and worse than for patients with other chronic conditions (Winkler, 2005). Some sub-groups of patients do better when receiving HPN than prior to treatment, e.g. patients with Crohn's disease.

Patients with malignancy commencing HPN with a Karnofsky Performance score of > 50 appear to survive longer, and QoL improves for those receiving HPN for longer than 3 months (Bozzetti, 2002). Weiss *et al*. (1982) identified six patient selection criteria (confirmed by Buchman, 2002). However, prevalence of HPN across Europe is still very variable and may be due to cultural differences and/or health-care provision.

From current studies it is difficult to untangle what are the effects of underlying disease and what are the additional problems attributable to HPN. Problems arising from underlying disease will remain, but it should be possible to remove or minimize those arising from HPN, once these are identified as a real problem rather than as a patient perception. For instance, patients identify sleep disturbance as a major concern, yet Scolapio *et al*. (2002) concluded that whilst sleep quality is reduced in patients with HPN compared to age-matched controls, it does not seem to be negatively effected by overnight HPN infusion.

Only the individual living the life can assess its quality. There is a need for objective assessment to identify the effects of treatment on individual patients in order to identify the range of problems that arise, and the processes which can be employed to minimize such problems. Only a universally validated, HPN-specific instrument developed through patient and professional collaboration, administered at agreed times, would produce those data (Baxter *et al*., 2005; Winkler, 2005). Such data can then be used to help future patients understand the consequences of treatment, adapt psychologically to long-term therapy and to make personal decisions about the benefits of transplantation.

Patients are at the centre of this treatment and individuals may have found ways of coping successfully with problems arising from HPN. The various national patient support groups have a wealth of knowledge, experience and resources that should be utilized to support and develop all aspects of HPN services.

The final word on this topic comes from the patient's perspective: 'HPN has been a double-edged sword. On the one hand, it has been nothing short of miraculous: I went from practically living in hospital to really living. On the other hand I can't help but worry about what will happen if I run out of access sites, if my liver malfunctions or if my insurance runs out' (Ehrenpreis and Hilf, 1998).

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31 Ethical and Legal Aspects of Home Parenteral Nutrition

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Key points

- Follow the four moral principles: (i) beneficence; (ii) non-maleficence; (iii) respect for autonomy; and (iv) justice.
- No one principle has supremacy over the others.
- Always try to defend the best interests and wishes of the patient.
- Consider the withholding or withdrawal of HPN as morally equal.
- Be aware that the concept of medical futility is ethically invalid and pragmatically ineffectual.
- Discuss frankly with patient and family the pros and cons of every deliberation; this will help to avoid conflicts and will pre-empt them from an excessive emotional impact.

Introduction

Ethical codes of caring professions include not only minimal standards of behaviour and morality but also ideals, and have been described as the 'collective conscience of our profession'. The law, on the other hand, defends individual rights and liberties and sets minimal standards below which conduct can be regarded as lacking in care, negligent or downright criminal. It also protects those who are unable or incompetent to make their own decisions. The legal frameworks may differ, in detail, from one country to another, but in European countries is based largely on a common ethical tradition. For these reasons we will focus mainly on the main principles underlying all medical ethics (Lennard-Jones, 1988; Macfie, 2000; Allison, 2004) rather than on legal issues that may vary between different countries.

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In particular, clinical decisions regarding patients undergoing HPN for conditions of intestinal failure associated with a severe underlying disease may be fraught with ethical – and sometimes legal – implications.

Reasons for this include: (i) the ability of medicine to prolong 'biologic' life through the use of technology; (ii) the worldwide acceptance, in Western countries, that the competent patient is empowered to participate in medical decisions; and (iii) concerns about financial constraints and cost containment.

In some sense, the benefits of medical advance and social progress have introduced a new set of burdens.

Principles of Moral Reasoning

The four clusters of principles as proposed by Beauchamp and Childress (1994) are: (i) beneficence; (ii) non-maleficence (both originally propounded by Hippocrates); (iii) autonomy; and (iv) justice.

No one principle enjoys automatic supremacy over the others, and over-reliance on them can be simplistic; rather, ethical decisions require the weighing and balancing of the various principles against one another in each particular situation.

Beneficence

Aim to do good and to foster the interests and happiness of the patient. This entails not only good intentions but also the necessity, first, to be equipped with the latest published knowledge concerning the benefits and risks of the HPN and, secondly, to support or participate in the research needed to obtain such knowledge.

Non-maleficence

Aim to avoid doing harm. Ask the question: 'Is HPN really in the patient's interests, or do the likely risks outweigh any possible benefits'?

Respect for autonomy

The Nuremberg code in 1945 added to the first two Hippocratic principles the principle of autonomy, recognizing the patient's human right to take all decisions concerning the management of his, or her, condition. This concept was confirmed in the Helsinki Declaration and the International Covenant on Civil and Political rights. The mentally competent patient, therefore, not only has the ethical – but also the legal – right to refuse

treatment. In numerous legal cases the courts have consistently reaffirmed that the refusal of treatment by a competent individual must be respected.

The converse of this is that – in Europe at least – no doctor can be forced by the patient, the patient's family or by anyone else to give treatment that he or she believes to be futile or to be against the patient's best interest.

In relation to the patient's competence, the British Medical Association and the Law Society have published clear guidelines on the assessment of mental capacity. A person should be able to:

- Understand in simple language what the medical treatment (or research intervention) is, its purpose and nature and why it is being proposed.
- Understand the principal benefits and risks of, and alternatives to, that treatment.
- Understand on broad terms what will be the consequences of not receiving the proposed treatment.
- Retain the information for long enough to make an effective decision.
- Make a free choice (without pressure).

As a consequence, if there is a programme of starting short-term HPN or withdrawing an already ongoing HPN in an incurable patient, an open discussion with the patient helps to define his or her exact wishes about the future and allow him or her to maintain dignity as a morally autonomous agent.

Justice

This concept, which evolved through the 20th century, demands that there should be equal access to health care for all. However, the increasing complexity and cost of treatment technology, exemplified by HPN, faces all societies with the problem of satisfying increasing demands from finite resources (Kitzhaber, 1993).

The above principles, while appearing straightforward in many cases, also involve the duty of society to husband resources and to use them effectively. Although we should be wary of allowing ourselves to be swayed by short-term administrative, business or political considerations, which have little to do with clinical benefit or justice, none the less every health care system operates under some rationing constraints – by ability to pay, reimbursement, waiting lists or political decisions concerning state funding (Herrmann, 1999).

Examples

Some practical examples concerning HPN will illustrate the role of ethical and legal considerations. Short-term hospital care will not be discussed and

the focus will be mainly on the treatment of patients in their own home. It will be relevant, however, to consider long-term care in community institutions such as nursing homes for the elderly.

HPN is essentially the treatment of gastrointestinal failure that is permanent or likely to last for many months before it is corrected by definitive treatment. In most cases, the clinical, ethical and legal decisions are straightforward. In some cases, however, there may be some doubt concerning the patient's capacity to cope with the technical demands of this treatment, without a high risk of serious and possibly life-threatening complications. This may be due to mental or emotional limitations or to the lack of resources in the patient's home. Doubt may be resolved by a well-supervised and time-limited trial of treatment, with agreement to withdraw treatment if complications prove prohibitive.

The doctor should also consider carefully whether he/she and his/her team have the requisite resources, training and experience to carry out HPN in an optimal way (Allison, 1992) or whether the patient should be referred to the nearest specialist centre. To carry out treatment without such considerations could be construed as unethical, or even negligent. In this respect, it is the duty of treatment centres to keep careful records of their outcomes and complication rates in order that adequate judgements of risk can be made. Difficulties arise in the case of frail, elderly patients living on their own but, with some extra support, it is remarkable how some patients manage.

In other cases, however, the risks prove so great that alternative – if less nutritionally effective – approaches are appropriate, including optimal oral and drug therapy combined with subcutaneous fluid and electrolyte administration (Martinez-Riquelme *et al.*, 2005). It may also be possible in some cases to use less risky enteral nutrition to provide at least part of the patient's needs. In every instance the issues should be discussed fully with the patient, the family and other carers before coming to a final judgement in which clinical and ethical issues are closely involved.

Ethical Dilemmas

Despite the wide acceptance of the above-mentioned principles, controversy may frequently arise, especially in severely ill patients, depending on the different perspectives of the individuals involved in the ethical debate.

People mainly concerned with the intrinsic merits or otherwise of a medical initiative rather than with its consequences – the 'duty-based moralist' - will always tend to feed the patient regardless of the final outcome, because this is the 'mission' of the physician.

The 'utilitarian moralist' is more concerned with the consequences of an act rather than the act itself, and would privilege the indication for a HPN programme on the basis of the scientific evidence.

Finally, the 'rights-based moralist' mainly relies for any deliberation on the free choice of the patient, who has to be adequately informed.

Nowadays, few people would agree with a rigid position of a wholly committed 'duty-based moralist' supporting the sanctity of life at all costs. The Roman Catholic Church, too, has the following position on the use of artificial nutrition and hydration near the end of life: 'There should be a presumption in favour of providing nutrition and hydration to all patients who require medically-assisted nutrition and hydration', and this approach is warranted only as long as 'there is sufficient benefit to outweigh the burden to the patient' (National Conference of Catholic Bishops, 1995).

The 'utilitarian moralist' will accept an indication for HPN in incurable pre-terminal patients only if there is an evidence-based demonstration of its effectiveness. He/she tends to consider nutrition as drug, starting from the original definition of drug as 'any chemical agent which affects living processes' (Goodman and Gilman, 1941). He/she ignores the ASPEN Guidelines (2002), which state:

> A major distinction between therapeutic trials of efficacy of a drug or a procedure and the feeding of nutrients known to be essential to maintenance of human health and survival must be made. Withholding a drug or an invasive procedure will not produce disease in otherwise healthy humans, whereas essential nutrients must be provided to both healthy and ill people.

He/she also disregards the fact that: 'The ethics of clinical research requires a state of genuine uncertainty on the part of the clinical investigator or the expert community regarding the comparative therapeutic merits of each arm in a trial' (Freedman, 1987) and that, consequently, if one is taking care of malnourished, aphagic people, it is unacceptable to have a control group which is randomized to 'no-nutrition'. In other words, it is almost impossible to get an evidence-based proof of effectiveness if the treatment one is investigating may represent a life-prolonging procedure.

The 'right-based moralist' will mainly focus on the wishes of the patient. Although in the USA and in most European countries total parenteral nutrition is now considered a medical treatment as opposed to a simple basic care, and hence subject to the same ethical constraints as regards initiation and withdrawal, the debate on this issue is still open (Bozzetti, 2003).

Autonomy, which is the preeminent theme in law in most democratic states, implies that the patient is aware of both the diagnosis and the prognosis of their disease and, more importantly, that their wishes are constant with the passage of time. However, Chochinov *et al*. (1999) have clearly shown that there is a substantial variation in the will-to-live score between those of 1 day, 1 week or 1 month in terminally ill cancer patients. Similarly there is a low percentage (10–14%) of individuals who, having survived a suicide attempt, commit suicide during the following 10 years (Diekstra and Garnefski, 1995).

Therefore, the assessment of the patient's will to live should be repeated several times and, only if answers are consistent should this information be

utilized to determine whether to initiate or withdraw a life-prolonging treatment such as HPN in patients affected by malignant diseases.

Finally, some patients prefer to avoid the trauma of a frank disclosure of the diagnosis and prognosis, depending on the different cultural background and religious traditions of various countries.

If we accept the principle of self-determination as a right and a duty of the individual, we have also to respect their wish not to know the diagnosis and/or the prognosis. The Council of Europe states, in Chapter III, Article 10, paragraph 2 of the Convention of Human Rights and Biomedicine, which came in force on 10 September 1996: 'Everyone is entitled to know any information collected about his/her health. However, the wish of individuals not to be so informed shall be observed'.

Futile care

The patient should be able to differentiate between benefit (that is, treatment conferring a net gain or advantage) and the simple effect of having an improvement in some physiologic functions.

This raises the problem of 'futile care', i.e. an action that cannot achieve the goals that are intended by the action, no matter how long it lasts or how often it is repeated. Futility has two aspects, one quantitative and the other qualitative. The first focuses on the probability that HPN can achieve the expected outcome, but who is entitled to judge the threshold below which it is no longer worthwhile to attempt it (i.e. it is futile)?

The second is the qualitative dimension of an effect/benefit. For instance, who can decide whether the benefit in quality of life associated with HPN is valuable or futile? Although ethics and law place a premium on patient autonomy, nevertheless we agree with ethicists who believe that 'Futile care is ethically unjustifiable, as it holds autonomy as an absolute in all situations and ignores other valid principles, such as non-maleficence and justice' (Pawlik and Curley, 2005). The concept of medical futility is, therefore, ethically invalid and pragmatically ineffectual (Hinshaw *et al.*, 2003).

When there is a conflict between the option of the physician and that of the patient, it is worth asking for wider consultation or considering a time-limited trial of nutritional support. In this scenario, definite goals are agreed and shared between the patient, relatives and medical staff, and outcome is carefully monitored over a previously determined period of time.

As has been recently emphasized by MacFie (2005), many studies have shown that ethical dilemmas can be emotionally pre-empted if they have been previously discussed with the patient, relatives and the health care team.

Withholding and withdrawing nutritional support

Although most ethicists believe that the distinction between withholding and withdrawing treatment is conceptually and morally incoherent, because treatment can always be withdrawn permissibly if it can be withheld permissibly, many clinicians, patients and relatives believe that such a distinction exists ethically and legally.

It is true, however, that many physicians feel ethically justified in withholding treatments that they never initiated, but not in withdrawing treatments that have already started. In addition, they find it harder to withdraw life-sustaining or long-standing treatment such as nutrition and hydration rather than limit resuscitative efforts or recently instituted interventions. Again, clinicians prefer to withdraw a treatment that supports organ failure for natural reasons than for iatrogenic factors (Christakis and Asch, 1993; Dowdy *et al*., 1998). One should also consider that withholding or withdrawing HPN does not mean that patients do not receive any fluid, and that home subcutaneous fluids can sometimes be used in truly terminal conditions or in patients unable to cope with HPN and whose main problem is recurrent fluid and electrolyte deficit due to gastrointestinal losses (Martinez-Riquelme *et al*., 2005).

Conclusion

It is often difficult to determine which principle pertains in any given situation and how that principle should be applied, especially when there is a conflict between the four principles of autonomy, beneficence, non-maleficence and justice and between different individuals' perspectives on ethical debate.

We would like to conclude with the very appropriate considerations by MacFie (2005):

> These conflicts serve to emphasize that ethics is a process of reasoning whereby a morally respectable and defensible position can be reached, which protects the best interests of the patient. There are no absolutely satisfactory resolutions of ethical dilemmas and the most that one can hope to achieve is a balance between the conflicting interests and goals of different individuals involved in patient care.

We would add that it is extremely important that any crucial deliberation concerning commencement or withdrawal of HPN follows an effective communication between physicians, nurses, the patient and their family to discover which are the best interests and wishes of the patient. It has been demonstrated that components for a 'good death', as perceived by the patient, are not deemed to be of the same importance by their physician (Steinhauser, 2000a, b). Therefore, it is only within a relationship of empathy and sensitivity with the patient that the physician can help him/her to prolonging life or to prepare him/her for the process of dying.

Summary

The main principles of moral reasoning (respect for autonomy, justice, beneficence and non-maleficence) and the potential onset of conflicts therein are discussed.

No one single principle enjoys automatic supremacy over the others, and blind over-reliance on them can be simplistic and detrimental. Rather, ethical decisions require weighing and balancing the various principles against one another in each particular situation.

Since HPN is a life-prolonging treatment, it is not possible to reach – in severely ill patients with malignant intestinal failure – an evidence-based demonstration of efficiency or non-efficiency, which usually relies on clinical trials that randomize nutritional support *versus* non-nutrition.

The concept of futile care, which has proved to be ethically invalid and pragmatically ineffectual, has been discussed.

Any distinction between withholding and withdrawing HPN is conceptually and morally incoherent.

The authors emphasize the concept of a frank and open discussion between the medical staff and the patient and their family to be able to understand what are the wishes of the patient that have to be respected, and to pre-empt from emotional conflict any potential ethical controversy.

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32 Legislation on Home Parenteral Nutrition

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Key points

- Standards of practice should be developed for the initiation, preparation, education, equipment, provision, safe delivery and monitoring of patients discharged on home nutritional support.
- No formal European policy has been developed or proposed to ensure safe, cost-effective and patient-centred use of home parenteral nutrition (HPN).
- A complete home care policy should include organizational initiatives that promote collaboration and relationships of trust between organizations, service providers and public health and voluntary organizations.
- Although legislation differs between countries, the funding is relatively uniform: national health systems support all the costs of HPN.
- New organizational changes should be implemented to ensure equity of access to HPN all over Europe.

Introduction

Most industrialized countries have initiated health care system reforms aiming to increase the number and scope of health services delivered on an ambulatory basis and at the patient's home. Although 'traditional' home health care services as nursing or personal care have been available for a long time, this shift is mainly related to the so-called high-tech home care: 'methods of diagnosis, treatment or rehabilitation which are embodied in or supported by specialized equipment' (Kaye and Davitt, 1995).

Home artificial nutrition has been an expanding area of home care in

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many countries around the world over the past 30 years. Home parenteral nutrition (HPN) was developed as a life-saving treatment for patients who were unable to ingest food or absorb sufficient amounts of nutrients, thus avoiding the problems of chronic undernutrition.

In a large survey carried out in Montreal, Canada, in 2002, HPN was the third most frequent home care service provided by local community health centres, after provision of home IV and oxygen therapies.

The Resolution on Food and Nutritional Care in hospitals, adopted by the Committee of Ministers of the Council of Europe on 12 November, 2003 at the 860th meeting of the Ministers' Deputies (ResAP (2003/3), stated that 'standards of practice should be developed for the initiation, preparation, education, equipment provision, and safe delivery and monitoring of patients discharged on home nutritional support' (https://wcm.coe.int/rsi/CM/index.jsp).

It is essential for people working in home artificial nutrition and for the European Society for Clinical Nutrition and Metabolism (ESPEN) to take a leading role in this area, contributing to legislative advancements that would help to develop the previous statement. Unfortunately, HPN programmes were often initiated prior to regulations established by the various national health systems, leading to the adoption of widely differing policies between various European countries.

By and large, funding for home care has markedly increased over the past 10 years, but there are wide differences between countries/territories. Therefore, the organization of services – as well as specific arrangements for the funding and delivery of home care – vary widely. Consumer involvement appears limited and inconsistent. No formal European policy has been developed or proposed to ensure safe, cost-effective and patient-centred use of HPN.

Four aspects of the development and increased use of HPN require attention:

- The weak connection between community-based and specialized, hospital-based home care.
- The delegation to patients and caregivers of increased responsibility.
- The importance of the risks associated with the home environment.
- The implementation of home care services despite the lack of evidence about cost-effectiveness.

Along with the technical aspects regarding the introduction of sophisticated technologies into the home setting, organizational and social dimensions also arise. Social dimensions refer to the capacity of the patients and their relatives to maintain satisfying relationships, to engage in leisure activities, to raise a family, to carry out social roles, etc. (Agence d'évaluation des technologies et des modes d'intervention en santé, 2004). Frequently, women in particular suffer the consequences of the burden of home care, since their role as 'natural' caregivers is often taken for granted; their careers and health are often affected due to the time and effort devoted in taking care of their relatives.

Thus, a complete home care policy should include organizational initiatives that promote collaboration and trusting relationships between organizations, service providers and public health and voluntary organizations.

Present Legislation

The USA

Coverage of nutritional therapy, tube feeding and parenteral nutrition as a Part B benefit is provided under the prosthetic device benefit provision defined in section 1861 (s)(8) of the Social Security Act of 1997, which requires that the patient must have a permanently inoperative internal body organ or function. This coverage does not require a medical judgement that this impairment will persist throughout the patient's remaining years (http://cms.hhs.gov/manuals/pub06pdf/pub06pdf.asp, last visited 23 January 2005). Since 1 October 2000 the unit of payment under the Medicare Home Health Prospective Payment System is a national, standardized 60-day episode rate, adjusted for case mix and wage index. These rates are updated yearly (Centers for Medicare and Medicaid Services (CMS), HHS, 2001; Department of Health and Human Services, 2004).

Daily parenteral nutrition is considered as reasonable and necessary for a patient with severe pathology of the alimentary tract which does not allow absorption of sufficient nutrients to maintain weight and strength. Medicare guidelines specifying candidates for HPN allow reimbursement for the following conditions: (i) massive small bowel resection; (ii) short bowel syndrome; (iii) symptomatic pancreatitis; (iv) proximal enterocutaneous fistulas; (v) severe regional enteritis requiring bowel rest; (vi) small bowel obstruction without surgical options; (vii) fat malabsorption; (viii) motility disorder; and (ix) malnutrition and failed enteral nutrition (Williams, 1998).

It is also necessary to justify the use of a pump in order to receive payment for the pump. Regarding the intravenous solutions, payment is calculated for the solution components and, exceptionally, for more expensive, pre-mixed solutions.

There is a body of opinion that suggests re-evaluation reimbursement systems and regulation for nutrition services along the continuum of care in the elderly (Institute of Medicine, 1999).

The private insurance companies apply, generally, the same criteria and guidelines for funding as do Medicare (AETNA, 2004). If the criteria for parenteral nutrition are met, medically necessary nutrients, administration supplies and equipment are considered medically necessary and are, therefore, funded.

Canada

HPN programmes are well funded, mainly by the provincial departments of health and, to a lesser extent, by private insurance, user fees and the federal government (Issenman and Sauvé, 1987; Therapeutic Nutritional Products Task Force, 2004).

Europe

It is difficult to identify regulations covering HPN in the various European countries. A survey on legislation and funding of HPN was promoted by the Home Artificial Nutrition Working group of ESPEN in 2000, which gathered information from 12 countries (Moreno *et al.*, 2001).

HPN is regulated in at least six countries: Belgium, Czech Republic, Denmark, Italy, France and Poland. Denmark was the first country in Europe to have a regulation, in 1975. Except in Italy, where there is regional scope, the rules apply nationwide. The regulation is common to both adults and children but, in Belgium, children deserve special consideration. Two different models of organization in Europe have evolved: 50% of the countries do not have specific restrictions on underlying disease or on the type of hospital or physicians prescribing HPN, while others – France, Denmark, Croatia, Czech Republic and Poland – restrict the indication to some hospitals. In those countries with HPN regulation, there are no clear instructions about the provision of disposables and pumps.

France had the model of a centralized system, in which HPN centres were approved by a national expert medical committee. Regional HPN centres had to be teaching hospitals (12 centres were agreed for adults and six for children; Circulaire 14 December 1984). However, more recently, the use of standard, commercial, all-in-one solutions that can be prescribed by any physician (Circulaire, MESSOO23522A, 2000; Legifrance, 2001) has been approved. In this later case, the duration of HPN should be < 2 months and the feeding solution should not contain vitamins or minerals. This new approach has raised bitter argument (Reimund, 2003).

Hospital pharmacies, private pharmacists and home care companies are involved to varying degrees in providing and distributing solutions and disposables (Table 32.1). Although legislation differs between countries, the funding is relatively uniform: the national health systems support all the costs of HPN, but in Germany private insurance may cover all the expenses. On the contrary, in Israel HPN is funded by private insurance.

Proposal for a Legislation for HPN (within the European Union)

Several trends help explain the increase in home care activity in Western countries: (i) an ageing population; (ii) the substitution of hospital-based

Table 32.1. Provision of parenteral nutrition solutions, disposables and pumps in European countries.

	Solutions[a]	Disposables[b]	Pumps[c]
Hospital	All except A, G, Is	All except A, G, Is	All except D
Private pharmacists	A, G	A, G	G
Home care firms	All except B, C, Cz, F	All except C, Cz, F, S	A, C, G, I, Is
Primary care	I	I	I

A, Austria; B, Belgium; C, Croatia; Cz, Czech Republic; D, Denmark; F, France; G, Germany; I, Italy; Is, Israel; P, Poland; S, Spain; UK, United Kingdom.
[a] P, 100% Home care; UK: 85% Home care; [b] G, 100% private pharmacists; [c] D, others (local community); P, hospital (children), other – e.g. foundations; G, 25% others (adults, foundations).

care by home care; (iii) a growing delegation of responsibility to patients; (iv) a social demand for home care; and (v) the cost containment initiatives in health care.

Regarding HPN, it could be interesting to establish general recommendations in the EU that could be applied in each country according to the national regulations of health care. The experience of other countries, such as Canada (Romanov, 2002) or the USA (ASPEN Board of Directors, 1999), could be very helpful. We delineate some of the issues that should be tackled in these recommendations. In order to use the same terms as other nutrition societies, we consider helpful those included in the definitions of terms used by ASPEN (ASPEN Board of Directors, 1995).

Organization

1. Collaboration of the referring physician, the nutrition support team and, if available, home care companies is desirable. HPN programmes require easy access to medical expertise, well-trained nursing staff, multidisciplinary teams and specialized equipment. HPN is far beyond the possibilities of the local community centres and they should cooperate with the hospital where HPN has been started or is controlled.
2. A physician with expertise in HPN should be primarily responsible. He/she should collaborate with a nurse, a dietician, a pharmacist and other health care professionals as needed.
3. There should be written policies and procedures designed to address the needs of the patients and caregivers at home.
3. 24-hour on-call services should be available for every HPN patient.
4. An individualized medical record should be maintained. Confidentiality and integrity of the data and information should follow the present legislation on the management of medical data, and also the tradition of a trusting relationship between the physician and his/her patient.
5. Outcomes should be assessed in relation to internal, national or international benchmarks.

Patient selection

1. Those patients who have either a permanent non-function or disease of the bowel that does not permit food to reach the small bowel (as in a severe motility disorder) or a disease of the small bowel that impairs digestion and absorption of an oral diet, and in which enteral nutrition support has failed (SBS, for instance). It does not need to be a decision on whether the condition may improve in the future; but the impairment can reasonably be expected to exceed 3 months.
2. The patient should be clinically stable, have an appropriate indication for HPN and be capable of being educated in the technique and willing to go home.
3. Before the initiation of HPN, a nutritional assessment should be performed, as well as a psychosocial evaluation.
4. The patient's home should be determined as being appropriate for the administration of HPN (cleanliness, sanitary water supply and electricity, access to telephone, etc.).

General issues in organization and delivery of HPN programme

Interventions should be carried out at three different levels: socio-political context; community environment and home environment.

Socio-political context

1. It is necessary to articulate and redefine the roles of hospital and primary care in HPN.
2. Dispersion of services is likely to increase patient mobility and reduce the overall effectiveness of services. In order to allow equity of access to optimal care by adoption of evidence-based procedures and protocols, clinical networks should be promoted (Baxter and McKee, 2003).
3. The cost of equipment essential to assure safe delivery of HPN should be subsidized.

Community environment

1. HPN often relies on the delegation of important clinical/technical tasks and responsibilities to the patient and caregiver. These technologies impose considerable burdens on patients and families. There is a need to evaluate both knowledge and skills and the socio-economic burdens of the technique.
2. Increase the level of support for patients and caregivers, including the possibility of providing direct economic support to informal caregivers.
3. Improve the learning process.
4. Promote social support: self-help groups, patient and caregivers associations, etc.

Home environment

Measurements of home care effectiveness. HPN influences the home environment: it may modify family relationships and social networks, but may even modify the place where the patient lives. There is a requirement for storing supplies and infusion bags, what to do with biological waste, etc.

Summary

As the availability of HPN has progressed over the past 30 years, the context for its use in the clinical arena has also changed markedly. It is necessary to define the indications and contraindications of HPN according to evidence-based protocols. If HPN is considered necessary, then medical equipment for parenteral nutrition administration should be provided, as well as the parenteral nutrition solutions.

Technological advances such us the development of stable, complete admixtures in multi-chambered bags that need no patient additives may facilitate the practice. HPN should be provided in a cost-efficient manner. New organizational changes should be implemented to ensure equity of access to HPN all over Europe. Special attention should be paid to social issues such as the care of the caregivers and the cooperation between primary care and hospitals (Box 32.1).

Box 32.1. Proposals for the content of legislation pertaining to HPN in Europe.

1. Indication and contra-indication criteria for HPN.
2. List of clinical conditions where HPN could be indicated.
3. Characteristics of the centres that could develop an HPN programme. Health care professionals involved in the programme.
4. Identification of responsibilities for nutritional assessment, diagnosis and treatment of complications associated with HPN.
5. Relations between different health care levels (hospital-based programmes and primary care).
6. Logistics issues:
- Safe nutrient mixing and distribution.
- Pumps, sets and other ancillary material.

7. Funding.
8. Social support for family and caregivers.

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33 Surgical Alternatives in Patients with Short Bowel Syndrome

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Key points

- The surgical alternatives to Home Parenteral Nutrition (HPN) and small bowel transplantation in patients with short bowel syndrome are reported.
- Indications (small bowel remnant < 100 cm, absence of ileocolonic junction, indications for re-establishment of jejunocolic continuity) and technique of segmental reversal of the small bowel are described.
- Other techniques are considered, including proximal colonic interposition, creation of an intestinal valve and small bowel tapering or lengthening.
- These procedures can be useful in weaning patients from parenteral nutrition and should be proposed early, before life-threatening HPN-related complications occur.

Introduction

Short bowel syndrome (SBS) due to extensive resection of the small bowel results in diarrhoea and malabsorption. In SBS patients, adaptation of the remnant bowel, although of modest importance, is generally observed within months following resection. However, many patients with SBS may remain indefinitely dependent on parenteral nutrition, especially those with < 1 m remnant small bowel and without either the ileocolonic junction or the remnant colon (Thompson, 1993).

HPN has been clearly demonstrated as being the most determinant technique responsible for prolonging the life of patients with SBS (Messing *et al.*, 1995). Since the 1970s, the feasibility and safety of HPN has been

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demonstrated. In our experience of HPN, the probability of survival was 80 and 62% at 2 and 5 years, respectively in 217 non-malignant patients receiving long-term HPN, of whom 60% suffered from SBS (Messing *et al*., 1995). However, patients receiving long-term HPN are still exposed to catheter-related complications, bone disease, cholelithiasis or liver failure. Furthermore, HPN impairs work and social activities and costs over $70,000 per year (Wolfe *et al*., 1983; Messing *et al*., 1995).

Since the introduction of the new immunosuppressant drug FK506, intestinal transplantation has gained interest in clinical practice. However, to date, intestinal transplantation remains a difficult procedure, and carries high morbidity and mortality rates. Despite improvements in the control of graft rejection, about 40% of patients die within 2 years of transplantation, the graft survival rate at 1 year being about 50–60%, and a significant percentage of those surviving have to resume HPN whether the graft remains functional or has been removed (Todo *et al*., 1995; Rovera *et al*., 2003).

Obviously, recent reports of HPN may compare favourably with intestinal transplantation: among 41 patients younger than 60 years of age receiving HPN and presenting with extreme SBS (< 50 cm) who, theoretically, represent suitable candidates for small bowel transplantation, the probability of survival after 1 and 2 years was 98 and 90%, respectively (Messing *et al*., 1995). Intestinal transplantation must stand the test of time before it can be proposed for all patients with SBS (Todo *et al*., 1995). At the present time, for SBS patients who are HPN-dependent, intestinal transplantation should be considered as a life-saving procedure in cases where life-threatening, HPN-related complications or associated liver failure occur, provided no other available alternative surgical treatment can be proposed.

Reconstructive surgical procedures, first proposed in the early 1960s, must be discussed today in the light of recent results reported for HPN and intestinal transplantation.

Surgical 'rehabilitation' of the intestine aims to improve the function of the existing small bowel remnant and to potentially expand the intestinal surface area (Thompson, 2004). The choice of surgical treatment is influenced by the existing bowel length, function and calibre (Dibaise *et al*., 2004).

Besides restoring intestinal continuity (which is clearly beneficial in order to recruit small bowel and colonic segments) and relieving obstruction (by stricturoplasty or limited resection), non-transplant surgical options for SBS include the following: (i) tapering dilated segments (i.e. reduction of the circumference of the intestine by either imbrication or excision of redundant bowel wall along the anti-mesenteric border); (ii) lengthening the intestine (longitudinal transection of the intestine between the mesenteric and anti-mesenteric edges and anastomosis of these parallel intestinal segments); and (iii) prolonging intestinal transit time by either artificial intestinal valve construction (distal intussusception of a segment of

small intestine), colonic interposition or segmental reversal of the small bowel (Thompson, 1993).

Only a few cases for each procedure have been reported to date. The aim of this review is to report the results of such conservative operations in SBS, with special reference to segmental reversal of the small bowel, for which we now have experience of 15 cases.

Segmental Reversal of the Small Bowel

Principles and previously reported experience of the procedure

Segmental reversal of the small bowel (SRSB) may act in SBS patients as an ileocolonic junction, prolonging both transit time and contact between luminal nutrients and remnant mucosal surface. Experimentally, SRSB has been found to increase water, nitrogen and fat absorption in dogs (Venables *et al*., 1966). The anti-peristaltic segment was observed to cause retrograde peristalsis and to disrupt the motility of the proximal intestine. The disruption of the intrinsic nerve plexus slows distal myoelectrical activity (Tanner *et al*., 1978).

Details of some 25 patients treated by SRSB have been reported so far. Analysis of these cases appears difficult because: (i) most of them are anecdotal; (ii) in most reports follow-up was only in the short term; and (iii) in some cases the indications for surgery were debatable (> 1.5 m remnant small bowel). Approximately 70% of patients appear to derive some benefits from SRSB. However, initial manometric abnormalities of proximal intestine were shown to attenuate, but not to disappear, with time (Pigot *et al*., 1990), and the initially increased absorption was no longer present 6 months after surgery (Wilmore and Johnson, 1968). These findings raised the issue of long-term function after SRSB. However, as we observed in our patients (see below), the beneficial effects of this surgery have been maintained for up to 9 years, the longest follow-up and the best results to date.

The ideal segment length to be reversed seems to be 10 cm, since shorter segments may be inefficient in slowing transit time, whereas longer segments may create a clinical bowel obstruction syndrome. In addition, to achieve optimal benefit, the reversed segment should be located in the most distal part of the small bowel. The main limitation of SRSB is the very short length of remnant small bowel, which may not allow the sacrifice of a 10 cm segment for reversal. In our experience, SRSB proved feasible if remnant small bowel was 25 cm long, but was not indicated for a remnant > 1 m. Despite careful attention during the operation, SRSB has been said to expose the patient to the risks of ischaemia and anastomotic leakage (Shanbhogue and Molenaar, 1994). No such complication was observed in our series.

The Lariboisière Intestinal Failure Centre experience

Because tapering and lengthening can only be performed in a dilated bowel, and an artificial intestinal valve construction constitutes a difficult surgical procedure, we felt that segmental reversal of the small bowel (SRSB) could be seen as an acceptable alternative to intestinal transplantation in patients with SBS deemed to be absolutely dependent on HPN.

Our experience of SRSB included 15 adult patients with very short bowel syndrome (11 men and four women whose mean age was 54 ± 19 years; range 18–77). Before SRSB, all patients except one were totally dependent on HPN, 7 days a week, for 1–189 months before reversal. SBS was secondary to extensive bowel resection for mesenteric infarction in seven patients, to radiation enteritis in two, to gunshot wounds in one, to Crohn's disease in one, to laparoschisis in one and to post-operative fistula in two cases. In all these patients, sub-total enterectomy was performed elsewhere and then they were later referred to our tertiary care centre for HPN and SRSB. The 15th patient, with familial adenomatous polyposis, had 100% oral nutrition before SRSB. He presented with intestinal occlusion secondary to desmoid tumour and simultaneously underwent sub-total enterectomy and SRSB, before being included in our HPN programme.

At our institution, SRSB was considered for SBS patients in whom the three following conditions were present: (i) a post-duodenal small bowel remnant of < 1m; (ii) an absence of the ileocolonic junction; and (iii) an indication for re-establishment of jejunocolic continuity.

Operative procedure

Before SRSB, the mean length of the remnant small bowel, measured intra-operatively, was 49 ± 20 cm (range 20–90). The ileocolonic junction had been effectively removed in all patients. One patient had no remaining colon, but the other 14 had a partial colectomy only.

The first step of SRSB consisted of preparing a short segment of the distal remnant small bowel. In one patient a proximal, instead of a distal, segment was reversed, for technical reasons. The mean length of the segment used for SRSB was 12 ± 3 cm (extr. 6–15). The technique has previously been described elsewhere (Panis *et al*., 1997). Briefly, the distal segment was separated from the remaining small bowel, leaving its blood supply intact, and then reversed.

Next, the segment was re-anastomosed, proximally to the remaining small bowel and distally to the remaining colon (Fig. 33.1). Complete 360° mesenteric rotation was avoided by correct positioning of the proximal and distal parts of the intestine before anastomosis (rotation of both segments was approximately 90°). This meant that the necessary mesenteric rotation of the reversed segment was only about 180°.

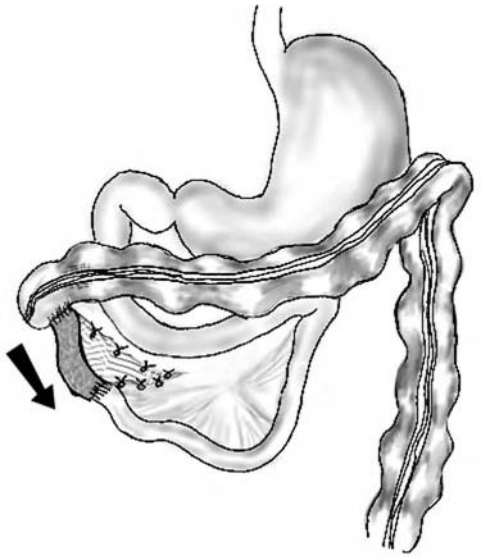

Fig. 33.1. Segmental reversal of the small bowel (SRSB) with jejuno-transverse anastomosis in a patient with short bowel syndrome (SBS).

After SRSB had been completed, anastomosis was jejuno-transverse in eight patients, jejuno-rectal in one, jejuno-left colonic in four and jejuno-right colonic in two. Among these, two patients had a terminal left colostomy.

During the entire follow-up period, patients were placed on free oral diet and were encouraged to eat as much as they could (Messing *et al.*, 1991).

Post-operative morbidity and mortality

There were no post-operative deaths. Four patients were re-operated on for sepsis of unknown origin, wound dehiscence, acute cholecystitis and intraperitoneal bleeding, respectively. Three patients experienced transient intestinal obstruction and were treated conservatively. One patient presented with intestinal fistula was treated conservatively. The mean duration of hospital stay was 18 ± 8 days (range 10–36) in the surgical unit, and was subsequently 34 ± 4 days (range 28–39) in the gastroenterology nutritional unit.

Long-term results

The mean follow-up period was 54 ± 38 months (range 10–130).

Three patients died during follow-up: one died 7 months after surgery (pulmonary embolism), one at 35 months (unknown origin) and one at 37

months (immune nephropathy). At the time of death, HPN had been reduced from 7 to 3 days per week in two patients. The last patient was weaned from HPN. One patient experienced, at 5 months and 6 years post-operatively, attacks of transient intestinal obstruction partly due to Ca, K and Mg blood disturbances and partly to loperamide abuse; this patient was successfully treated conservatively with both oral vitamin D and intramuscular mineral supplementation.

By the end of the follow-up period, six patients (44%) had been weaned from HPN. HPN had definitely ceased between 6 and 28 months following the SRSB procedure, and normal nutritional status was maintained under 100% oral nutrition until the end of the follow-up period. The length of the remnant small bowel (including the reversed segment) in these patients ranged from 25–60 cm. In one of these HPN-weaned patients, HPN was stopped, but he needed fluid and electrolyte infusions at the frequency of 2–4 days per week.

Two other patients were temporarily weaned from HPN, for 13 and 20 months, respectively. At the end of follow-up, the HPN infusion rate was reduced to three infusions per week. For the seven remaining patients, the rate of HPN delivery was reduced from 7 to 4 days per week (range 3–5). In one of them, a proximal instead of a distal SRSB had been performed. Persistent and permanent nausea in this patient has resulted in superimposed depression. He was the only patient of the present series where oral hyperphagic feeding was not observed (i.e. more than twice the basal energy needs of the patient) (Messing *et al.*, 1991).

Finally, the actuarial rate of weaning-off HPN was 29% at 1 year, 33% at 2 years, 40% at 3 years, 50% at 4 years and 60% at 5 years (3/5 cases) (Panis, 2001; Fig. 33.2).

Indication and timing for SRSB

There is general agreement that SRSB should not be performed at the time of initial resection, because of the possibility of intestinal adaptation (Thompson, 1993). We performed both at the same time in one patient. However, in patients with very short remnant small bowel and no ileocolonic junction in whom there is no hope of early weaning off HPN, the SRSB procedure can be proposed at the time of intestinal continuity restoration. In patients older than 60 years, for whom transplantation will probably be contraindicated, SRSB can be proposed at this time, avoiding further surgery.

Finally, we suggest that the SRSB procedure should be performed first for younger patients, in whom intestinal transplantation is advocated, provided jejunal remnant length is present (i.e. 25 cm); if it fails to allow patients to wean off HPN, intestinal transplantation remains a possibility.

As we have demonstrated, it is indeed difficult to be sure that SRSB *per se* was the factor responsible for the weaning of patients from HPN, and not just intestinal adaptation. In this series, all the patients underwent

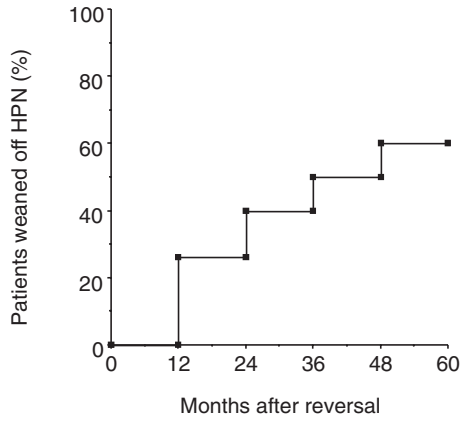

Fig. 33.2. Actuarial rate of patients weaned from HPN after segmental reversal of the small bowel (SRSB).

SRSB at the time of intestinal continuity restoration. Thus, no comparison of intestinal function with intestinal continuity (but without SRSB) was available for the same patients. Only a long-term, prospective study, comparing a sufficient number of patients with and without SRSB, would answer this question. This point raised the necessity of performing SRSB in tertiary care centres.

Nevertheless, this study provides arguments suggesting that SRSB *per se* plays a role in weaning from HPN. First, as we demonstrated in one case (Pigot *et al.*, 1990), intestinal absorptive capacity reached subnormal values allowing him oral nutritional autonomy, demonstrating a delayed intestinal transit time, which extended for up to 9 years. Secondly, we and others have observed that the probability of weaning from long-term HPN in patients with a post-duodenal small bowel length < 0.70 m and without the ileocolonic junction (as was the case with all of our patients) is very low (Thompson *et al.*, 1995; Messing *et al.*, 1999). In contrast, the probability of our patients weaning off HPN was 50% at 4 years.

Other Conservative Surgical Procedures for Short Bowel Syndrome

Proximal colonic interposition

Proximal colonic interposition has been performed in 12 infants and in only one adult (Brolin, 1986). It may be a useful technique in cases when the small bowel is too short to be used for reversal. Poor results have been reported for anti-peristaltic distal colonic interposition (Carner and Raju, 1981), which resulted in increased morbidity, even though some improved absorption was obtained.

Intestinal valve creation

The creation of an intestinal valve by constricting the intestine externally and intussuscepting an intestinal segment has also been proposed (Chardovoyne *et al*., 1983). Technical problems have led to inconsistent results (Carner and Raju, 1981). However, Thompson reported good results of artificial valve creation in one adult and one child, with rapid transit time, reduced ostomy output and discontinuing HPN after 2 months for one patient. The other remained off HPN for 4 years (Thompson, 1993).

Small bowel tapering or lengthening

Neither procedure can be performed in cases of non-dilated bowel (Thompson, 1993), and have been performed in a few adults only (Shanbhogue and Molenaar, 1994). Long-term complications of lengthening have included anastomotic stricture, fistula formation and proximal intestinal dilatation (Huskisson *et al*., 1993). Among 11 children with dilated bowel undergoing tapering, nine were on enteral nutrition only at the end of the follow-up period.

Similarly, among 14 patients (one adult and 13 children) undergoing lengthening, at the end of follow-up seven were weaned from HPN, five had reduced HPN infusion and only two remained on HPN at the same rate (Thompson, 1993). Of approximately 100 patients undergoing this procedure so far, approximately 90% have demonstrated improvement. However, in the long-term, only half of them will have sustained benefit for up to 10 years (Thompson, 2004).

Conclusion

After massive small bowel resection in adults, definitive HPN can be anticipated if the post-duodenal length of the remaining small bowel is < 60–80 cm, together with the absence of ileocolonic junction and a partial colonic resection. Our experience suggests that segmental reversal of the small bowel could be safely proposed for these patients with a very short remnant small bowel requiring definitive HPN. Despite a significant morbidity rate, no mortality was observed in our patients and SRSB allowed almost 50% of them to be free of HPN. Recently, we have also successfully proposed such a procedure for salvaging an ileal pouch-anal anastomosis with SBS (Loriau *et al*., 2005).

Finally, we believe that SRSB, as well as other conservative surgical procedures (i.e. tapering, lengthening, artificial intestinal valve construction, colonic interposition) for which reported experience still remains very small, could be proposed early in the course of SBS, before life-threatening, HPN-related complications arise. In the future, tissue

engineering (i.e. fabrication of 'new' intestine with biodegradable organoid units containing multicellular units derived from neonatal rat intestine) could constitute a new way of treating patients with SBS (Grikcheit *et al.*, 2004).

Summary

Short bowel syndrome (SBS) requiring definitive HPN can be expected if < 60 cm of small bowel (with absence of ileocolonic junction) remains after surgery. In these cases, before proposing intestinal transplantation, segmental reversal of the small bowel (as well as other conservative surgical procedures such as tapering or lengthening) could be proposed early, before life-threatening, HPN-related complications arise, because it will allow almost 50% of patients to be free of HPN.

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34 The Use of Growth Factors in Short Bowel Syndrome

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Key points

- At present, growth factors in the treatment of short bowel patients should be considered experimental and should only be initiated in the research settings.
- Since the effect of the growth factors, growth hormone and glucagon-like peptide 2, is only present during treatment, the long-term monitoring of treatment complications will be necessary.
- Growth hormone in high doses may have effect on wet weight absorption, but treatment is often accompanied by side effects. In a single study, low-dose growth hormone treatment had a beneficial effect on energy absorption, but partly this effect may be due to a stimulatory effect on energy intake. The positive effects are mainly described in patients with a preserved colon.
- The beneficial effect of glucagon-like peptide 2 treatment mainly relates to wet weight absorption, and is seen in both short bowel patients with and without a colon in continuity.

Introduction

Malabsorption of non-essential and essential nutrients, fluids and electrolytes, if not compensated for by increased intake, will lead to diminished body stores and subclinical and (eventually) clinical deficiencies. By definition, intestinal failure prevails when parenteral support is necessary to maintain nutritional equilibrium. After intestinal resection, adaptation – a progressive recovery from the malabsorptive disorder – may be evident. Research has focused on optimizing remnant intestinal function through dietary or pharmacological interventions. This

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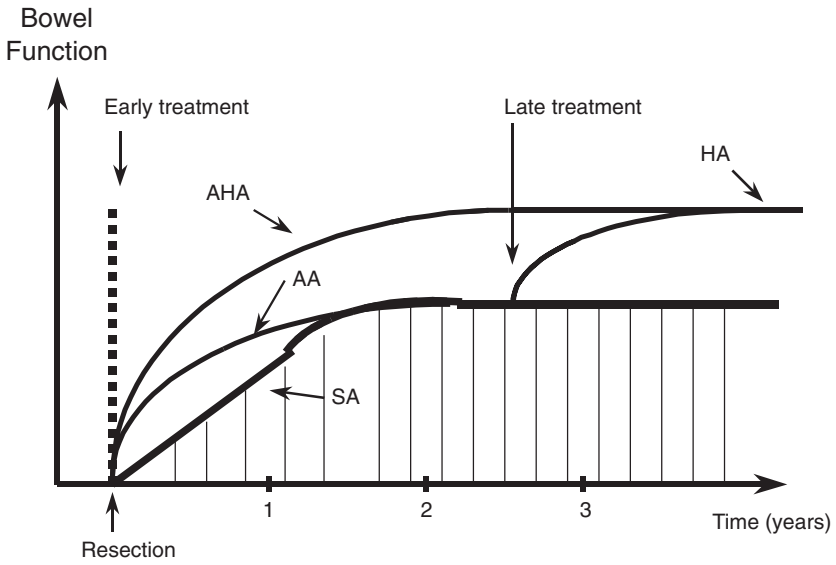

Fig. 34.1. Schematic presentation of intestinal adaptation following surgery or intestinal failure. SA, spontaneous adaptation; AA, accelerated adaptation; HA, hyper-adaptation; AHA, accelerated hyper-adaptation.

review describes factors responsible for the morphological and functional changes in the adaptive processes and presents published results of clinical trials that employ either growth hormones or glutamine and glucagon-like peptide (GLP)-2 in short-bowel patients.

Intestinal Adaptation

The term 'intestinal adaptation' may be applied to the progressive recovery from intestinal insufficiency or failure that follows a loss of intestinal length. Figure 34.1 illustrates a theoretical graphic presentation of intestinal function in relation to the time elapsing following intestinal resection. A 'spontaneous adapation', or recovery of intestinal function, is generally described, reaching a plateau at a certain time (SA in Fig. 34.1).

When trying to improve intestinal adaptation, therapies could either reach a higher plateau phase ('hyperadaptation', HA in Fig. 34.1) or reduce the time period until the plateau is reached ('accelerated adaptation' or 'accelerated hyper-adaptation', AA and AHA, respectively, in Fig. 34.1). The time issue may be relevant in patients who are difficult to maintain on parenteral nutrition (PN). However, the maximal increase in the functional absorptive capacity obtained by hyper-adaptation, represented by the level of the plateau, is the aim when trying to wean stable patients from parenteral support.

Morphological, biochemical, hormonal and neural systems appear to be involved in intestinal adaptation. Data supporting this are mainly derived from animal studies in which the process of compensatory

hyperplasia is extraordinary in some species. It is important to realize that an overall translation of these data to humans cannot be presumed. In the rat, the ileal villi grow to their fully adapted height within about 2 weeks after jejunal resection (Forrester, 1972).

In the human, this process has been demonstrated in patients with jejuno-ileal bypass operations, following which villus height increased and reached a plateau after 1 year (Friedman *et al.*, 1978). Most animal and human resection studies describe jejunal changes in short bowel with colon-in-continuity. Thus, conclusions drawn may not hold for patients with a jejunostomy.

The process of epithelial turnover is highly dynamic in the intestine. Thus, within 3–6 days, the epithelial cells proliferate within the crypts at the base of the villi, mature, differentiate, then move upward toward the tip of the villus, from which they are shed into the bowel lumen (Eastwood, 1977). Adaptation is characterized by cellular hyperplasia that increases the crypt depth and villus size (Porus, 1965; Dowling and Booth, 1967; Nygaard, 1967; Obertop *et al.*, 1977). The morphological changes are more marked in the mucosal surface area, but changes are also seen in the submucosa or muscularis layers (Hanson *et al.*, 1977).

The intensity of the adaptive response appears to be proportional to both the total length and specific areas of the bowel resected. It is greater in the distal small bowel following proximal resection compared with the proximal bowel after distal resection (Eastwood, 1977; Hanson *et al.*, 1977). Thus, a significant morphologic adaptive response is seen after proximal resection in the ileum in animal models (Dowling, 1967; Nygaard, 1967; Tilson and Wright, 1970; Weser and Hernandez, 1971). Adaptive hyperplasia of colonic mucosa occurs after both jejunal and ileal resection (Tilson *et al.*, 1976; Nundy *et al.*, 1977; Solhaug and Tvete, 1978; Williamson *et al.*, 1978).

The adaptive response also occurs in the jejunal remnant after ileal resection, but it is less dramatic, more variable and may partly be related to adaptive changes in food intake (Young and Weser, 1974). Finally, ileal mucosa may also undergo hyperplasia after colectomy (Wright *et al.*, 1969; Woo and Nygaard, 1978).

Only a few longitudinal studies have been performed in humans with respect to functional changes following intestinal resection. However, it is the clinical experience that short-bowel patients with an intact colon show improved absorption with time, whereas patients with jejunostomy do not (Nightingale and Lennard-Jones, 1993). Diminished faecal water losses and increased absorption of glucose, galactose, amino acids and fats during the period after extensive small bowel resection has been described in two short-bowel patients with preserved colon (Dowling and Booth, 1966).

The jejunal absorptive capacity of short-bowel patients has also been examined by segmental perfusion techniques, and the absorption of glucose, water and sodium was increased per unit of length compared to that of control subjects (Dowling and Booth, 1966; Weinstein *et al.*, 1969). Ileostomy adaptation does occur within a period of 6 months; however, this response is lacking in 'ileostomists' who have undergone an ileal resection (Hill *et al.*, 1974). Thus, the preservation of the terminal ileum

and the colon seems to be of importance in the adaptive response following intestinal resection. The time required to reach maximum adaptation is not certain. Studies of calcium absorption have suggested that it may continue for more than 2 years (Gouttebel *et al.*, 1989), although the main adaptive response seems to take place within a few months.

It seems that the increase in intestinal function with time following intestinal resection may simply be related to the morphologically demonstrated villus hyperplasia, because only minor changes in the activity of specific intestinal disaccharidases, hydrolases, enterokinase and sodium-potassium-ATPase have been demonstrated (Tilson and Wright, 1971; Weser and Hernandez, 1971; McCarthy and Kim, 1973). However, functional adaptation may also involve a trend towards normalization of gastric hyper-secretion, gastric emptying and rapid intestinal transit reported in short bowel syndrome (SBS) (Remington *et al.*, 1983).

The signals and precise mechanisms that trigger the hyperplastic adaptive response after small bowel resection are not completely understood. The main factors thought to influence intestinal adaptation are: (i) exposure of the remaining mucosa to luminal nutrients and non-nutritive components of the diet; (ii) various factors related to the provision of enteral feeding (e.g. pancreatic-bilary secretions and enteric hormones); and (iii) possibly various growth factors and hormones not secreted from the intestine.

Hormonal Stimulation of Intestinal Adaptation

Two major hormonal candidates – growth hormones and Glucagon-like Peptide 2 (GLP-2) – have been suggested and employed in the treatment of patients with SBS. Currently, hormonal therapy in short-bowel patients should be considered as experimental and only to be recommended in research settings. The overall aim of any given treatment in short-bowel patients is to improve the quality of life. Quality of life may be estimated by the use of standardized questionnaires; however, at present, it is difficult to establish which numerical improvement on the disease-specific or non-disease-specific inflammatory bowel disease questionnaire impact profile scales would justify the introduction of a new treatment.

The main focus of research performed in SBS has been to increase absolute intestinal absorption. However, in most studies assessing the effects of pharmacological interventions, the dietary intake has been fixed during balance studies. Therefore, in contrast to these 'physiological studies', the effect on the dietary intake of these interventions and, thereby on the true absolute absorption, has not yet been established *in vivo* in the everyday settings of the patients. For instance, pharmacological agents could (i.e. due to an effect on gastric emptying) induce a sensation of satiety, thereby also reducing the overall dietary intake.

Even in studies in which a true increase in the intestinal absorption has been established, the outcomes may differ in individual patients. It is possible that an improved energy and macronutrient balance in some

patients may lead to changes in body weight and composition and, in others, to a change in basal metabolic rate, whereas some may increase their physical activity. Improved fluid and electrolyte balance may allow for increased perspiration and production of urine and sweat.

Thus, to get a more precise picture of the individual short-bowel patient, each of these parameters should, ideally, be measured in long-term experiments. Because of the vast requirements and efforts in conducting such experiments, the ability to wean patients from parenteral support has been used as a surrogate marker of an effect of given treatments. However, unless the pre-treatment need for parenteral support has been verified, such an end point is invalid. Most HPN patients can see a reduction in parenteral support for shorter or longer periods, especially for those with colon-in-continuity, and they may even compensate for these changes in their energy, macronutrient, fluid and electrolyte balances.

In spite of these difficulties, the search for factors to enhance bowel adaptation and increase the assimilation of macronutrients and absorption of wet weight, thereby decreasing the need for PN, is intensive. Although the evidence-based knowledge is weak, a comparison of the results obtained in short-term clinical trials employing growth hormone and GLP-2 is presented.

Effects of Growth Hormone, Glutamine and Glucagon-like Peptide 2 in Clinical Studies

Wet-weight absorption

Byrne and Wilmore were the first to introduce the concept of 'bowel rehabilitation', with the introduction of high-dose (0.14 mg/kg/day) growth hormone, glutamine and a high-carbohydrate diet in the treatment of short-bowel patients (Byrne *et al.*, 1995a, b). In the first study published by Byrne and Wilmore, the wet-weight absorption increased from 1.7 to 2.4 kg/day, and sodium absorption increased from 74 to113 mmol/day over 5 weeks of treatment. From the baseline absorptive parameters, the actual need for parenteral fluid and sodium could be questioned in the majority of the patients in that study, according to the borderlines of intestinal failure defined by Jeppesen and Mortensen (2000). All eight patients in the Byrne and Wilmore study had a colon-in-continuity and, in addition to dietary changes toward a high-carbohydrate diet, they were also given oral rehydration solutions as part of the 'rehabilitation'.

Despite claims to the contrary, the effects may, in fact, have been related to dietary changes and the rehydration solutions, rather than to growth hormones and glutamine. Although significant, the effect of growth hormones (0.13 mg/kg/day) and oral glutamine on intestinal sodium and potassium absorption was < 5 mmol/day in the placebo-controlled, double-blind study by Scolapio *et al.* (1997).

In contrast, growth hormone (0.11 mg/kg/day) and glutamine, both

orally and parenterally administered, tended to decrease wet-weight absorption and increase faecal excretion of both sodium and potassium, which reached significance ($P < 0.05$) in comparison with baseline values from the study of Szkudlarek *et al.* (2000).

However, these findings were in contrast to clinical findings of generalized oedema, increased body weight, a need for diuretics and a reduction in parenteral saline during treatment. The patients were probably in the process of excreting water and sodium accumulated during the treatment at the time of the post-treatment balance studies 5 days after termination of treatment. In the lower-dose studies from Ellegåard (growth hormone 0.024 mg/kg/day) (Ellegård *et al.*, 1997) and Seguy (0.05 mg/kg/day) (Seguy *et al.*, 2003), no significant positive effects on either wet-weight or sodium absorption were seen.

The efficacy data of somatotropin (0.1 mg/kg/day for 4 weeks) in a randomized, double-blind parallel group study of 41 patients with SBS (mainly with a preserved colon and stool volume less than 3 l/day) who were dependent on parenteral nutrition has been obtained from the manufacturer's prescribing information (Serono Inc. Zorptive™, 2005). The protocol for weaning from parenteral support is not given, but it seems mainly to be based on body weight, measurement of total body water by BIA and measurements of serum sodium, potassium and bicarbonate.

A significantly greater reduction from baseline in total parenteral volume occurred in recipients of somatotropin (Zorptive™) plus glutamine or somatotropin (Zorptive™) alone than in placebo plus glutamine recipients (−7.7 and −5.9 vs. −3.8 l/week). Thus, the effect of somatotropin (Zorptive™) and glutamine averages 557 ml/day. Balance studies on intestinal absorption were not performed and the results on urinary excretions are not given.

The effects of growth hormone are global and not specific for the intestine. It has recently been reported that growth hormone increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis (Johannsson *et al.*, 2002). Therefore, when employing bioelectrical impedance analysis (BIA) in the weaning from parenteral support, it should be considered that the effects of growth hormone on fluid balance in short-bowel patients may be related to effects on the kidneys and the extracellular space rather than on the intestine.

The effects of GLP-2 are presumed to be more specific for the intestine. In a study with native GLP-2 by Jeppesen *et al.* (2001b), eight patients were treated with 400 μg of GLP-2 twice a day, given subcutaneously for 35 days in an open-label study (corresponding to 0.013 ± 0.002 mg/kg/day, a range of 0.011–0.017 mg/kg/day). Four patients with a mean residual jejunum of 83 cm received HPN, whereas four patients with a mean ileal resection of 106 cm did not. None of the patients had colon-in-continuity. Their average wet-weight absorption was 1.2 ± 1.7 kg/day at baseline and the wet-weight absorption increased by 420 ± 480 g/day ($P = 0.04$), whereas the effect on sodium absorption did not reach statistical significance (33 ± 49 mmol/day; $P = 0.10$).

In a subsequent open-label pilot study employing a dipeptidyl peptidase IV resistant GLP-2 analogue, Teduglutide, in doses of 0.03–0.15 mg/kg/day in 16 short-bowel patients (six with remnant parts of the colon), wet-weight absorption increased by 743 ± 477 g/day ($P < 0.001$), thereby significantly increasing both urine weight (555 ± 485 g/day, $P < 0.001$) and sodium excretion (53 ± 40 mmol/day, $P < 0.001$) (Jeppesen *et al.*, 2005).

Energy absorption

In studies using growth hormone, there have been conflicting results on intestinal energy and macronutrient absorption. In the study by Byrne and Wilmore, the baseline dietary energy intake was 2692 kcal/day, and 1618 kcal/day (~ 6773 kJ/day, 60%) were absorbed (Byrne *et al.*, 1995a). Thus, according to the guidelines that define intestinal failure suggested by Jeppesen and Mortensen (2000), the majority of these patients did not need parenteral energy. After 3 weeks of treatment, the intake and absorption were 2367 and 1759 kcal/day (~ 7363 kJ/day, 74%), respectively, which was a significant improvement in percentage ($P < 0.003$), but an increase of only 141 kcal/day (~ 590 kJ/day) in absolute amounts. In this study by Byrne and Wilmore, all eight short-bowel patients had a colon-in-continuity. As stated, the 'rehabilitation' included a high-carbohydrate, low-fat diet, which in itself is known to increase the energy absorption in this category of short-bowel patients.

Supporting the hypothesis that diet alone resulted in this effect, intestinal fat absorption did not improve. In the study by Scolapio *et al.* (1997), where only two of eight patients had colon-in-continuity, high-carbohydrate diets were provided in both the placebo and treatment arms (Scolapio *et al.*, 1997). Energy absorption was not measured, but no changes were observed regarding nitrogen or fat absorption.

In the studies by Ellegård *et al.* (1997) and Szkudlarek *et al.* (2000), no changes were found in intestinal energy or in fat or nitrogen absorption. The study by Seguy *et al.* (2003), involving growth hormone (0.05 mg/kg/day, nine of 12 patients with colon-in-continuity) and an unrestricted hyperphagic diet, showed increased intestinal absorption of nitrogen by 14 ± 6% ($P < 0.040$), carbohydrates by 10 ± 4% ($P < 0.040$) and energy by 15 ± 5% ($P < 0.002$), which in absolute terms was 427 kcal/day (~ 1787 kJ/day) (Seguy *et al.*, 2003). Fat absorption was unaffected by the treatment. During growth hormone treatment the mean dietary energy intake was 192 kcal/day (804 kJ/day) higher.

In the study on somatotropin (Zorptive™), the mean reductions from baseline in total parenteral calories were significantly greater in recipients of somatotropin (Zorptive™) plus glutamine or somatotropin (Zorptive™) alone than in recipients of placebo plus glutamine (5751 and 4338, respectively, vs. 2633 kcal/week, Serono Inc. Zorptive™, 2005). Thus, the effect of the combined therapy of somatotropin (Zorptive™) plus glutamine would correspond to an effect of 445 kcal/day (1863 kJ/day).

Apparently, there were no changes in the dietary energy intake in the three parallel study groups.

In the study with native GLP-2, the absolute energy absorption tended to increase by 441 ± 634 kJ/day (105 ± 151 kcal/day, $P = 0.09$). Treatment with GLP-2 increased the energy absorption by 3.5 ± 4.0% (from 49.9 ± 20.3% to 53.4 ± 18.1% ($P = 0.04$)) which was equivalent to an increase of 13.1 ± 22.3% in percentage of the absorption at baseline (49.9%). Absorption of carbohydrates improved by 347 ± 444 kJ/day ($P = 0.06$), which was borderline significant, whereas the relative absorption showed a non-significant increasing trend of 4.4 ± 7.5% ($P = 0.14$) from 69.7 ± 22.0% to 74.1 ± 15.9%. Excretion of protein (nitrogen) decreased by 143 ± 127 kJ/day ($P = 0.02$), but the effect on absolute absorption did not reach statistical significance ($P = 0.16$).

This was in contrast to the improvement in the relative absorption of protein, which increased by 4.7 ± 5.4% from 47.4 ± 29.3% to 52.1 ± 28.4% ($P = 0.04$). The effect of GLP-2 on fat absorption was not significant. The improvement in the absolute amount of energy absorbed was obtained in spite of a non-significant decrease in intake of 173 kJ/day, which means that the reduction in the energy malabsorbed (equal to the stomal excretion) was proportionally larger, at 617 kJ/day.

In the study employing the dipeptidyl peptidase IV resistant GLP-2 analogue, Teduglutide, in doses of 0.03–0.15 mg/kg/day in 16 short-bowel patients (six with remnant parts of the colon), faecal energy excretion was reduced by 808 ± 1453 kJ/day ($P = 0.04$), but this only translated to a significant increase in intestinal absorption (963 ± 1290 kJ/day, $P = 0.05$) in a subset of patients with high dietary compliance during balance studies. No significant changes were seen in the absorption of individual macronutrients (Jeppesen *et al.*, 2005).

Body weight, composition and urinary creatinine excretion

In the growth hormone study by Byrne *et al.* (1995a), a weight gain of 5.4 ± 1.2 kg was described in the eight patients after 21 days of treatment. Occurrence of oedema was not reported, but increases in body weight are difficult to explain considering the magnitude of the effect of approximately 12.4 MJ (590 kJ/day) on the energy balance over the 21 days of treatment. In this study neither body composition nor urine creatinine excretion was measured.

In the 8-week growth hormone (0.024 mg/kg/day) study by Ellegård *et al.* (1997), an increase in lean body mass of 2.5 kg and a decrease in fat mass of 0.1 kg were found. Total body potassium increased by 4.7%, equivalent to 1.1 ± 0.4 kg of body cell mass, which was parallel to the 5.6% increase in lean body mass measured by dual-energy x-ray absorptiometry (DXA). Ellegård *et al.* (1997) concluded that the increase in lean body mass was derived from both increased body cell mass and extracellular water.

Using DXA measurements, Scolapio *et al*. (1997) found an increase in lean body mass of 3.96 ± 0.5 kg and a decrease in the percentage of body fat

of 2.51 ± 0.4%, which corresponded to approximately 1.0 kg compared to placebo (Scolapio, 1999). Scolapio *et al.* (1997) concluded that the increased body weight during treatment with high doses of growth hormone was mainly caused by the increase in extracellular water and the presence of peripheral oedema, which was encountered in all eight patients treated.

In the study by Szkudlarek *et al.* (2000), a weight gain of 1.0 ± 0.3 kg ($P < 0.050$) was measured daily for 5 days after 4 weeks of treatment. DXA evaluation indicated that lean body mass had increased by 2.9 kg ($P < 0.001$) and fat mass had decreased by 2.4 kg ($P < 0.001$) compared with baseline, whereas the changes were not significant in comparison to placebo. No changes were seen in urinary creatinine excretion (Jeppesen *et al.*, 2001b).

The most likely explanation of the rather modest weight gain and increase in lean body mass in the study of Szkudlarek *et al.* (2000) could be the timing of measurements. The patients had been off growth hormone and glutamine for 5 days when the DXA-scan measurements were performed. At this time, generalized oedema, which occurred in all eight patients, was on the decline. In the other studies, lean body mass was measured while patients were still receiving treatment.

In the study by Seguy *et al.* (2003), body weight increased 2.0 kg ($P < 0.003$) and the lean body mass, measured by BIA, increased 2.2 kg ($P < 0.006$) (Seguy *et al.*, 2003). No adverse reactions to the growth hormone treatment were encountered.

In the study on somatotropin (Zorptive™), a weight loss of 5.2 kg of body weight (from 63.9 kg to 58.7 kg) was observed from week 2 (pre-treatment) to week 18 (12 weeks post-treatment) in patients treated with the combined therapy of somatotropin (Zorptive™) plus glutamine. This weight loss closely reflects the anticipated weight loss derived by calculation of the energy deficit obtained by reduction of the parenteral energy support of 1863 kJ/day (Serono Inc. Zorptive™, 2005).

In the 35-day study with native GLP-2 treatment, the overall increase in energy absorption of 15 MJ translated into a significant increase in body weight of 1.2 ± 1.0 kg ($P = 0.010$) (Jeppesen *et al.*, 2001a). Lean body mass increased by 2.9 ± 1.9 kg ($P = 0.004$) and fat mass decreased by 1.8 ± 1.3 kg ($P = 0.007$). The study demonstrated positive findings on urine creatinine excretion (0.7 ± 0.7 mmol/day, $P = 0.02$), which suggests an increase in muscle mass in relation to GLP-2 treatment.

In the 3-week study of the GLP-2 analogue, Teduglutide, the increase in body weight of 0.9 ± 2.1 kg did not reach significance ($P = 0.12$).

Conclusion

In recent years, increased attention has been addressed to the pharmacological enhancement of bowel adaptation aimed at weaning patients with intestinal failure from parenteral support. In these patients, apart from posing a threat of causing line sepsis, thrombosis and liver

damage, the complex technology of HPN significantly impairs quality of life (Jeppesen *et al.*, 1999). Although the initial trials employing growth hormone and glutamine were positive, the subsequent controlled trials have demonstrated conflicting findings.

Regarding improvements in wet-weight absorption, the largest effects seem to be seen in studies employing the highest doses and mainly in short-bowel patients with a preserved colon. The maximum effect reported on wet-weight absorption was approximately 700 g/day, but it is not possible to determine whether this effect was due to the combination of growth hormone and glutamine and a high-carbohydrate, low-fat diet, oral rehydration solutions or a combination thereof. The effect on wet-weight absorption in jejunostomy short-bowel patients without colon-in-continuity seems limited.

Regarding the intestinal energy absorption, the effects seem to be limited in the high-dose studies, whereas the low-dose study of Seguy *et al.* (2003) demonstrated an impressive effect of 427 kcal/day (~ 1787 kJ/day). This effect was, however, obtained at a higher dietary intake (192 kcal/day, ~ 804 kJ/day), possibly reducing the true effect to around 200 kcal/day, ~ 1000 kJ/day. The indirectly demonstrated effect on energy absorption by weaning from parenteral energy support in relation to somatotropin (Zorptive™) treatment is 445 kcal/day, ~1863 kJ/day, but the 5.2 kg weight loss after weaning from parenteral support raises concern.

The overall impression is that the effects of high doses of growth hormone are related to the wet-weight absorption (or fluid retention) and mainly in patients with a preserved colon, whereas the effects on energy absorption are minor. With the lower doses of growth hormone there may be an effect on energy absorption in short-bowel patients with a colon-in-continuity, whereas there is no effect on wet-weight absorption regardless of intestinal anatomy. This may restrict the benefit of this therapy, since the majority of the patients in an HPN population are jejunostomy patients without a colon-in-continuity.

Since none of the studies have demonstrated ongoing effects after termination of treatment, there is a need for sustained treatment. Therefore, the presence and severity of adverse events is a concern. Thus, the myalgia, arthralgia, gynecomastia, carpal tunnel syndrome, nightmares and insomnia reported in many growth hormone studies in short-bowel patients may jeopardize the positive effects on quality of life, which should be the ultimate goal of such treatment.

Hopes have been directed towards GLP-2 because the physiologic effects of GLP-2 appear rather specific for the gut, which is concordant with the localization of the GLP-2 receptor. This peptide has intestinotrophic, anti-secretory and transit-modulating effects in short-bowel patients and the adverse events, even in supra-physiological doses, seem limited. So far, the effects of GLP-2 are not clinically dramatic; an increase in energy absorption of 105 kcal/day, ~ 441 kJ/day, and a wet-weight absorption of 420 g/day but, in the first human trial, the dose of GLP-2 and the duration of therapy were chosen arbitrarily.

The GLP-2 analogue, Teduglutide, which is more slowly degraded

(Drucker *et al.*, 1997), doubled the effects seen in the study employing native GLP-2, increasing the energy absorption by 189 kcal/day, ~ 792 kJ/day, and the wet-weight absorption by 743 g/day (Jeppesen *et al.*, 2005). The optimal dosage and administration of these new treatment to short-bowel patients to induce beneficial effects on intestinal secretion, motility, morphology and (most importantly) absorption are not known, but since the effect is seen in short bowel both with and without a colon-in-continuity, it may eventually result in long-term improvements in nutritional status and independence from PN in a larger fraction of short-bowel patients.

However, the long-term use of GLP-2 in human patients has been questioned, because of the theoretical risk of stimulating tumour growth (Thulesen *et al.*, 2004). It is therefore recommended that treatment is initiated in research settings only and that close monitoring of the long-term effects is a part of the protocol.

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35 Intestinal Transplantation

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Key points

- The indication for intestinal transplantation is irreversible, benign, chronic intestinal failure associated with either life-threatening complications of long-term home parenteral nutrition or high risk of death due to the underlying gastrointestinal disease.
- Four types of transplant may be performed: (i) isolated small bowel transplant; (ii) combined liver–small intestine transplant; (iii) multivisceral transplant (stomach, pancreas, duodenum, jejunum and ileum); (iv) as for (iii) but also including the liver.
- The 2003 report of the International Registry of Intestinal Transplantation shows both patient and graft survival steadily improved over time, with better results achieved after 1998. Patient survival rates were 80% at 1 year and 62% at 3 years for intestinal grafts; 70% at 1 year and 65% at 3 years for multivisceral grafts; and 60% at 1 year and 50% at 3 years for small bowel and liver grafts.
- Improved patient survival rates following transplantation were associated with the following factors: (i) patient at home rather than in hospital; (ii) younger patient; (iii) antibody induction immune suppression; and (iv) centres with experience of at least ten cases.
- Timing of patient referral is a key point for good graft and patient survival. Late referral may increase mortality rates among those on the waiting list or following transplantation.
- The difficulty with donor/recipient matching is the main cause of lengthy waiting times and for the high mortality rate for those on the waiting list, especially for candidates for combined liver–intestine transplantation.

 Home Parenteral Nutrition (eds F. Bozzetti, M. Staun and A. Van Gossum)

Introduction

Intestinal transplantation has become a therapeutic option for irreversible chronic intestinal failure associated with life-threatening complications due to long-term home parenteral nutrition (HPN). It is a relatively new procedure, performed worldwide in less than 1000 patients by the year 2003 (Grant *et al*., 2005).

The first experimental transplant was performed on animals in 1958 by Lillehei *et al*. (1959), who transplanted an isolated small bowel in a dog. In 1959, Starzl and Kaupp (1960) performed the first multivisceral transplant in dogs, including liver with stomach, duodenum, pancreas and intestine. Their results were catastrophic due to the high rejection rate. The intestine was found to be very immunogenic, in contrast to the liver or kidney.

From 1967 to 1987 a dozen patients underwent intestinal transplantation in different centres, but the outcome was disappointing. In November 1987, Starzl *et al*. (1989) performed the first successful multivisceral transplant with liver in a human recipient. The patient was a 3-year-old child who survived 6 months after the transplant, but died because of the onset of lymphoma. In 1988, other centres started clinical trials in intestinal transplantation.

The first isolated small bowel transplant was described by Goulet *et al*. (1988) in a child recipient, who had a good outcome. After the introduction of tacrolimus (FK-506) in 1989 (Ochiai *et al*., 1987; Hoffman *et al*., 1990), an intestinal transplant programme started in Pittsburgh, USA. Five patients underwent transplantation at this centre in 1990, four receiving a combined liver–intestine and one an isolated graft. Better results were obtained in a series from London, Ontario (Canada) (Grant *et al*., 1990), where one patient underwent multivisceral transplant with liver and another two received a combined intestine–liver graft, with the best survival being up to 5 years.

In the following years, many intestinal transplant centres started their activities, accounting for a total of 61 programmes by 2003. In 1994, the Intestinal Transplant Registry was set up. This organization collects data from all over the world and organizes a biannual international symposium reporting a data collection update.

The current experience of intestinal transplantation can be categorized into four types of transplant:

- Isolated small bowel transplant, including jejunum and ileum (Fig. 35.1).
- Multivisceral transplant, including stomach, pancreas, duodenum, jejunum and ileum (Fig. 35.2).
- Combined liver–intestine transplant, including jejunum and ileum (Fig. 35.3).
- Liver–multivisceral transplant, including liver with the multivisceral graft (Fig. 35.4).

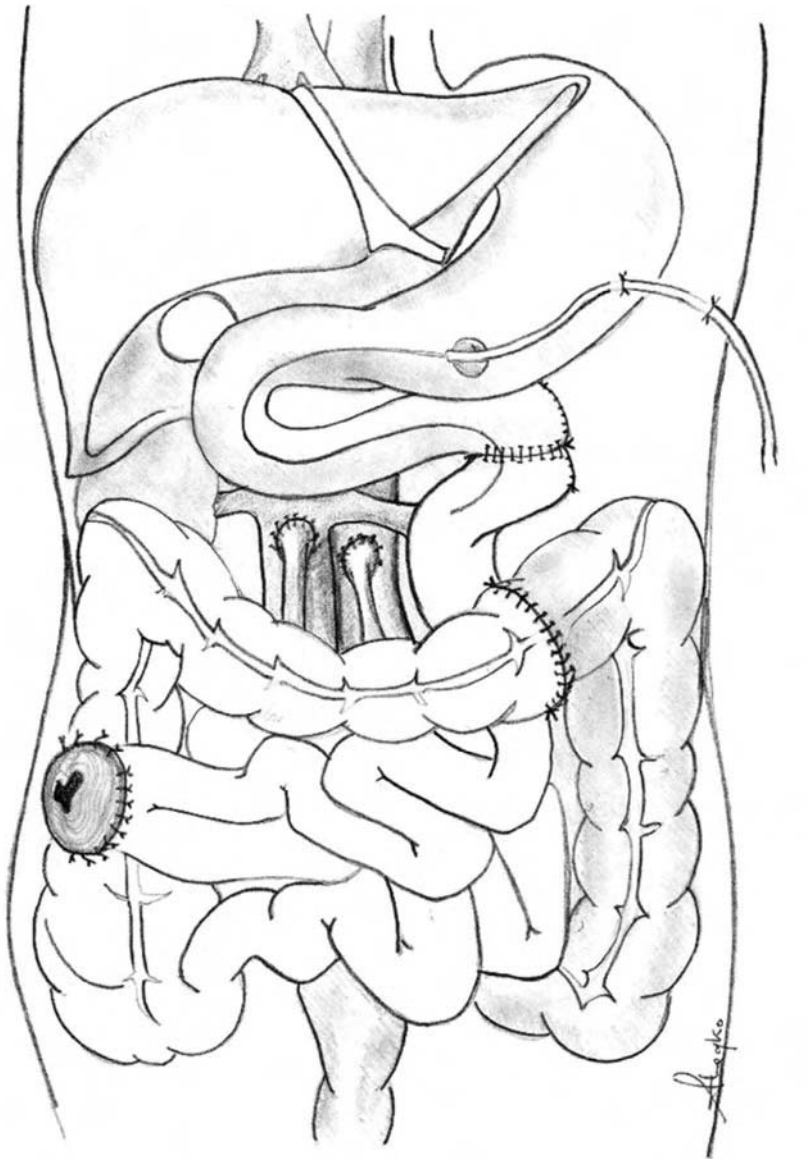

Fig. 35.1. Isolated small bowel transplant, including jejunum and ileum.

Indications (for internal transplantation)

The indication for isolated small bowel transplantation is irreversible intestinal failure with no possibility of bowel rehabilitation, with normal liver function, associated with one or more of the other HPN-related, life-threatening complications (Fishbein *et al*., 2003a).

The indication for multivisceral transplantation is irreversible intestinal

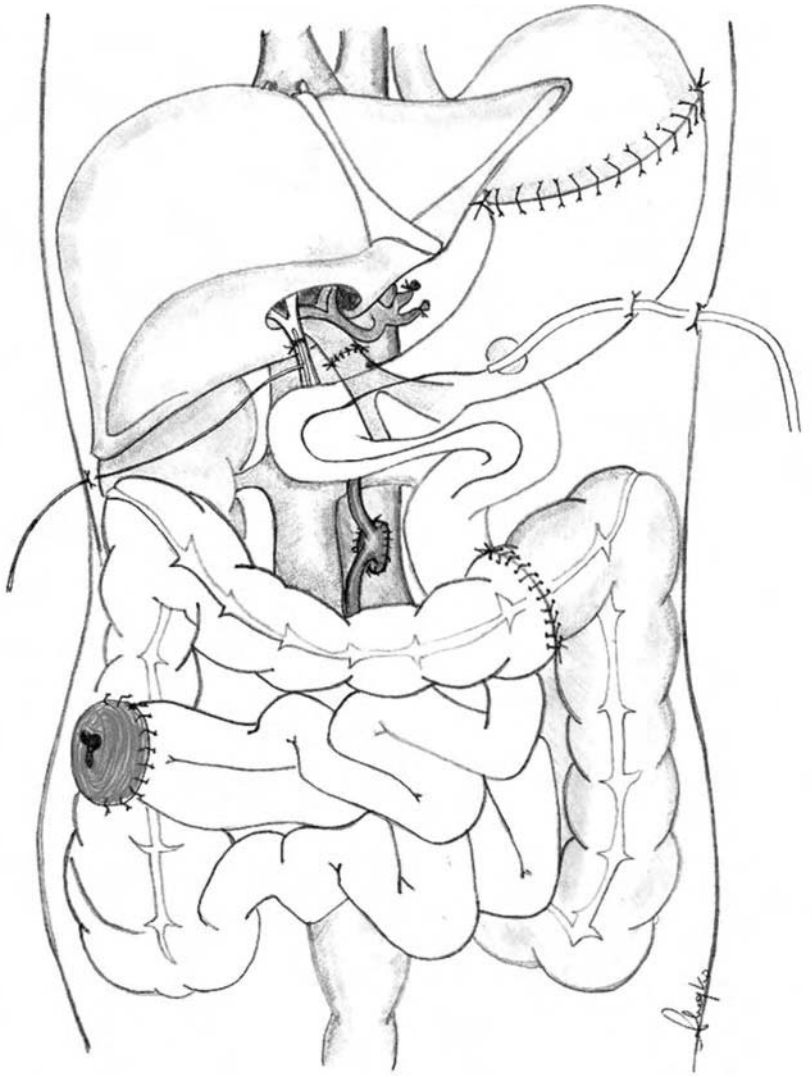

Fig. 35.2. Multivisceral transplant, including stomach, pancreas, duodenum, jejunum and ileum.

failure with no possibility of bowel rehabilitation associated with HPN-related complications and disorders involving the upper gastrointestinal tract.

The indications for combined liver–intestinal transplantation are irreversible intestinal failure associated with irreversible liver failure or irreversible liver failure associated with superior mesenteric venous thrombosis.

The indications for liver–multivisceral transplantation are irreversible liver failure associated with irreversible intestinal failure and upper gastrointestinal disorders or splanchnic thrombosis.

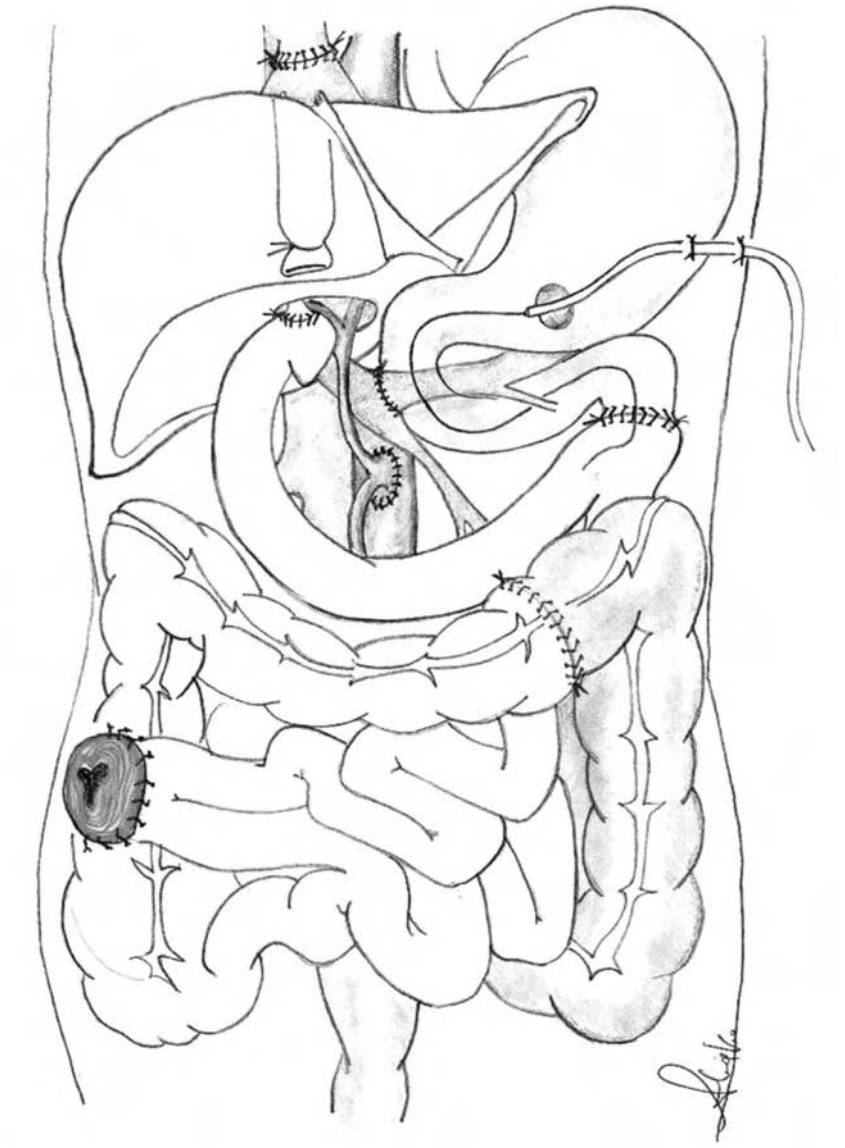

Fig. 35.3. Combined liver–intestinal transplant, including liver with jejunum and ileum.

The USA Center for Medicare and Medicaid Services has approved the payment for intestinal transplantation when the following life-threatening complications related to the HPN occur (Buchman *et al*., 2003):

- Impending or overt liver failure with elevated serum bilirubin and/or liver enzymes; splenomegaly; thrombocytopenia; gastro-oesophageal varices; coagulopathy; stomach bleeding; hepatic fibrosis; or cirrhosis.
- Thrombosis of two or more of these six major central venous channels: the subclavian, jugular or femoral veins.

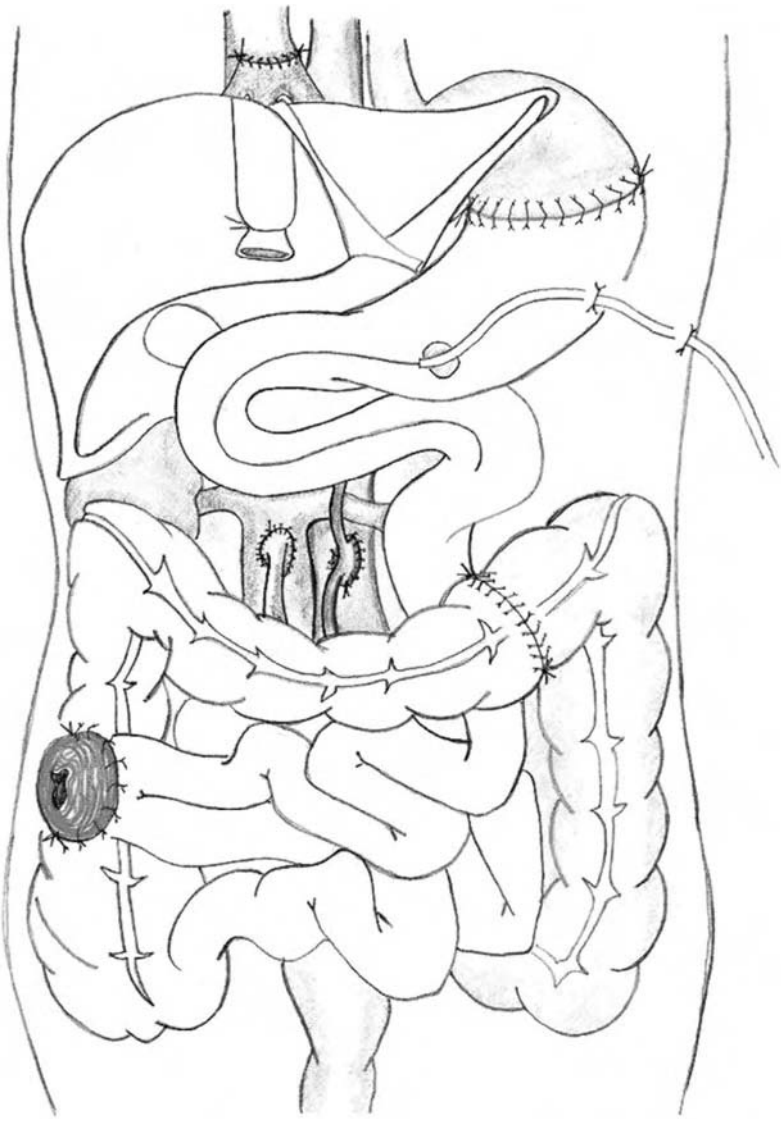

Fig. 35.4. Combined liver–multivisceral transplant, including liver with the multivisceral graft.

- Frequent central line sepsis; two or more episodes of systemic sepsis secondary to line infections per year; one episode of line-related fungaemia; septic shock; or acute respiratory distress syndrome.
- Frequent severe dehydration.

The American Society of Transplantation position-paper on paediatric intestinal transplantation considers candidates for intestinal transplantation also those patients with a high risk of death or with very poor quality of life related to the following underlying intestinal failure conditions

(Kaufman *et al*., 2001): (i) locally invasive tumours (e.g. desmoids in familiar polyposis); (ii) extreme short bowel: (< 10 cm jejunum in children); (iii) congenital intractable mucosal disorders: microvillus inclusion disease; tufting enteropathy; and (iv) intestinal failure with high morbidity and poor quality of life, e.g. severe, chronic intestinal pseudo-obstruction (CIPO); high-output stoma.

A multicentre survey in Europe evaluated the prevalence of candidacy for intestinal transplantation on the basis of the Medicare and of the American Society of Transplantation indication criteria. Forty-one HPN centres from nine countries enrolled 688 adults (> 18 years old) and 166 children. Candidacy overall was 15.7 and 34.3% in adults and children, respectively; due to HPN failure 62.1 and 28.1%, respectively; due to high-risk gastrointestinal disease 25.9 and 59.6%, respectively; and due to high-morbidity intestinal failure 12.0 and 12.3%, respectively. Among the major contributing countries, the prevalence of candidacy ranged from 0.3 to 0.8 per million inhabitants for adults and from 0.9 to 2.0 per million inhabitants ⩽ 18 years (Pironi *et al.*, 2006).

The gastrointestinal diseases and the causes of intestinal failure of the recipients differed between children and adults (Grant *et al*., 2005). In children, gastroschisis (21%), necrotizing enterocolitis (12%) and intestinal volvulus (19%) can lead to short bowel syndrome (SBS), accounting for the 50% of paediatric transplants. Other minor diseases included intestinal atresia (8%) and motility disorders such as intestinal pseudo-obstruction (9%) and aganglionosis/Hirshsprung's disease (7%).

In adults the main indication is SBS due to intestinal ischaemia (23%), trauma (10%), volvulus (7%) or Crohn's disease (14%). Motility disorders account for 8% of transplants. Desmoid/Gardner syndrome, responsible for 12% of procedures, and abdominal neurofibromatosis are rare indications, requiring an isolated intestinal transplant if the tumour is confined to the mesentery, or a multivisceral transplant if the other upper gastrointestinal organs are affected. A specific indication for a combined liver–intestine transplant is mesenteric vein thrombosis associated with protein-S or protein-C deficit, because a transplant could correct this deficiency.

The main contraindications for intestinal transplantation are advanced cardiopulmonary disease and non-resectable malignancy (local or metastatic). Patients with an active infection should be put on hold as candidates for transplantation.

Referral for transplantation should be considered as soon as HPN-related complications occur, because a late referral may increase mortality rates among those on the waiting list or following surgery. An early referral can offer a better chance for the patient to receive a transplant and to have a better chance of survival, because of the better pre-transplant clinical condition. This is important especially in children with liver failure, due to the risk of rapid, progressive hepatic damage leading to multi-organ failure and sepsis. A late referral could result in patients dying on the waiting list. The United Network for Organ Sharing (UNOS) report showed that the death rate on the waiting list for intestinal transplants is

significantly higher than that seen with any other solid organ transplant waiting list (UNOS reports).

Pre-surgical Considerations

Pre-transplant evaluation

All potential candidates for intestinal transplantation must undergo a multidisciplinary assessment evaluating the gastrointestinal tract, the nutritional status and the hepatic, renal, cardiopulmonary, haematological and immunological functions – as well as investigation for infectious diseases. Also, a psychosocial assessment must be carried out, and a final anaesthesiology evaluation. The aetiology, extent and severity of the primary disease must be accurately assessed in every patient. A radiological and endoscopical (with biopsies) examination of the remaining, native gastrointestinal tract is carried out to plan the appropriate surgical strategy.

When required, gastrointestinal motility tests and an angiography should be added. A computer tomography (CT) scan should be performed to evaluate the extent of the neoplastic lesions of Gardner's syndrome or abdominal neurofibromatosis and, in some cases, to evaluate properly the abdominal cavity and the remnant space in relation to donor/recipient weight matching.

Donor selection and organ procurement

Donor evaluation is the first step towards reaching good results. Donors should be young and haemodynamically stable with minimal amine support, because the intestine is very sensitive to ischaemia. ABO compatibility is mandatory, while the ratio of donor weight:recipient weight should not exceed 1.1. The organ should be evaluated intra-operatively for appearance, motility and integrity. Organ harvesting (Di Benedetto *et al*., 2004) requires superior mesenteric vessel isolation for an isolated intestinal graft, and include the aorta and vena cava for a multivisceral graft. Half of the colon, close to the medium colic vein, is harvested with the graft, which is preserved with cold University of Winsconsin or Celsior solution. The difficulty with donor/recipient matching is the main cause for a long period on the waiting list.

Surgical Considerations

Transplant options

Isolated small bowel transplant

This technique can be summarized in four surgical steps:

- The diseased organ is removed and a proper space for the allograft is created; during this step, access to the aorta and vena cava is gained.
- The vascular anastomoses are performed, either orthotopic on mesenteric vessels or hetenotopic on aorta and vena cava; occasionally a vascular graft extension is required.
- The upper and lower intestinal anastomoses are completed; an ileostomy is performed and a gastrostomy tube is positioned.
- The abdominal wall is closed; in some patients, this can prove very difficult, thus requiring an abdominal wall transplant (Levi *et al*., 2003) or the use of a myo-cutaneous flap (Alexandrides *et al*., 2000).

Multivisceral transplant

This requires the resection of all the tributary organs to the portal vein, including stomach, intestine, pancreas and spleen, so that the portal vein of the graft is anastomosed to the recipient portal vein. Arterial blood flow is supplied by an aortic conduit (from the thoracic aorta of the donor), anastomosed to the recipient aorta and, subsequently, to a patch including the mesenteric and coeliac arteries of the graft. Biliary reconstruction could be performed in a duct-to-duct fashion or by a Roux and Y loop biliojejunostomy.

Combined liver–intestine and liver–multivisceral transplants

These both have the venous outflow connected to the recipient hepatic veins.

Living donor intestinal transplantation

Living donation may be suitable for intestinal transplant, too. By May 2003, 32 patients had undergone living donor intestinal transplantation. Donor evaluation is comprehensive with regard to infectious and gastrointestinal assessment, with particular attention to absorption tests, abdominal CT-scan and selective superior mesenteric angiography or 3D-angio-CT-scan. The intestinal graft is a segment of the ileum of 150–200 cm, resected 20 cm proximal to the ileocaecal valve. Ileum is actually preferred to a jejunal segment. A distal segment of the superior mesenteric artery and a proximal segment of the superior mesenteric vein

represent the arterial inflow and venous outflow, reconstructed on the recipient aorta and vena cava (Gruessner and Sharp, 1997; Testa *et al.*, 2004).

Reduced-size organs

The critical shortage of size-matched donor organs for infants and small children needing isolated small bowel or combined liver and intestine transplantation has led to long waiting times and a high risk of death before transplantation. Utilizing grafts from larger donors could alleviate this problem, but the use of these larger composite grafts in small children has been challenging and unsuccessful in the past. The ability to create suitable reduced-size small bowel or liver grafts (in the case of a combined transplant) from adult cadaveric donors has been reported in recent studies (Bueno *et al.*, 2000; Delriviere *et al.*, 2000; de Ville de Goyet *et al.*, 2000).

Clinical Management

The immediate post-operative period is the most difficult for intestinal transplant recipients. Close surveillance is required to prevent or treat promptly those complications that may put at risk the graft and the patient's survival – such as rejection or infection. Also, re-laparotomy is often required and post-transplant lympho-proliferative disease (PTLD) may develop (Kato *et al.*, 2002). All these complications, which can be very harmful in the immediate post-operative period, can occur even years after transplantation.

Early post-operative complications

Surgical complications

These include the following: (i) anastomotic stenosis or leak; (ii) arterial or venous thrombosis; (iii) intestinal mal-rotation; (iv) bleeding; (v) small bowel compression; (vi) eventration; (vii) abdominal collections; and (viii) stomal infarction. Treatment of these complications is managed, obviously, by surgeons or interventional radiologists.

Renal failure

The most frequent medical complications requiring intensive care support are renal and respiratory failure. Renal failure is caused mainly by two factors, negative fluid balance and immunosuppression toxicity. In intestinal transplantation, fluid balance is an extremely important

landmark. Post-operatively, the small bowel is oedematous and the patient may require abdominal decompression in order to breath properly. At the same time, during intestinal transplantation the fluid loss is extremely high. After the operation, commencing immunosuppression with calcineurin-inhibitors can damage the kidney and precipitate an acute renal failure. Thus, optimal post-operative fluid support is mandatory in order to maintain a normal urinary output.

Respiratory failure

This can be due to post-operative pneumonia, oedema, pneumothorax, pleural effusion, lung atelectasia or the eventual scenario of sepsis and multi-organ failure. Management is based on broad-spectrum antibiotics, diuretics, thoracic drainage and operative bronchoscopy. Intubation and ventilator support may be necessary.

Neurological complications

These too can occur after intestinal transplantation, mainly related to immunosuppressive therapy with calcineurin-inhibitors (primarily FK-506), whose toxic effect may be a direct one or secondary to high blood concentration. The neurological impairment varies from mild involvement to coma.

Rejection and Immunosuppression

In the early intestinal transplantation era, rejection was a very severe complication, because it was very frequently the cause of graft loss and patient death. The introduction of new immunosuppressive drugs and induction agents has significantly decreased the rejection rate and improved the graft survival. The UNOS data reports show that, in more than 50% of patients, the immunosuppressive regimens were based on induction protocols, using daclizumab, basiliximab or thymoglobulin (UNOS reports). In very recent years new inductor agents such as Alemtuzumab have been successfully used (Tzakis *et al.*, 2004).

Immunosuppression is maintained with FK-506 at high doses, intravenously and through the gastrostomy tube during the first post-operative days, but a few days later the oral route remains the only way of administration. The FK-506 blood concentrations should be monitored daily, because of both the rapid improvement of the drug absorption by the graft and the frequent variation of renal failure and fluid balance that can alter FK-506 pharmacokinetics. FK-506 is frequently administered together with steroids.

The UNOS data show that sirolimus and mycophenolate mofetil were also given to 19.2% and 11.4% of the recipients, respectively (UNOS reports). In the case of relapsing rejections or of ongoing renal toxicity,

sirolimus has been reported to be very effective in association with, or in place of, tacrolimus (Fishbein *et al*., 2003b).

The monitoring of the intestinal mucosa plays key roles in the early detection of graft rejection and in its timely treatment. Temporary ileostomy allows frequent ileoscopies and mucosal biopsies and a direct view of the intestinal mucosa. The histological evaluation of the biopsies takes into account the apoptotic index, the cryptal injury and the presence of haemorrhages and of inflammatory cells (Lee *et al*., 1996; Ruiz *et al*., 2003). A diagnosis of rejection is made when all these three aspects are present.

According to the extent of the alterations, acute cellular rejection is classified as mild, moderate or severe, the latter being diagnosed when necrosis of the intestinal mucosa is observed. Zoom endoscopy and histological findings must be evaluated when considering the clinical symptoms too. The clinical signs of acute intestinal rejection are fever, nausea, vomiting, high stomal output, mucosal oedema and intestinal bleeding. Chronic rejection is clinically represented by diarrhoea, abdominal pain, progressive weight loss and intermittent intestinal bleeding.

Treatment of rejection episodes is established according to the histological degree and the clinical features. The first choice is steroid bolus and tapering and increasing of FK-506 dosage. In the case of steroid resistance or of severe rejection, monoclonal or polyclonal antibodies, such as OKT-3 or infliximab, are given. Rejection, if not treated, can lead to graft removal.

Graft versus host disease was a frequent complication in the early days of intestinal transplantation, represented clinically by skin rash. Nowadays, due to selective immunosuppression, it is a less frequent finding.

Post-operative Infection

Transplantation patients runs a considerable risk of infection for many reasons:

- Heavy immunosuppression.
- Presence of a central line in the first post-operative period.
- Bacterial translocation, especially in the case of rejection.
- Aggressive abdominal surgery.
- Malnutrition.
- Renal failure.

Infections are the primary cause of death after intestinal transplantation. Thus, prophylaxis for bacterial, viral and fungal agents is mandatory. Gut decontamination through the gastrostomy tube, with a solution containing nystatin, gentamicin and polymyxin E, prevents intraluminal bacterial overgrowth. Intravenous antibiotic prophylaxis with ampicillin is administered too. Pneumonia and intra-abdominal abscesses are the most frequent life-threatening infections.

In the case of fever, after having excluded a rejection, chest X-ray and CT-scans should be performed in order to search for these foci. The most frequent germs are *Enterobacterium*, *Staphylococcus* and *Streptococcus*. Fungal infections are rare and are represented mainly by oral or oesophageal candidiasis (responsive to fluconazole) and *Aspergillus* (pulmonary localization); fungaemia is very harmful and requires aggressive treatment.

Viral pre-emptive therapy is based on: (i) ganciclovir given intravenously during the first post-operative month, and thereafter by the oral route; and (ii) IgG anti-cytomegalovirus (CMV) – during the first month as well. Virus-like CMV and Epstein-Barr virus (EBV) are responsible for enteritis and pulmonary infections. EBV is also associated with PTLD. PTLD can be treated by monoclonal antibodies such as rituximab and local ablative surgery (Tzakis *et al.*, 2002). EBV PCR and CMV antigen in blood, as well as CMV and EBV PCR in mucosal biopsies, should be routinely searched for, a positive test requiring prompt treatment. The incidence of severe viral infections has dropped thanks to these early-detection methods.

Haemodynamic and infective complications are often related to each other. Hypotension, if not related to fluid imbalance, is often an expression of sepsis and requires the use of intravenous pressor agents, such as dopamine, norepinephrine or epinephrine.

Nutritional Management

In the early post-operative days, nutritional support is achieved through parenteral nutrition until the graft function allows nutritional autonomy. Enteral feeding is begun approximately 4–7 days after the transplant to maintain mucosal integrity and function. First, a 5% dextrose solution is administered through the gastrostomy tube, later replaced by an isotonic enteral diet. As soon as bowel movement appears through ileostomy, a regular oral diet is encouraged. The parenteral nutrition is discontinued when the patient is able to maintain nutritional status by the gastrointestinal route alone.

The main metabolic complication is represented by a metabolic acidosis due to the systemic consumption and gastrointestinal loss of bases, requiring bicarbonate support by the intravenous or oral route.

Results and Update

The last report from the Intestine Transplant Registry shows that between 1985 and 2003, 61 centres performed 989 transplants in 923 patients, with a re-transplant rate of 7% (Grant *et al.*, 2005; Intestinal Transplant Registry). Thirty-two patients received an intestinal graft from living donors. The number of cases per year has increased over time, reaching

more than 120 transplants in 2002. The paediatric population (⩽ 18 years) represented the majority of the recipients – 606 grafts (61%). The types of grafts were: (i) isolated intestine (433 grafts); (ii) combined intestine and liver (386 grafts); and (iii) multivisceral with or without liver (170 grafts).

As of May 2003, there were 484 survivors (52.4%), about 80% of whom were off parenteral nutrition and had resumed normal daily activity. The overall patient survival rates were 65 and 50% at 1 and 3 years, respectively, and graft survival rates were 60 and 46%, respectively. Graft removal was necessary in 190 patients. Rejection was the main cause, accounting for 56% of them. Causes of death were represented by infections in 202 patients, rejections in 49, respiratory failure in 29, PTLD in 27, technical reasons in 27 and by other causes in 76.

Both patient and graft survival steadily improved over time, with better results achieved after 1998. Considering data after 1998 from centres that performed more than ten transplants, patient survival was 80% at 1 year and 62% at 3 years for intestinal grafts, 70 and 65%, respectively for multivisceral grafts and 60 and 50%, respectively for small bowel and liver grafts.

A multivariate analysis of cases transplanted after 1998 revealed that transplantation of patients waiting at home, recipient age (better in younger patients), antibody induction immunosuppression and centres with experience of at least ten cases were associated with improved patient survival.

Conclusions

Intestinal transplantation has become a therapeutic option for irreversible benign chronic intestinal failure associated with life-threatening complications of long-term HPN or high risk of death due to the underlying gastrointestinal disease.

Four transplant types can be performed: (i) isolated small bowel; (ii) multivisceral; (iii) combined liver–intestine; and (iv) liver–multivisceral.

The International Transplant Registry report shows overall patient survival rates of 65 and 50% at 1 and 3 years, respectively and graft survival of 60 and 46%, respectively. More than 80% of survivors had stopped parenteral nutrition and resumed normal daily activities.

Both patient and graft survival steadily improved over time. After 1998, in centres with experience of more than ten transplants, survival rate was 80 and 62% at 1 and 3 years, respectively, in isolated intestine recipients, 70 and 65%, respectively, in multivisceral recipients and 60 and 50%, respectively, in liver–intestine recipients.

Recipient and donor selection is a landmark for good graft and patient survival and further improvement in survival is expected from a timely patient referral.

The main complications encountered after intestinal transplantation were rejection, infection, re-laparotomy and post-transplantation lympho-

proliferative disease. Complications account for most of the post-transplantation deaths and graft failure.

Acknowledgements

The authors wish to thank Dr Augusto Lauro, MD and Dr Alessandro Dazzi, MD for support in writing the manuscript and Dr Alessandro Cucchetti, MD for the drawings.

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36 Home Parenteral Nutrition: Perspectives

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The administration of parenteral nutrition at home was initiated in the early 1970s for patients with life-threatening intestinal failure. Short bowel syndrome was the major indication for initiating home parenteral nutrition (HPN) in patients with benign underlying diseases. On the basis of the experience that had been collected by some specialized centres in Europe and in North America, this method is now routinely practised in industrialized countries around the world.

For 20 years, the use of HPN has been extended to patients with advanced cancer who are unable to be fed enterally. For this group of patients, the concerns and objectives of HPN are different from those for patients with benign diseases but, in any case, HPN tends to improve the quality of life (Van Gossum and Messing, 1997). The specificity of providing HPN in cancer patients – including medical, psychological and ethical issues – should be carefully recognized by the caregivers.

In this book all the authors – who have considerable expertise in the field of HPN – have presented an update of the best practice in this field. Nevertheless, we have to admit that the recommendations that are described in the various chapters are more often based on experts' consensus or personal experience than on well-documented, evidence-based medicine. The lack of randomized, controlled trials in some areas of HPN is probably related to the difficulty in performing such trials by using a method that has been recognized as being life-saving.

What are the perspectives in the field of HPN? First, we should expect some significant changes in terms of underlying diseases and indications. Indeed, although the incidence of newly enrolled HPN patients is continuously increasing in many countries, it is probably not due to an increase in the incidence of underlying diseases but to a better usage of HPN, at least for patients with benign diseases (Ireton-Jones and De Legge, 2005).

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It is clearly evident that the number of patients with Crohn's disease – which used to be the most frequent underlying disease – who might require HPN is sharply decreasing. This trend is related to an improving therapeutic strategy, especially the development of biologics such as anti-TNFα medication.

Even if it is not yet apparent in epidemiological surveys, we could also expect to observe a decreased incidence of vascular mesenteric infarction due to better prevention of cardiovascular diseases and a decrease in the habit of cigarette smoking.

On the contrary, the use of HPN will continue to grow for cancer patients; this is related to the ever-growing incidence of cancer as well as to the development of more aggressive multimodal therapies for cancer (Hoda *et al.*, 2005).

Independently of the underlying diseases, the use of HPN will progressively increase in the future in relation to political and economic trends. Indeed, a major effort is made in all the industrialized countries to control the cost to health services by limiting the duration of hospitalizations. In parallel, we observe the expanding development of home care services. We also hope that the use of HPN will be initiated in countries in which this method is not yet available for medical and economic reasons.

Secondly, the growing use of HPN should continue to assure and even improve the quality of care. Indeed, epidemiological surveys have raised some concerns about the growing number of HPN centres with only limited experience. It is suspected that complications and mortality rates are negatively related to the level of experience. However, a recent report stated that HPN which was practised at a non-specialist district general hospital achieved complication rates comparable to those of large, specialist centres (Freshwater *et al.*, 2005).

Moreover, for patients with advanced cancer, home care services which are handled by private companies – and which are very beneficial for logistic support – should not substitute for specialized HPN teams. In the same way, the use of the tri-chamber bags should not hide the need for prescription of 'tailored' parenteral support in patients on long-term HPN.

In other words, the difficulty of running an HPN programme should not be minimized; HPN needs to be performed by expert, multidisciplinary teams. Teaching and continuous education in the field of HPN is mandatory. We should also encourage transferring our expertise to newly qualified HPN centres in emerging countries.

Thirdly, we also may expect striking improvement in the medical management of chronic intestinal failure by improvements in the different mechanisms of adaptation: the remaining small bowel, the colon (when possible) and the patient (hyperphagia) (Brown and Dibaise, 2004).

In the area of intestinal adaptation, research is ongoing on the potential benefits of specific nutrients (glutamine, citrulline, etc.) and on growth hormone factors (Jackson and Buchman, 2005).

Fourthly, the progress in intestinal transplantation, as well as the

improved life expectancy of small bowel-transplanted patients, should also encourage HPN teams to improve the quality of their programmes (Tzakis *et al.*, 2005). Indeed, up to now, intestinal transplantation has been reserved mainly for HPN patients who had developed HPN-related complications. In the future, we may consider earlier organ transplantation in HPN patients who cannot be weaned off TPN.

Furthermore, although still a matter of debate, research into cloning of cells or cell therapy using autologous stem cells could be revolutionary – as for other organ failure – for palliation of intestinal failure (Vats *et al.*, 2005; Weissman, 2005).

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