Nutrition

8

Agostino Pierro and Simon Eaton

Contents

8.1 Introduction

The nutrition of neonates and children has significantly improved over the last 20 years. Most of the nutritional challenges in paediatrics are related to the first year of life. For this reason this chapter focuses on the nutrition of neonates and infants.

The newborn infant is in a "critical epoch" of development not only for the organism as a whole but also for the individual organs and most significantly for the brain. Adequate nutrition in the neonatal period is necessary to avoid the adverse effects of malnutrition on morbidity and mortality and to minimise the future menace of stunted mental and physical development.

The survival rate of newborn infants affected by isolated congenital gastrointestinal abnormalities has improved considerably and is now in excess of 90% in most paediatric surgical centres. The introduction of parenteral nutrition and advancement in nutritional management are certainly among the main factors responsible for this improvement.

8.2 Historical Background

Parenteral nutrition has progressed from numerous historical anecdotes in the 1930s with the first successful infusion of protein hydrolysates in humans, followed by the first report of successful total parenteral nutrition in an infant in 1944 and has been given a huge boost by the first placement of a catheter in the superior vena cava to deliver nutrients for prolonged periods. Using this system, Dudrick and Wilmore showed that adequate growth and development could be achieved in beagle puppies and in a surgical infant. Following these initial reports, Filler and co-authors

P. Puri and M. Höllwarth (eds.), *Pediatric Surgery: Diagnosis and Management,*
DOI: 10.1007/978-3-540-69560-8_8,

reported the first series of surgical neonates with gastrointestinal abnormalities treated with long-term total parenteral nutrition. During the 1970s and 1980s significant improvements were made in the technique itself and in the reduction of complications, and the last 10 years have seen considerable changes in the nutritional management of surgical neonates. Various investigators have highlighted the importance of introducing enteral nutrition as soon as possible in surgical neonates. The beneficial effects of minimal enteral feeding on the immune system, infection rate and liver function have been elucidated.

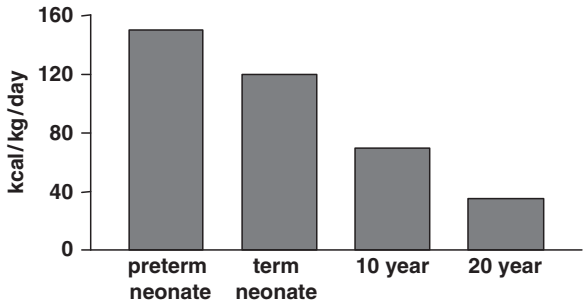

Fig. 8.1 Total energy requirement according to age

8.3 Body Composition

Newborn infants grow very rapidly, have lower caloric reserves than adults and therefore do not tolerate prolonged periods of starvation. The body composition of newborn infants is markedly different from that of adults. The total body water varies from 86% of body weight at 28 weeks of gestation to 69% at 40 weeks of gestation and 60% in adulthood. This decline in body water reflects also an increase in energy content of the body. The ratio between minimal metabolic rate to non-protein energy reserve is only 1:2 at 28 weeks of gestation, it decreases to 1:29 for term infants and 1:100 for the adult, which explains the urgent need for adequate caloric intake in very-low-birth-weight infants after birth. Full-term neonates have a higher content of endogenous fat (approximately 600 g) and therefore can tolerate few days of undernutrition.

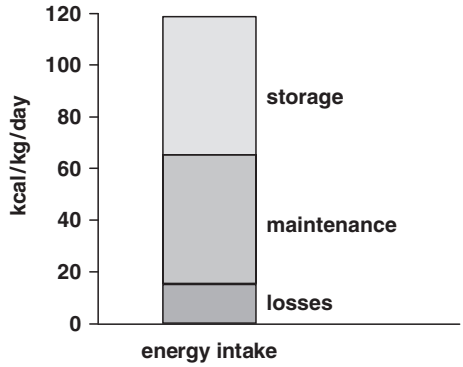

Fig. 8.2 Partition of energy metabolism in surgical newborn infants. (Adapted from Pierro et al. 1991)

8.4 Energy Metabolism

Newborn infants have a significantly higher metabolic rate and energy requirement per unit body weight than children and adults (Fig. 8.1). They require approximately 40–70 kcal/kg/day for maintenance metabolism, 50–70 kcal/kg/day for growth (tissue synthesis and energy stored) and up to 20 kcal/kg/day to cover energy losses in excreta (Fig. 8.2). The total energy requirement for a newborn infant fed enterally is 100–120 kcal/kg/day, compared to 60–80 kcal/kg/day for a 10-year-old and 30–40 kcal/kg/day for a 20-year-old individual. Newborn infants receiving total parenteral nutrition (TPN) require fewer calories (80–100 kcal/kg/day). This is due to the absence of energy losses in excreta and to the fact that energy is not required for thermoregulation when the infant is nursed in a thermoneutral environment using a double-insulated incubator. Although energy expenditure may double during periods of activity, including crying, most surgical infants are at rest 80–90% of the time. Significant differences in resting energy expenditure (REE) have been reported among full-term surgical newborn infants (range 33.3–50.8 kcal/kg/day) and between premature and full-term babies. A full-term infant requires 100–120 kcal/kg/day and a premature infant 110–160 kcal/kg/day (Fig. 8.1). These variations in maintenance metabolism explain the different growth rates frequently observed in surgical neonates receiving similar caloric intakes, and probably represent differences in metabolically active tissue mass, i.e. organ and muscle size. Several equations have been published to predict energy expenditure in adults and equations have been developed to predict REE in

stable surgical neonates, to which the major contributing predictors are body weight, heart rate (providing an indirect measure of haemodynamic and metabolic status) and post-natal age.

8.4.1 Operative Trauma

In contrast with adults, the energy requirement of infants and children undergoing major operations seems to be modified minimally by the operative trauma *per se*. In adults, trauma or surgery causes a brief "ebb" period of a depressed metabolic rate followed by a "flow phase" characterised by an increase in oxygen consumption to support the massive exchanges of substrate between organs. In newborn infants, major abdominal surgery causes a moderate (15%) and immediate (peak at 4 h) elevation of oxygen consumption and resting energy expenditure and a rapid return to baseline 12–24 h post-operatively. There is no further increase in energy expenditure in the first 5–7 days following an operation. The timing of these changes corresponds with the post-operative changes in catecholamine levels and other biochemical and endocrine parameters. It has been demonstrated that the post-operative increase in energy expenditure can, at least partially, result from severe underlying acute illness, which frequently necessitates surgery (i.e. sepsis or intense inflammation, see below). Interestingly, infants having a major operation after the second day of life have a significantly greater increase in resting energy expenditure than infants undergoing surgery within the first 48 h of life. A possible explanation for this may be greater secretion of endogenous opioids in the perinatal period blunting the endocrine and metabolic responses.

Resting energy expenditure is directly proportional to growth rate in healthy infants, and growth is retarded during acute metabolic stress. Studies in adult surgical patients have shown that operative stress causes marked changes in protein metabolism characterised by a post-operative increase in protein degradation, negative nitrogen balance and a decrease in muscle protein synthesis. However, changes in whole body protein flux, protein synthesis, amino acid oxidation or protein degradation do not seem to occur in infants and young children undergoing major operations, which led us to speculate that infants and children divert protein and energy from growth to tissue repair, thereby avoiding the overall increase in energy expenditure and catabolism seen in the adult.

8.4.2 Critical Illness and Sepsis

Nutritional problems in infants and children requiring surgery are not unusual. The real nutritional challenge is not represented by the operation *per se* but by the clinical condition of the patient. Examples include intrauterine growth retardation in small-for-gestational age preterm infants, infants who have suffered massive intestinal resection for necrotizing enterocolitis and infants with motility disorders of the intestine following surgery for atresia, malrotation and midgut volvulus, meconium ileus or gastroschisis.

Nutritional integrity particularly in the neonatal period should be maintained regardless of the severity of the illness or organ failure due to the limited energy and protein stores in neonates. Infants and children require nutrition for maintenance of protein status as well as for growth and wound healing. One considerable challenge in paediatrics is represented by nutrition support during critical illness and sepsis. Keshen et al. have shown that parenterally fed neonates on extracorporeal life support are in hypermetabolic and protein catabolic states. These authors recommend the provision of additional protein and non-protein calories to attenuate the net protein losses.

Sepsis is an intriguing pathological condition associated with many complex metabolic and physiological alterations. Studies in adults have shown that the metabolic response to sepsis is characterised by hypermetabolism, increased tissue catabolism, gluconeogenesis and hepatic release of glucose. Energy is largely derived from fat, and increased protein catabolism provides precursors for enhanced hepatic gluconeogenesis. However, fat mobilisation is far greater than fat oxidation, implying considerable cycling, and in later stages of sepsis, oxidative metabolism and fat utilisation may become impaired.

The existing knowledge on the metabolic response to sepsis in infants is limited. There are conflicting reports on whether critically ill infants are hypermetabolic. However, recent studies suggest that infants with sepsis do not become hypermetabolic (Fig. 8.3) and that septic neonates with necrotizing enterocolitis do

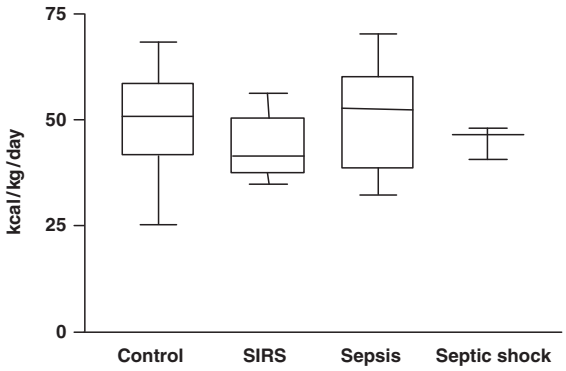

Fig. 8.3 Resting energy expenditure in critically ill infants and controls. Indirect calorimetry was performed on infants and children with systemic inflammatory response syndrome (SIRS), sepsis, septic shock and controls. Results are expressed as median, range and interquartile range. There were no significant differences between the groups (see Turi et al., 2001)

not show any increase in whole body protein turnover, synthesis and catabolism.

From these studies, it is clear that the metabolic rate and hormonal response to surgery, stress and sepsis in infants may well be different from that of adults and therefore it is not possible to adapt nutritional recommendations made for adults to the neonatal population. It is possible that neonates divert the products of protein synthesis and breakdown from growth into tissue repair. This may explain the lack of growth commonly observed in infants with critical illness or sepsis. Further studies are needed in this field to delineate the metabolic response of neonates and children to trauma and sepsis, to explore the relationship between nutrition and immunity and to design the most appropriate diet.

8.5 Parenteral Nutrition

8.5.1 Indications

Parenteral nutrition should be utilised when enteral feeding is impossible, inadequate or hazardous for more than 4–5 days. The most frequent indication in neonatal surgery is intestinal obstruction due to congenital anomalies. Frequently, after an operation on the gastrointestinal tract, adequate enteral feeding cannot be achieved for more than 1 week and parenteral nutrition becomes necessary. This modality of therapy has significantly improved the survival rate of newborns with gastroschisis—a condition that requires intravenous administration of nutrients for 2–3 weeks. Parenteral nutrition is also used in cases of necrotizing enterocolitis, short-bowel syndrome and respiratory distress.

8.5.2 Components of Parenteral Nutrition

The parenteral nutrition formulation includes carbohydrate, fat, protein, electrolytes, vitamins, trace elements and water. The caloric needs for total parenteral nutrition are provided by carbohydrate and lipid. Protein is not used as a source of calories, since the catabolism of protein to produce energy is an uneconomic metabolic process compared to the oxidation of carbohydrate and fat, which produces more energy at a lower metabolic cost. The ideal total parenteral nutrition regimen therefore should provide enough amino acids for protein turnover and tissue growth and sufficient calories to minimise protein oxidation for energy.

8.5.2.1 Fluid Requirements

Any newborn infant deprived of oral fluids will lose body fluids and electrolytes in urine, stools, sweat and evaporative losses from the lungs and the skin. The insensible water losses from the skin are particularly high (up to 80–100 ml/kg/day) in low-birth-weight infants. This is due to the very large surface area relative to body weight, to the very thin and permeable epidermis, to reduced subcutaneous fat and to the large proportion of total body water and extracellular water. The preterm infant requires larger amounts of fluid to replace the high obligatory renal water excretion due to the limited ability to concentrate urine. In surgical newborns, it is not unusual to have significant water losses from gastric drainage and gastrointestinal stoma. In order to reduce the water losses, it is important to use double-walled incubators, to place the infant in relatively high humidity, to use warm humidified air via the endotracheal tube and in premature babies to cover the body surface with an impermeable sheet. However, overhydration is potentially a problem, leading to complications such as pulmonary oedema.

8.5.2.2 Energy Sources

Carbohydrates and fat provide the main energy sources in the diet, and this is reflected by their importance as a source of calories in parenteral nutrition.

Glucose is a main energy source for body cells and is the primary energy substrate in parenteral nutrition. The amount of glucose that can be infused safely depends on the clinical condition and maturity of the infant. The ability of neonates to metabolise glucose may be impaired by prematurity and low birth weight. Conversion of carbohydrate to fat (lipogenesis) occurs when glucose intake exceeds metabolic needs. The risks associated with this process are twofold: accumulation of the newly synthesised fat in the liver and aggravation of respiratory acidosis resulting from increased CO_2 production, particularly in patients with compromised pulmonary function.

Since the 1960s, safe commercial intravenous fat emulsions have become widely used. These preparations have a high caloric value (9 kcal/g of fat), prevent essential fatty acid deficiency and are isotonic, allowing adequate calories to be given via a peripheral vein. A number of studies in both adults and infants have shown that combined infusion of glucose and lipids confers metabolic advantages over glucose, because it lowers the metabolic rate and increases the efficiency of energy utilisation.

It has been shown that in surgical infants receiving parenteral nutrition there is a negative linear relationship between glucose intake and fat utilisation (oxidation and conversion to fat). Net fat synthesis from glucose exceeds net fat oxidation when the glucose intake is greater than 18 g/kg/day (i.e. in excess of energy expenditure) (Fig. 8.4). There is a significant relationship between glucose intake and CO_2 production. The slope of this relationship (i.e. increased CO_2 production) was steeper when glucose intake exceeded 18 g/kg/day than when glucose intake was less than 18 g/kg/day, indicating that lipogenesis results in a significantly increased CO_2 production. More recent studies on stable surgical newborn infants receiving fixed amounts of carbohydrate and amino acids and variable amounts of intravenous long-chain fat emulsion have shown that at a carbohydrate intake of 15 g/kg/day, the proportion of energy metabolism derived from fat oxidation does not exceed 20% even with a fat intake as high as 6 g/kg/day. At a carbohydrate intake of 10 g/kg/day this proportion can be as high as 50%. This study seems to indicate that during parenteral nutrition in surgical infants the majority of the intravenous fat infused is not oxidised but deposited.

Fat tolerance has been extensively studied by monitoring fat clearance from plasma. However, clearance from plasma does not imply that the fat is being utilised to meet energy requirements, since it may be being stored instead. Pierro et al. have studied intravenous fat utilisation by performing a "lipid utilisation test". This consisted of infusing lipid for 4 h in isocaloric and isovolaemic amounts to the previously given mixture of glucose and amino acids. Gas exchange was measured by indirect calorimetry to calculate the patient's O_2 consumption and CO_2 production, and net fat utilisation (Fig. 8.5). The study showed that within 2 h, more

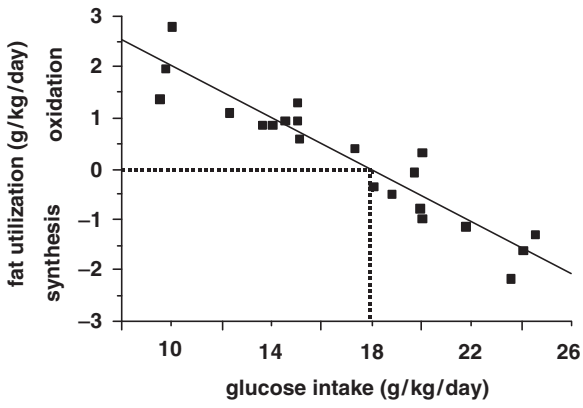

Fig. 8.4 Linear relationship between glucose intake and fat utilization ($r = -0.9$; $p < 0.0001$). Lipogenesis is significant when glucose intake exceeds 18 g/kg/day. (Adapted from Pierro et al., 1993)

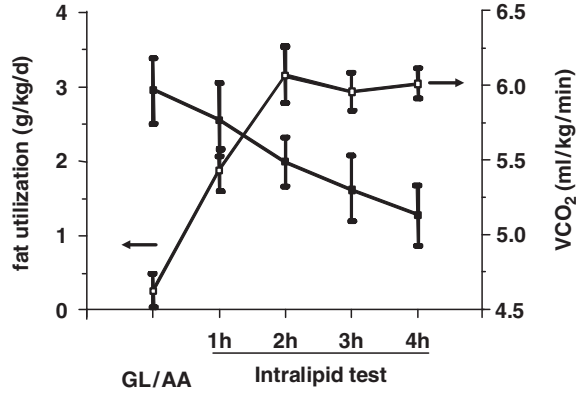

Fig. 8.5 Intralipid utilisation test: surgical newborn infants adapt very rapidly to the infusion of intravenous fat. The oxidation of exogenous fat is associated with a significant reduction in CO_2 production. Fat utilisation open symbols; CO_2 production (VCO_2 closed symbols). (Adapted from Pierro et al., 1989)

than 80% of the exogenous fat can be oxidised and that CO_2 production is reduced during fat infusion as a consequence of the cessation of carbohydrate conversion to fat (lipogenesis).

Net fat oxidation seems to be significantly influenced by the carbohydrate intake and by the resting energy expenditure of the neonate. When the intake of glucose calories exceeds the resting energy expenditure of the infant, net fat oxidation is minimal regardless of fat intake. In order to use intravenous fat as an energy source (i.e. oxidation to CO_2 and H_2O), it is necessary to maintain carbohydrate intake below basal energy requirements. Glucose intake exceeding 18 g/kg/day is also associated with a significant increase in respiratory rate and plasma triglyceride levels. It is advisable therefore in stable surgical newborn infants requiring parenteral nutrition to not exceed 18 g/kg/day of intravenous glucose intake.

Commonly used fat emulsion for parenteral nutrition in paediatrics is based on long-chain triglycerides (LCT). The rate of intravenous fat oxidation during total parenteral nutrition could potentially be enhanced by the addition of L-carnitine and medium chain triglycerides (MCT) to the intravenous diet. L-Carnitine is required for the oxidation of long-chain triglycerides and although it is present in breast milk and infant formula, it is not present in parenteral feeds. Although some authors have found decreased carnitine levels in parenterally fed neonates and reported enhanced fat oxidation upon carnitine supplementation, carnitine levels have to fall extremely low before fatty acid oxidation is impaired and although supplementation has been recommended by some groups, a systematic review found no evidence to support the routine supplementation of parenterally fed neonates with carnitine. MCT are both cleared from the blood-stream and oxidised at a faster rate than LCT, and various studies have suggested that MCT–LCT mixtures in paediatric parenteral nutrition provide benefits over LCT alone. However, randomised controlled trials are necessary before MCT–LCT mixtures find routine use in parenteral nutrition of neonates. We have recently investigated the metabolic response to intravenous medium-chain triglycerides in surgical infants and found that, providing that carbohydrate calories do not exceed energy expenditure, partial replacement of LCT by MCT can increase net fat oxidation without increasing metabolic rate (Fig. 8.6).

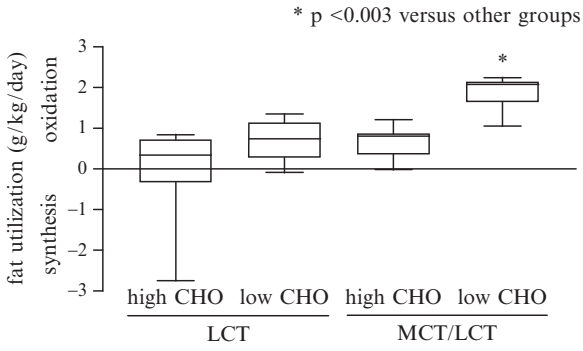

Fig. 8.6 Fat utilisation: a positive value represents net fat oxidation and a negative value represents fat synthesis from carbohydrate. LCT patients received a fat emulsion containing 100% long-chain triglycerides. MCT and LCT patients received a fat emulsion containing 50% medium-chain triglycerides (MCT) and 50% long-chain triglycerides. High carbohydrate (CHO) intake was 15 g/kg/day and low CHO intake was 10 g/kg/day (Reproduced with permission from Donnell et al. 2002)

8.5.2.3 Amino Acids

In contrast to healthy adults who exist in a state of neutral nitrogen balance, infants need to be in positive nitrogen balance in order to achieve satisfactory growth and development. Infants are efficient at retaining nitrogen, and can retain up to 80% of the metabolizable protein intake on both oral and intravenous diets. Protein metabolism is dependent on both protein and energy intake. The influence of dietary protein is well established. An increased protein intake has been shown to enhance protein synthesis, reduce endogenous protein breakdown and thus enhance net protein retention. The protein requirements of newborn infants are between 2.5 and 3.0 g/kg/day. The nitrogen source of TPN is usually provided as a mixture of amino acids. The solutions commercially available contain the eight known essential amino acids and histidine, which is known to be essential in children. Complications like azotemia, hyperammonaemia and metabolic acidosis have been described in patients receiving high levels of intravenous amino acids but rarely seen with amino acid intake of 2–3 g/kg/day. In patients with severe malnutrition or with additional losses (i.e. jejunostomy, ileostomy), protein requirements are higher.

The influence of non-protein energy intake on protein metabolism is more controversial. Protein retention can be enhanced by giving carbohydrates or fat, which are said to be protein sparing. Although some

studies have suggested that the protein sparing effect of carbohydrate is greater than that of fat, others have suggested that the protein sparing effect of fat may be either equivalent to, or greater than, that of carbohydrate. The addition of fat calories to the intravenous diet of surgical newborn infants reduces protein oxidation, protein contribution to the energy expenditure and increases protein retention. In a further study, we compared protein metabolism in two groups of neonates receiving isonitrogenous and isocaloric total parenteral nutrition: one group received a high fat diet and the other, a high carbohydrate diet. There was no significant difference between the two groups with regard to any of the components of whole body protein metabolism: protein synthesis, protein breakdown, protein oxidation and excretion and total protein flux, thus supporting the use of fat in the intravenous diet of surgical newborn infants.

The ideal quantitative composition of amino acid solutions is still controversial. In a newborn infant, cysteine taurine and tyrosine seem to be essential amino acids. However, the addition of cysteine in the parenteral nutrition of neonates does not cause any difference in the growth rate and nitrogen retention.

8.5.2.3.1 Glutamine

Nutrients can modulate immune, metabolic and inflammatory responses. Of these nutrients, glutamine is of particular interest. Glutamine is the most abundant free amino acid in the body where it plays fundamental physiological roles. It is the predominant amino acid supplied to the fetus through the placenta and is normally present in the enteral diet. Glutamine can be synthesised in the human body in substantial amounts and therefore is usually considered to be non-essential. However, in patients with acute and long-term sepsis and trauma, glutamine stores decline. This may be due to a combination of reduced glutamine production, possibly reflecting low muscle glycogen levels, glucose intolerance and increased glutamine utilisation. During sepsis, the liver and the immune system become major glutamine consumers such that net glutamine utilisation exceeds production and glutamine becomes "conditionally essential". In rats, glutamine oxidation supplies a third of the total energy requirement of the gut. In humans who have sustained multi-system trauma or sepsis, glutamine concentration is 15% higher in arterial blood than in portal blood, confirming the selective uptake of glutamine in the gut.

Until recently glutamine has been excluded from parenteral nutrition because of low solubility and instability in solution. However, glutamine dipeptides with improved stability and solubility are now available making it possible to add glutamine to parenteral nutrition formulation. There are several reasons why glutamine may be beneficial for critically ill patients receiving parenteral nutrition. Firstly, glutamine supplementation has been shown to be beneficial, both *in vitro* and *in vivo,* for the immune system. The effect of glutamine supplementation on the prevention of infectious complications has been examined in randomised trials in *adult* patients receiving either glutamine-supplemented parenteral nutrition or isonitrogenous isocaloric parenteral nutrition. These trials included patients undergoing elective operation for colorectal cancer, patients with multiple trauma, critically ill patients and patients undergoing bone marrow transplantation. All these studies showed that parenteral glutamine administration does reduce infectious complications. Secondly, glutamine has multiple effects on gastrointestinal function. Glutamine deficiency leads to gut atrophy and bacterial translocation. Glutamine prevents deterioration of gut permeability, prevents intestinal mucosal atrophy and preserves mucosal structure in patients receiving parenteral nutrition. Reduced nitrogen loss has been demonstrated in adult patients receiving glutamine-supplemented parenteral nutrition after major abdominal operations.

Recent studies have shown that in a neonatal animal model, glutamine reverses the liver dysfunction caused by sepsis due to an increase in the production of glutathione, a major intracellular antioxidant, for which glutamine is an important precursor.

There have been several trials of glutamine parenteral nutrition supplementation in adults. However, a recent Cochrane systematic review has identified only two published randomised controlled trials of glutamine in neonates including one on parenteral nutrition supplementation. This trial did not identify any adverse effects attributable to glutamine. Glutamine administration was associated with a reduced duration of artificial ventilation, hospital admission and parenteral nutrition but effects on immunity or infection and its generalisability to other settings or patient groups remain unclear. The Cochrane Review highlighted the requirement for a large randomised controlled trial of

glutamine supplementation in neonates requiring parenteral nutrition.

8.5.2.4 Vitamins and Trace Elements

Vitamins and trace elements are important cofactors or components of enzymes, and provision of adequate supplies is important for the growing neonate. Vitamins and trace elements are particularly important in maintenance of the body's antioxidant defences: vitamins C and E, selenium (for glutathione peroxidase), copper, zinc and manganese (all for superoxide dismutases) are all added to parenteral nutrition. However, vitamins and trace elements are particularly vulnerable to photoxidation and loss or to increase lipid peroxide production, and various studies have suggested photoprotection of parenteral nutrition bags in order to minimise losses and peroxide generation. Free radical production and lipid peroxidation will be considered in more detail below.

8.5.3 Complications of Parenteral Nutrition

8.5.3.1 Infectious Complications

In spite of significant improvement in the management of parenteral nutrition including the introduction of nutrition support teams, recently published infection rates from large children's hospitals indicate that between 5% and 37% of infants may develop sepsis while receiving parenteral nutrition. This may lead to impaired liver function, critical illness and removal of central venous catheters. It has always been assumed that the central venous catheter is the major portal of entry for micro-organisms causing septicaemia in patients on parenteral nutrition. However, studies in animals and surgical neonates have reported microbial translocation (migration of micro-organisms from the intestinal lumen to the systemic circulation) during parenteral nutrition. In a study on surgical neonates on parenteral nutrition, all but one episode of microbial translocation occurred in patients with elevated serum bilirubin (cholestasis). Pierro et al. have reported that almost half the surgical infants on parenteral nutrition develop abnormal flora and that all cases of septicaemia were preceded by gut colonisation with abnormal flora. Furthermore, it has been reported that parenteral nutrition itself impairs host defence mechanisms and contributes to the occurrence of infection in neonates. This may be due to individual components of the parenteral nutrition solution, such as lipid emulsion, or due to a lack of nutrients, such as glutamine, normally present in the enteral diet.

Important factors in reducing the incidence of septic complications are placing intravenous catheters under strict aseptic conditions, preparing the parenteral nutrition solutions in pharmacy in aseptic conditions and using meticulous care when the catheters are used. Sepsis should be suspected when infants on parenteral nutrition present clinical features of generalised inflammation including one or more of the following features: temperature instability, poor perfusion, hypotension, lethargy, tachycardia, respiratory distress and fever. In these neonates, blood culture should be performed from the central venous line and from a peripheral vein.

8.5.3.2 Metabolic Complications

The metabolic complications most frequently observed in newborn infants receiving parenteral nutrition are listed in Table 8.1. These complications are related to inappropriate administration of nutrients, fluid, electrolytes and trace elements or to the inability of the individual patient to metabolise the intravenous diet.

Hyperglycaemia occurs frequently during the course of parenteral nutrition, particularly while the glucose concentration of the infusate is being increased, but most patients will produce adequate endogenous insulin to metabolise the carbohydrate load within hours. The treatment of symptomatic hyperglycaemia is usually by reduction of the infusion rate. Hypoglycaemia usually results from sudden interruption of an infusion containing a high glucose concentration.

High doses of fat or an accidental rapid infusion of fat may lead to fat overload syndrome, characterised by an acute febrile illness with jaundice and abnormal coagulation. The intravenous administration of fat emulsion in premature infants seems to increase the incidence of bronchopulmonary dysplasia and retinopathy. Peroxidation in stored fat emulsions and the generation of free radicals during intravenous infusion of fat in premature infants have been reported.

Table 8.1 Metabolic complications of TPN

Carbohydrate administration
Hyperglycaemia
Hypoglycaemia
Fatty infiltration of the liver
Hyperosmolarity and osmotic diuresis
Increased CO_2 production
Protein administration
Hyperammonaemia, azotemia
Abnormal plasma amino acid profiles
Hepatic dysfunction
Cholestatic jaundice
Fat administration
Hyperlipidaemia
Fat overload syndrome
Displacement of albumin-bound bilirubin by free fatty acids
Peroxidation and generation of free radicals
Fluid administration
Patent ductus arteriosus
Pulmonary oedema
Electrolyte imbalance
Sodium, potassium, chlorine, calcium, phosphate
Trace element and vitamin deficiency

The release of free radicals may overwhelm the endogenous protective mechanisms, resulting in cellular damage (see below).

8.5.3.3 Mechanical Complications

Mechanical complications related to the intravenous infusion of nutrients are not uncommon. Table 8.2 lists the mechanical complications reported in the literature. Extravasation of parenteral nutrition solution is a common complication of peripheral parenteral nutrition. Unfortunately, even a low osmolarity solution is detrimental for peripheral veins leading to inflammation and extravasation of the solution, which can cause tissue necrosis and infection. Intravenous lines may become clogged from thrombus formation, calcium precipitates or lipid deposition. There is disagreement on the ideal position of central venous lines (CVL) for parenteral nutrition in infants. Some authors advocate the atrium as the ideal position because this would give less chance of catheter dysfunction. Others believe that placement in the superior vena cava would reduce the risk of perforation. In a survey of 587 CVL inserted in neonates, cardiac tamponade was the cause of death in two neonates (0.3%). In most of the cases reported in the literature of cardiac tamponade following CVL insertion, the perforation was thought to be in the right atrium.

Table 8.2 Mechanical complications of parenteral nutrition

Extravasation of parenteral nutrition solution
Blockage of the central venous line
Migration of the central venous line
Breakage of the infusion line
Right atrium thrombosis
Cardiac tamponade (perforation of right atrium or vena cava)

8.5.3.4 Hepatic Complications

The hepatobiliary complications related to parenteral nutrition remain serious and often life threatening. The commonest hepatobiliary complication of parenteral nutrition in surgical neonates is cholestasis. The incidence of parenteral nutrition-related cholestasis varies widely from as low as 7.4% to as high as 84%. Although the frequency of this complication seems to be diminishing, this is probably related to the early initiation of oral feeding rather than to an improvement in the intravenous diet. The aetiology of cholestatic jaundice in infants requiring parenteral nutrition is still unclear. However, infants requiring long-term parenteral nutrition still develop progressive jaundice, commonly preceded by elevation of biochemical non-specific tests of hepatic damage, function and excretion.

Various clinical factors are thought to contribute to the development of parenteral nutrition-related cholestasis (Table 8.3). These include prematurity, low birth weight, duration of parenteral nutrition, immature entero-hepatic circulation, intestinal microflora, septicaemia, failure to implement enteral nutrition and number of operations. Parenteral nutrition-related cholestasis has a higher incidence in premature infants than in children and adults. This may be due to the immaturity of the biliary secretory system since bile salts pool size, synthesis and intestinal concentration are low in premature infants in comparison with full-term infants. Parenteral nutrition-related cholestasis is a diagnosis of exclusion without any specific marker yet available. Therefore, infants with cholestasis who are receiving or have received parenteral nutrition must have an appropriate diagnostic evaluation to exclude other causes of cholestasis. These include bacterial and viral infections, metabolic diseases and congenital anomalies. Gall bladder sludge, which can progress to

Table 8.3 Patient risk factors for the development of parenteral nutrition-related cholestasis

Age
Prematurity
Immaturity of biliary secretory system
Absence of oral or enteral intake
Septicaemia
Bacterial overgrowth in the small bowel
Short bowel length
Necrotising enterocolitis
Hypoxia
Major abdominal operations
General anaesthesia

"sludge balls" and gallstones, appeared in 18 neonates (44%) after a mean period of 10 days of parenteral nutrition. The cholestasis is progressive unless parenteral nutrition is ceased and enteral feeding introduced. Hepatosplenomegaly and severe jaundice are characteristic features of the advanced disease, and portal hypertension may develop. Although parenteral nutrition-related cholestasis resolves with time after discontinuation of parenteral nutrition, in a small percentage of cases it remains intractable and progresses to severe hepatic dysfunction and death.

The aetiology of parenteral nutrition-related cholestasis remains unclear. Possible causes include the toxicity of components of parenteral nutrition, lack of enteral feeding, continuous non-pulsatile delivery of nutrients and host factors. Most of the components of parenteral nutrition have been implicated in the pathogenesis of cholestasis. Hepatic damage from the components of intravenous diet may result from excessive nutrient administration, deficient nutrient administration, toxicity of by-products and abnormal metabolism in the neonate.

The clinical care of infants and children who require parenteral nutrition and develop progressive jaundice represents a real challenge, compounded by this lack of knowledge. Prevention of parenteral nutrition-related cholestasis is based on the early usage of enteral feeding and on the administration of intravenous feeding only when appropriate and necessary. In most patients the cholestasis resolves gradually as enteral feedings are initiated and parenteral nutrition is discontinued. It has been recently shown that minimal bolus enteral feeding (1 ml/kg) during parenteral nutrition in premature infants induces significant gall bladder contraction and after 3 days of starting minimal enteral feeds, the gallbladder volume returns to normal. Unfortunately, as a consequence of gut dysfunction, enteral feeding is often not feasible. It has been suggested that cycling the parenteral nutrition may diminish cholestatic hepatic changes in adults. This may explain the less frequent liver disease in children receiving their parenteral nutrition cyclically at home. Experience with this technique in premature infants is extremely limited but encouraging. Rebound hypoglycaemia is a common complication of this approach. Modification of the parenteral nutrition constituents has been proposed but no prospective trial has demonstrated any benefit in reducing or changing the intake of nutrients.

Several reports have described the attempts to use drug therapy to treat or prevent parenteral nutrition-related cholestasis. Cholecystokinin has been administered to diminish the gallbladder stasis and promote bile flow. It has been demonstrated in a randomised, double-blind controlled study in adults receiving parenteral nutrition that cholecystokinin given intravenously daily prevents stasis and sludge in the gallbladder. Rintala et al. reported the reversal of parenteral nutrition-related cholestasis in seven infants by intravenous administration of cholecystokinin; however, all the patients except one were completely weaned from parenteral nutrition before the treatment with cholecystokinin. Teitelbaum et al. conducted a prospective trial of cholecystokinin in the prevention of parenteral nutrition-related cholestasis; however, the patients were consecutive rather than randomised and there is a need for a randomized controlled trial of cholecystokinin in administration to neonates on parenteral nutrition.

Ursodeoxycholic acid can be used in infants and children on parenteral nutrition to correct the decreased secretion of endogenous bile acids. Ursodeoxycholic acid is non-toxic and acts as a natural bile acid after conjugation. Although there have been limited trials of the use of ursodeoxycholic acid in preterm neonates on TPN, results were inconclusive.

Cholecystectomy is the treatment of choice for patients with acute and symptomatic cholelithiasis and cholecystitis. Some authors proposed laparotomy and operative cholangiography followed by biliary tract irrigation in patients with progressive cholestatic jaundice not responding to medical treatment. In some patients the hepatic disease may progress to cirrhosis, portal hypertension and hepatic failure. In selected cases small bowel and liver transplantation have been used. The introduction of tacrolimus has allowed clinical intestinal transplantation to become feasible. However,

infectious and immunological problems still cause significant morbidity and mortality, even 1–3 years after transplantation.

8.5.3.5 Free Radicals and Parenteral Nutrition

Free radicals are highly reactive short-lived species in possession of an unpaired electron, and are produced during many physiological processes. When neutrophils and macrophages engulf foreign particles, the particle is exposed to superoxide and hydroxyl radicals and a variety of other reactive compounds during the so-called "respiratory burst," which occurs as the white cell destroys the bacteria. Intracellular and extracellular antioxidants protect against uncontrolled free radical activity. These include enzymes (e.g. superoxide dismutase, catalase, glutathione peroxidase) and chemical antioxidants such as vitamins E and C. A pathologic increase in free radical activity may occur when the normal balance between free radical formation and protective antioxidant activity becomes altered and free radicals can then attack and damage cells and tissues. TPN may exacerbate free radical activity in newborn infants by providing (1) the substrates for free radical production (polyunsaturated fatty acids), (2) the initiators of free radical reactions (carbon centred radicals derived from fatty acids) and (3) the catalysts (transition metal ions) for chain reactions. However, TPN also provides (1) vitamins C and E (antioxidants), (2) metal ions that are important components of antioxidant enzymes (Cu, Zn Mn, Se) and (3) amino acids that are components of glutathione, and important intracellular antioxidant. An increased generation of free radicals during total parenteral nutrition (TPN) in premature infants was reported. Bronchopulmonary dysplasia and retinopathy in premature infants are associated with fat infusions, and these conditions have been linked to free radical-mediated cell damage. Reducing the exposure of premature infants to any unnecessary source of oxidative stress would be desirable. To this end it has been suggested that the use of intravenous fat infusion should be restricted; however, we have shown that a reduction in the carbohydrate to fat ratio in PN diet will result in increased oxidation of administered fat and a decrease in free radical-mediated lipid peroxide formation (Fig. 8.7). It is interesting to note that the decrease in MDA accompanying increased fat utilisation was of a similar magnitude to

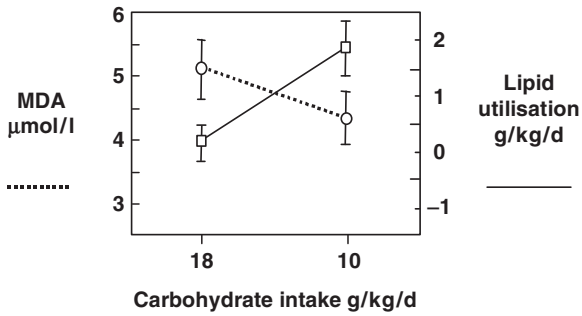

Fig. 8.7 Free radical production (assessed as plasma malondialdehyde, MDA, concentration) in response to different carbohydrate contents of PN (Data from Basu et al. 1999a)

that observed when the fat infusion was discontinued. Therefore, it is not necessary to discontinue the infusion of fat to reduce the production of oxygen-derived free radicals. Manipulation of the carbohydrate to fat ratio therefore may be a powerful tool in changing the metabolism of fat infusions to mitigate their toxic effects while allowing continued administration.

8.6 Enteral Nutrition

The energy requirement of an infant fed enterally is greater than the intravenous requirement because of the energetic cost of absorption from the gastrointestinal tract and energy lost in the stools. Even small amounts of enteral feeding allow the preservation of normal intestinal villi and the maintenance of the epithelial barrier function. Clinical and laboratory studies have shown that enteral feeding is associated with less infectious and immunological complications than parenteral nutrition. Patients receiving total enteral feeding experience significantly fewer septic complications than patients on parenteral and enteral nutrition. Kudsk et al. showed that enteral feeding improved survival after *Escherichia coli* peritonitis in both malnourished and well-nourished rats, compared with rats receiving total PN. The reason for these findings remains poorly understood. However, enteral feeding may act by stimulating more effective immune response. Enternal feeding in a rodent model maintains normal biliary concentrations of secretory IgA (S-IgA), which is an important component of mucosal immunity. In contrast, total parenteral nutrition decreases the biliary levels of this immunogloblin. Furthermore, it has been demonstrated that the level of

TNF-α in peritoneal lavage fluid was higher in enterally fed rats than in rats receiving total PN after 2 h peritoneal bacterial challenge. TNF-α, which is mainly produced by macrophages and lymphocytes, is an important factor in the activation of neutrophils, macrophages and lymphocytes and may therefore be required for effective eradication of bacterial infections.

In surgical infants, enteral feeding often results in vomiting, interruption of feeding, inadequate calorie intake and rarely in necrotizing enterocolitis. In infants with congenital gastrointestinal anomalies, exclusive enteral feeding is commonly precluded for some time after surgery due to large gastric aspirate and intestinal dysmotility. Therefore, appropriate calorie intake is established initially by total parenteral nutrition. Supplementary enteral feeding is introduced when intestinal motility and absorption improves. The percentage of calories given enterally is gradually increased at the expense of intravenous calorie intake. This transition time from total parenteral nutrition to total enteral feeding could be quite long. The presence of significant gastric aspirate often induces clinicians and surgeons not to use the gut for nutrition. However, minimal enteral feeding can be implemented early in these patients even if its nutritional value is questionable. Minimal enteral feeding may be all that is required to enhance some immunological function. This is supported by studies in animals and infants. Shou et al. reported that supplementation of parenteral nutrition with just 10% enteral calories as chew diet improved rat macrophage and splenocyte function, and the introduction of small volumes of enteral feed improved the impaired host bactericidal activity against coagulase negative staphylococci and the abnormal cytokine response observed during total parenteral nutrition. The increase in bactericidal activity against coagulase negative staphylococci after the addition of small enteral feeds in patients on parenteral nutrition was significantly correlated with the duration of enteral feeding. This implies that stimulation of the gastrointestinal tract may modulate immune function in neonates and prevent bacterial infection.

8.6.1 Feeding Routes

Oral feeding is the preferred modality of feeding with breast-feeding being the most physiological up to 6 months of age. Surgical infants do not always tolerate oral feeding due to prematurity, critical illness, abnormalities of the swallowing mechanism, oesophageal dysmotility, gastro-oesophageal reflux or gastric outlet obstruction. Alternative feeding routes in these clinical situations include naso-gastric or oro-gastric tubes, naso-jejunal tubes, gastrostomy tubes or jejunostomy tubes.

Gastric feeding is preferable to intestinal feeding because it allows for a more natural digestive process. In addition, gastric feeding is associated with a larger osmotic and volume tolerance and a lower frequency of diarrhoea and dumping syndrome. Neonates are obligatory nose breathers and therefore oro-gastric feeding is preferable over naso-gastric feeding in preterm infants to avoid upper airway obstruction.

In surgical infants requiring gastric tube feeding for more than 6–8 weeks, it is advisable to insert a gastrostomy tube. The tube can be inserted using an open, endoscopic or laparoscopic approach. In infants with significant gastro-oesophageal reflux, fundoplication with gastrostomy tube or enterostomy tube placement is indicated. In preterm infants with gastro-oesophageal reflux, enteral feeding can be established via a naso-jejunal tube inserted under fluoroscopy. Naso-jejunal feeding usually minimise the episodes of gastro-oesophageal reflux and their consequences. However, it is common for these tubes to dislocate back in the stomach. Regular analysis of the pH in the aspirate is essential to monitor the correct position of the tube. Feeding jejunostomy tubes can be inserted through existing gastrostomy or directly into the jejunum via laparotomy or laparoscopy.

8.6.2 Selection of Enteral Feeds

Breast milk is the ideal feed for infants because it has specific anti-infectious activities that protect them from gastrointestinal and respiratory diseases. In addition, breast milk has high content of non-protein metabolizable nitrogen notably urea. When breast milk is not available chemically defined formulae can be used. If malabsorption persists, an appropriate specific formula should be introduced. A soya-based disaccharide-free feed is used when there is disaccharide intolerance resulting in loose stools containing disaccharides. For fat malabsorption, a formula containing medium-chain triglycerides (MCT) should be used. An elemental formula may be indicated when

there is severe malabsorption due to short bowel syndrome or severe mucosal damage as in necrotising enterocolitis. Infants recovering from neonatal necrotising enterocolitis pose a particular problem, as malabsorption may be severe and prolonged. These infants may have had small bowel resected, in addition to which the remaining bowel may not have healed completely by the time feeds are begun. Feeding may provoke a relapse of the necrotising enterocolitis and feeding should therefore be introduced cautiously. Elemental formula preparations contain amino acids, glucose and fats, including MCTs. Dipeptide preparations that include dipeptides as well as amino acids have the advantage of a lower osmolality, are well absorbed and have a more palatable taste.

For persistent severe malabsorption, a modular diet may be necessary. Glucose, amino acid and MCT preparations are provided separately, beginning with the amino acid solution and adding the glucose and then the fats as tolerated. Minerals, trace elements and vitamins are also added. These solutions have high osmolality and if given too quickly may precipitate dumping syndrome, with diarrhoea, abdominal cramps and hypoglycaemia. It is important therefore to start with a dilute solution and increase the concentration and volume of each component slowly. This may take several weeks and infants will need parenteral nutritional support during this period.

8.6.3 Administration of Enteral Feeds

Enteral feeds can be administered as boluses, continuous feeds or as a combination of the two. Bolus feeds are more physiological and are known to stimulate intestinal motility, enterohepatic circulation of bile acids and gallbladder contraction. They mimic or supplement meals and are easier to administer than continuous feeds since a feeding pump is not required. Bolus feeds are usually given over 15–20 min and usually every 3 h. In preterm neonates or in neonates soon after surgery, 2-hourly feeds are occasionally given.

Continuous feeds should be administered via an infusion pump. This modality of feeding is used in infants with gastro-oesophageal reflux, delayed gastric emptying or intestinal malabsorption. Infants with a jejunal tube should receive continuous feeds and not bolus feeds. Continuous feedings are usually given over 24 h. Term infants can tolerate a period of 4 h without feeds before hypoglycaemia occurs. This modality of tube feeding can be very advantageous; however, there is evidence to suggest that normal physiology may be altered when this approach is adopted. Continuous enteral feeding leads to an enlarged, non-contractile gallbladder in infants. Contraction is observed immediately after resuming bolus enteral feeds and gallbladder volume returns to baseline after 4 days. Therefore the mode of feeding has important bearings on the motility of the extrahepatic biliary tree. Studies in adults have reported biliary sludging in patients receiving continuous enteral nutrition, implying gallbladder stasis. In one study, the sludge cleared within 2 weeks of starting bolus oral feeds. This complication has not been reported in infants or children undergoing continuous enteral feeding. In preterm infants, continuous enteral feedings are associated with lower energy expenditure and better growth compared with bolus feedings.

8.6.4 Complications of Enteral Tube Feeding

Enteral tube feeding is associated with fewer complications than parenteral feeding. The complications can be mechanical including tube blockage, tube displacement or migration and intestinal perforation. Other complications involve the gastrointestinal tract. These include gastro-oesophageal reflux with aspiration pneumonia, dumping syndrome and diarrhoea. Jejunostomy tubes inserted at laparotomy can also be associated with intestinal obstruction. The use of hyperosmolar feeds has been associated with development of necrotizing enterocolitis, dehydration and rarely intestinal obstruction due to milk curds.

Further Reading

Basu R, Muller DPR, Eaton S, Merryweather I, Pierro A (1999a) Lipid peroxidation can be reduced in infants on total parenteral nutrition by promoting fat utilisation. J Pediatr Surg 34:255–259

Donnell SC, Lloyd DA, Eaton S, Pierro A (2002) The metabolic response to intravenous medium-chain triglycerides in infants after surgery. J Pediatr 141:689–694

Pierro et al (1991) Partition of energy metabolism in the surgical newborn. J Pediatr Surg 26:581–586

Pierro A, Jones MO, Hammond P, Nunn A, Lloyed DA (1993) Utilisation of intravenous fat in the surgical newborn infant. In Proceedings of the Nutrition Society. In vol 52, p 237A

Pierro A, Camielli V, Filler RM, Smith J Heim T (1989) Metabolism of infravenous fat emulsion in the surgical newborn. J Pediatr surg 24:95–101

Puri P, Höllwarth ME (eds) (2006) Pediatric Surgery. Springer, Berlin, Heidelberg

Turi RA, Petros A, Eaton S et al (2001) Energy metabolism of infants and children with systemic inflammatory response syndrome and sepsis. Ann Surg 233:581–587