INTRODUCTION

Parenteral nutrition (PN) came of age in 1964 with the demonstration that beagle puppies could be nourished successfully from 12 weeks of age to maturity by providing all nutrients intravenously (1). The first total parenteral nutrition of an infant with extreme short bowel syndrome followed in 1967 (1). Since then many lessons have been learned as a result of complications of PN. These have included nutrient deficiencies and excesses, infections, complications of inadequate or excessive energy and protein intake, liver disease, and toxicities from product contamination. Our patients have paid the price for these lessons, but fortunately improved survival has also resulted. These incidents have reinforced to us the physicians the axiom that “good judgment comes from experience . . . and experience comes from bad judgment.” (2). Along the way we have learned much about nutrition, infection, liver pathophysiology, and child development (e.g., yes, infants really can “unlearn” how to suck and swallow). Have we learned so much that administration of PN can now be placed on autopilot?

The question posed to the authors when this review was solicited was whether the art and science of PN had reached the stage where administration could be treated as a routine clinical algorithm such as diarrhea or croup. Do we only need to check the weight, calculate the administration rate and check the box next to “Standard Child Solution” on the PN pharmacy order sheet? Is there really anything new in PN?

Our immediate reaction was to take offense, feel hurt, and shake our heads in disbelief that anyone could be so foolish as to think such things. However, as we thought about it, we realized that the question is pertinent and perceptive. Like the clinical pathways set out for common illnesses such as diarrhea and croup, the question is not so much how to follow the roadmap but rather, when not to follow it. Thus, our review will focus on two areas: 1) Common misconceptions surrounding the use of PN; and 2) When should “standard PN” (i.e., checking the weight and the box on the order sheet) not be used. These questions have lead us to review recent developments in PN (in the past 5–7 years). Whenever possible we will take an evidenced-based approach to the data. Unless specified, the studies we will discuss were carried out in pediatric patients. The risk of any review is that it is old hat to some and very new to others. We have done our best to strike a middle ground. Because it could be a subject unto itself, we will not review PN-associated cholestasis, although when pertinent, some comments will be made.

Energy Requirements, Energy Sources, and the Consequences of Overfeeding

Estimating the appropriate energy intake is a fundamental step in prescribing PN. Although we have long acknowledged the risks of underfeeding our patients, more recently we have come to reevaluate energy requirements in particular clinical scenarios and to appreciate the problems associated with excessive energy intake.
Energy Requirements

A few terms must be defined in order to discuss energy expenditure (3). Basal metabolic rate is the energy expenditure of a recumbent child or adult in a thermoneutral environment after a 12- to 18-hour fast just when the individual has awakened but before daily activities have commenced. Basal metabolic rate is a reflection of the energy expenditure required for vital processes. Resting energy expenditure refers to the energy expenditure of a person at rest in a thermoneutral environment. Basal metabolic rate and resting energy expenditure usually do not differ by more than 10% (3). Total energy expenditure is the sum of requirements for basal metabolism, thermic effect of ingested food, thermoregulation, and activity. In older children, activity accounts for a large proportion of total energy expenditure. Thus, the total energy expenditure of a child who is hospitalized and lying in bed is reduced.

Historically, it has been thought that the surgical patient requires an energy intake proportional to the severity of the illness. By definition, the energy intake would be increased compared with that of a “non-stressed” patient. However, from a practical standpoint this concept does not seem to be the case as the increased energy expenditure is short-lived. For example, although newborns have a 20% increase in resting energy expenditure after major surgery, this elevation returns to baseline within 12-24 hours (4). Infants who remain critically ill and require PN also do not appear to require increased energy intakes. Jaksic et al. measured energy expenditure in eight non-ventilated surgical neonates (gastrochisis, atresia, volvulus) on postoperative day 16 (± 12, SD) and compared them with ten infants on extracorporeal life support studied at 7 ± 3 days of age (5). There were no differences in energy expenditure between the groups (53 ± 5 vs. 55 ± 20 kcal · kg⁻¹ · d⁻¹) (5). This level of energy expenditure is comparable to that of “non-stressed” infants (see below). The similarity in energy expenditure was present despite the finding that IL-6 and C-reactive protein levels were significantly greater in the extracorporeal life support group reflecting an increased degree of illness, and ultimately, mortality (30% vs. 0) (5). This same group of investigators recently has shown that preterm infants (25 weeks gestation) behave similarly (6).

Lloyd recently reviewed the data regarding energy requirements in surgical newborns and children (7). The evidence reveals that the increase in energy expenditure associated with surgery only lasts for 24 hours after the procedure (7). Estimating energy expenditure during the first 24 hours after surgery will overestimate the energy requirements for the entire postoperative period, potentially resulting in excess energy intake with its potential consequences (see below).

Energy requirements also have been examined in non-operated children in the intensive care unit. In a group of mechanically ventilated critically ill children (N = 33; 6 ± 5 years of age) whose mean length of stay in the intensive care unit was approximately 2 weeks, measured energy expenditure was only about 8 kcal · kg⁻¹ · d⁻¹ (17%) above expected based on more recent data (8,9). Joosten et al. found even smaller increases in energy expenditure in a more heterogeneous group of 36 infants and children in an intensive care unit (10). Finally, Turi et al. measured energy expenditure in 21 patients in the intensive care unit with systemic inflammatory response syndrome or sepsis and compared their energy expenditure to a group of hospitalized control children (11). No differences were noted between the groups (11).

Taken together, these data support the idea that in most cases there is little need to provide post operative or critically ill infants and children with much more than their resting energy expenditure, which in most cases will be an amount similar to their basal metabolic rate. The information in Table 1 can be used to calculate basal metabolic rate in normal children (9). A recent report by Duro et al. used the Enhanced Metabolic Testing Activity Chamber (EMTAC) to predict REE in 50 normal infants up to 7 months of age with a maximum weight of 9 kg (12). Their data suggest that for this age group the values of Shofield may be an underestimation (9,12). However, part of this difference may be explained by the fact that the values for Shofield are for BMR and those of Duro et al. are for REE (9,12). The equations described by Duro et al. are:

REE (kcal/d) = [84.5 x Weight (kg)] – 117.33
(R² = 0.65, P < 0.01)

The prediction is improved somewhat by including length:

REE (kcal/d) = [10.12 x Length (cm)]
+ [61.02 x Weight (kg)] – 605.08
(R² = 0.7, P < 0.01)

It is evident in the study by Jaksic et al. that there may be significant interindividual variations in energy expenditure (5,7). This should not be surprising, as even among normal newborns energy requirements do not fall within narrow margins (13). White et al. have shown that in pediatric intensive care unit patients that there is little within-day variation in energy expenditure but day-to-day variation is as high as 21 ± 16% (mean ± SD) (14).

Ideally, energy expenditure should be measured in critically ill patients. However, it may not be practical because of the expensive equipment and the expertise required. At the very least, one should be flexible regarding the “appropriate” energy intake and monitor the patient for weight gain (fluid vs. tissue) and evidence of overfeeding (e.g., CO₂ production; see below). Two recent studies may be of value in calculating resting energy expenditure for surgical infants and intensive care patients.
TABLE 1. Equations for estimating basal metabolic rate (MJ/day)*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>0.249 wt − 0.127</td>
<td>0.244 wt − 0.130</td>
</tr>
<tr>
<td>&lt;3</td>
<td>0.007 wt + 6.349 L − 2.584</td>
<td>0.068 wt + 4.281 L − 1.730</td>
</tr>
<tr>
<td>3-10</td>
<td>0.095 wt + 2.110</td>
<td>0.085 wt + 2.033</td>
</tr>
<tr>
<td>10-18</td>
<td>0.074 wt + 2.754</td>
<td>0.056 wt + 2.898</td>
</tr>
<tr>
<td>18-30</td>
<td>0.063 wt + 2.896</td>
<td>0.062 wt + 2.036</td>
</tr>
</tbody>
</table>

* Notes:
1. To convert to kcal/day multiply by 239
2. Wt = weight in kilograms
3. L = Length in meters. Only predictions for children <3 years of age are improved by including length in the equation.

From (9).

Using indirect calorimetry and a number of covariates in a group of surgical infants, Pierro et al. developed the formula shown below to calculate energy expenditure (15,16).

Resting energy expenditure (kcal/d) = −74.436 + [34.661 x weight (kg)] + [0.496 x heart rate (beats/min)] + [0.178 x age (days)] x [1.44]

The prediction has an error of −0.95 ± 3.65%; an R² = 0.85; and a P < 0.00001

White et al devised the following formula for estimating energy expenditure in intensive care patients (17):

Energy expenditure (kcal/day) = [(17 x age in months) + (48 x weight in kg) + (292 x body temperature in °C) − 9677] x [0.239] (R² = 0.867)

Obese adolescents are an exception to the basal metabolic rate calculations provided in Table 1. The basal metabolic rate for obese children can be calculated as follows (18):

For Boys: BMR = [16.6 x weight (kg)] + [77 x height (meters)] + 572
For Girls: BMR = [7.4 x weight (kg)] + [482 x height (m)] + 217

The clinical significance of energy expenditure, particularly in the critically ill patient, also has an impact on the timing of PN initiation. If very ill patients are going to be “hypermetabolic”, available data suggest that it will be early in the disease process. PN administration itself increases metabolic rate (19,20). The more malnourished the patient, the greater the stimulatory effect of PN on metabolic rate (20). Thus, administration of PN which provides all nutritional requirements should be avoided in the first couple of days of a patient’s critical illness, as it will further increase the metabolic rate and do little to stem the protein catabolic response to the illness. An exception is the preterm infant. PN is required after birth because of the premature infant’s limited nutritional stores (21). A recent randomized controlled study compared preterm infants (27 weeks gestational age, N = 125) receiving PN on the first day of life to those in whom it was started in the first few days of life and advanced more slowly (22). Infants in the early PN group had fewer infections during hospitalization and were more likely to be above the 10th percentile for weight or height at the time of discharge (22).

Energy Sources

There is controversy around the choice of nutrients to provide energy requirements via PN. There are glucose advocates, lipid believers, and argument as to whether protein (i.e., amino acids) should be counted as part of the total administered energy. At the expense of over-simplification and wounding the true believers in each camp (the authors are active participants in these controversies), we submit that a few basic principles can be agreed upon. 1) There is a minimum amount of glucose that must be provided in order to prevent hypoglycemia and a maximum that results in the production of excessive CO₂ and/or hepatic steatosis (see below); 2) There is a minimum requirement (both dose and frequency) for intravenous fat emulsion to prevent essential fatty acid deficiency but a maximum beyond which intravenous fat may have deleterious effects; and 3) Amino acids must be provided in adequate amounts to prevent hypoproteinaemia but there are adverse consequences of giving an excess. Both the size and the age of the pediatric patient are important in determining the appropriate quantities of glucose, fat and amino acids administered in PN.

Glucose

Estimates of glucose utilization by the brain are shown in Table 2 (23). These estimates vary with age and, at first glance, reflect the minimum amount of glucose that must be provided to prevent hypoglycemia (23). Some investigators have argued that gluconeogenesis provides a significant amount of glucose (even in preterm infants) and suggest that not all the glucose shown in Table 2 need be provided exogenously (24,25). However, these estimates are limited nutritional stores (21). A recent randomized controlled study compared preterm infants (27 weeks gestational age, N = 125) receiving PN on the first day of life to those in whom it was started in the first few days of life and advanced more slowly (22). Infants in the early PN group had fewer infections during hospitalization and were more likely to be above the 10th percentile for weight or height at the time of discharge (22).

Energy Sources

There is controversy around the choice of nutrients to provide energy requirements via PN. There are glucose advocates, lipid believers, and argument as to whether protein (i.e., amino acids) should be counted as part of the total administered energy. At the expense of over-simplification and wounding the true believers in each camp (the authors are active participants in these controversies), we submit that a few basic principles can be agreed upon. 1) There is a minimum amount of glucose that must be provided in order to prevent hypoglycemia and a maximum that results in the production of excessive CO₂ and/or hepatic steatosis (see below); 2) There is a minimum requirement (both dose and frequency) for intravenous fat emulsion to prevent essential fatty acid deficiency but a maximum beyond which intravenous fat may have deleterious effects; and 3) Amino acids must be provided in adequate amounts to prevent hypoproteinaemia but there are adverse consequences of giving an excess. Both the size and the age of the pediatric patient are important in determining the appropriate quantities of glucose, fat and amino acids administered in PN.

Glucose

Estimates of glucose utilization by the brain are shown in Table 2 (23). These estimates vary with age and, at first glance, reflect the minimum amount of glucose that must be provided to prevent hypoglycemia (23). Some investigators have argued that gluconeogenesis provides a significant amount of glucose (even in preterm infants) and suggest that not all the glucose shown in Table 2 need be provided exogenously (24,25). However, these estimates are limited nutritional stores (21). A recent randomized controlled study compared preterm infants (27 weeks gestational age, N = 125) receiving PN on the first day of life to those in whom it was started in the first few days of life and advanced more slowly (22). Infants in the early PN group had fewer infections during hospitalization and were more likely to be above the 10th percentile for weight or height at the time of discharge (22).

Energy Sources

There is controversy around the choice of nutrients to provide energy requirements via PN. There are glucose advocates, lipid believers, and argument as to whether protein (i.e., amino acids) should be counted as part of the total administered energy. At the expense of over-simplification and wounding the true believers in each camp (the authors are active participants in these controversies), we submit that a few basic principles can be agreed upon. 1) There is a minimum amount of glucose that must be provided in order to prevent hypoglycemia and a maximum that results in the production of excessive CO₂ and/or hepatic steatosis (see below); 2) There is a minimum requirement (both dose and frequency) for intravenous fat emulsion to prevent essential fatty acid deficiency but a maximum beyond which intravenous fat may have deleterious effects; and 3) Amino acids must be provided in adequate amounts to prevent hypoproteinaemia but there are adverse consequences of giving an excess. Both the size and the age of the pediatric patient are important in determining the appropriate quantities of glucose, fat and amino acids administered in PN.

Glucose

Estimates of glucose utilization by the brain are shown in Table 2 (23). These estimates vary with age and, at first glance, reflect the minimum amount of glucose that must be provided to prevent hypoglycemia (23). Some investigators have argued that gluconeogenesis provides a significant amount of glucose (even in preterm infants) and suggest that not all the glucose shown in Table 2 need be provided exogenously (24,25). However, these estimates are limited nutritional stores (21). A recent randomized controlled study compared preterm infants (27 weeks gestational age, N = 125) receiving PN on the first day of life to those in whom it was started in the first few days of life and advanced more slowly (22). Infants in the early PN group had fewer infections during hospitalization and were more likely to be above the 10th percentile for weight or height at the time of discharge (22).

Energy Sources

There is controversy around the choice of nutrients to provide energy requirements via PN. There are glucose advocates, lipid believers, and argument as to whether protein (i.e., amino acids) should be counted as part of the total administered energy. At the expense of over-simplification and wounding the true believers in each camp (the authors are active participants in these controversies), we submit that a few basic principles can be agreed upon. 1) There is a minimum amount of glucose that must be provided in order to prevent hypoglycemia and a maximum that results in the production of excessive CO₂ and/or hepatic steatosis (see below); 2) There is a minimum requirement (both dose and frequency) for intravenous fat emulsion to prevent essential fatty acid deficiency but a maximum beyond which intravenous fat may have deleterious effects; and 3) Amino acids must be provided in adequate amounts to prevent hypoproteinaemia but there are adverse consequences of giving an excess. Both the size and the age of the pediatric patient are important in determining the appropriate quantities of glucose, fat and amino acids administered in PN.

Glucose

Estimates of glucose utilization by the brain are shown in Table 2 (23). These estimates vary with age and, at first glance, reflect the minimum amount of glucose that must be provided to prevent hypoglycemia (23). Some investigators have argued that gluconeogenesis provides a significant amount of glucose (even in preterm infants) and suggest that not all the glucose shown in Table 2 need be provided exogenously (24,25). However, these
studies have used isotopic tracers to measure gluconeogenesis and it has been shown that this method underestimates the contribution of glucose to CO₂ when compared with data obtained from indirect calorimetry (23). Thus, the data in Table 2 probably do reflect the amount of exogenous glucose required to prevent hypoglycemia under most circumstances (23). Kalhan and Kiliç reviewed the evidence that this amount of exogenous glucose also is sufficient to minimize nitrogen loss (23).

What about the maximum rate of glucose oxidation? Lafeber et al. found a glucose oxidation rate of 6.6 ± 1.2 mg · kg⁻¹ · min⁻¹ (9.5 g · kg⁻¹ · d⁻¹) in appropriate for gestational age preterm infants (birth weight: 1613 ± 151 g, gestational age: 31.1 ± 1.5 wk; mean ± SD) (26). The rate was minimally greater than that found in small for gestational age infants (26). In contrast, in term surgical infants Jones et al. measured a maximal glucose oxidation rate of 12.5 mg · kg⁻¹ · min⁻¹ (18 g · kg⁻¹ · d⁻¹) (27). This rate is comparable to that of stable patients both on long-term PN (N = 7, 30 ± 41 months of age) or short-term PN (N = 36, 6 ± 4 months of age) (28, 29).

Clinical status can modify glucose oxidation capacity significantly. For example, Sheridan et al. noted that in critically burned children the maximal rate of glucose oxidation was 5 mg · kg⁻¹ · min⁻¹ (30).

**Consequences of Overfeeding with Glucose**

In critically ill individuals, glucose intakes above the maximal glucose oxidation rate will result in the non-oxidative production of fat, hence, are unlikely to enhance energy balance, or even reduce protein catabolism (23). On the other hand, glucose intakes above the maximal oxidation rate promote fat deposition, which may be a nutritional goal in specific clinical situations (e.g., preterm infants). We will use the term overfeeding to mean a nutritional goal in specific clinical situations (e.g., pre-term infants). We will use the term overfeeding to mean providing calories in excess of the amount required for normal weight gain.

A number of recent reviews have addressed issues related to carbohydrate overfeeding in the intensive care unit patient (31–35). Unfortunately, the relationship between carbohydrate feeding and impaired pulmonary function (in the form of increased CO₂ production) as well as the development of fatty liver often is oversimplified.

When glucose is administered in excess of the amount that can be directly oxidized for energy production and glycogen production, the excess is directed to fat synthesis (lipogenesis) (Fig. 1) (36, 37). This conversion is inefficient and probably accounts, in part, for the increase in energy expenditure seen with high rates of glucose infusion (Fig. 1) (20). This inefficiency can have clinical consequences besides simply producing hyperglycemia.

Nose et al. studied energy expenditure and CO₂ production in 7 infants receiving long term PN (28). Three PN regimens were tested: 87:5:8 (glucose:fat:amino acids as percent of total energy), 60:32:8, and 34:58:8 Total energy intake was comparable to the recommended daily allowance. The increase in resting energy expenditure (although reported as basal metabolic rate) induced by the high glucose regimen was nearly 5 times greater than that of the other two regimens (28). Bresson et al. also noted increased energy expenditure in relationship to increasing glucose intake, albeit to a lesser extent, amounting to 16% of the energy value of infused glucose (29).

In the study by Nose et al. the respiratory quotient (RQ = CO₂ production/O₂ consumption) was significantly greater on a high glucose regimen compared to lower glucose regimens (28). The data suggest that in this population of stable patients on long-term PN, glucose intakes in excess of 10 mg · kg⁻² · min⁻¹ result in conversion of glucose to fat (RQ > 1) (28). As seen in Figure 1, lipogenesis from glucose results in a large increase CO₂ production relative to O₂ consumption (i.e., high RQ).

Talpers et al. (among others) examined the effect of different glucose/fat ratios on CO₂ production in adults (19, 38). In contrast to the studies of Nose et al (and other investigators), they were unable to detect a change in CO₂ production as a consequence of alterations in the glucose/fat ratios (19, 38). It is possible that the discrepancy between these studies is a result of the higher proportion of total energy provided by amino acids in Talpers’ study (20% of total energy) than in Nose’s study (8% of total energy) (28, 38). Amino acids also can affect ventilatory drive and the response to CO₂. Increasing amino acid intake (with energy intake constant) leads to an increase in minute ventilation and more importantly, an enhanced response to CO₂ (i.e., minute ventilation increases in a more responsive fashion to increasing levels of CO₂ (39, 40). Thus, the higher percentage of amino acids provided in the adult studies may have blunted the differences in CO₂ production at different glucose/fat ratios.

Another factor with an impact on CO₂ production is total energy intake. There is a linear relationship between energy intake and CO₂ production and increased minute ventilation (presuming glucose is providing a portion of the energy) (38, 40). Indeed, the patients reported to have developed respiratory failure (i.e., CO₂ retention and increased minute ventilation) as a consequence of PN with high concentrations of glucose were receiving excessive energy intakes (see reference 35 for a review). Under normal circumstances the increased CO₂ production is handled easily by increasing the respiratory rate and/or depth. Problems potentially arise in patients with respiratory compromise. The respiratory response to enteral carbohydrate intake and enteral overfeeding mirrors what is seen with PN (41).

In summary, the greater the proportion of glucose in the PN energy mix, the larger the increase in CO₂ production and minute ventilation. Malnourished patients
are least and hypermetabolic individuals are most susceptible. Normally nourished and metabolically normal patients have an intermediate response (42). The greater the total energy intake, the greater the effect.

In selected patient groups, giving glucose in amounts above the maximal oxidative rate may be appropriate (e.g., preterm infants who need to deposit fat). However, the greater the amount of glucose, the greater the risk of adverse consequences. Unfortunately, the absolute intake at which the adverse consequences occur is poorly defined.

Overfeeding of glucose also can affect liver function although its contribution to the development of cholestasis in humans is unclear. Burke et al. observed a relationship between glucose infusion rate and the development of fatty infiltration of the liver in necropsies of children who died of severe burns (43). In a study in 37 catabolic adults, Tulikoura et al. administered PN using glucose and glucose and fat as energy sources (44). There was a significant increase in hepatic steatosis in the glucose group but none when glucose and fat were used in combination (44). Steatosis was associated with a rise in serum transaminases but no cholestasis was noted (44). Studies in normal adult volunteers suggest that high carbohydrate feeding leads to an increase in total VLDL triglyceride secretion rate from de novo synthesis primarily due to stimulation of the secretion of preformed fatty acids (45). The results imply that the liver derives all its energy from carbohydrate oxidation as opposed to fatty acid oxidation such that fatty acids taken up by the liver are channeled into VLDL triglycerides (45). Hepatic steatosis results when export of the VLDL triglycerides does not keep pace with production (34,45).

Another potential complication of overfeeding with glucose is an increase in infectious complications. PN has been associated with an increased risk of infectious complications compared with enteral feeding or no nutritional support in adult studies (46-49). Recent data suggest that this finding may actually be explained by overfeeding with glucose (50). Hyperglycemia is a risk factor for infection (51,52). Recently, hyperglycemia

![FIG. 1. Respiratory quotient (CO2 production / O2 consumption) and caloric yield from the oxidation of glucose, fat, amino acids, and the conversion of glucose to fat. *Energy production values shown are theoretical. Actual energy production is less efficient. For conversion of palmitate it is about 41% (980/2398) whereas glucose conversion to fat is only about 20% efficient. Adapted from Flatt JP: Energetics of intermediary metabolism. In Assessment of Energy Metabolism in Health and Disease, p. 77 (ed.) JM Kinney, Report of the First Ross Conference on Medical Research. Columbus, Ohio, Ross Laboratories, 1980.](image-url)
was associated with an increased risk of infection in children with burns (53). In a prospective randomized trial in adults there was no difference between groups receiving hypocaloric intravenous fluids and those receiving PN that did not overfeed the patients or induce hyperglycemia (54). These intriguing results require further verification but may have great implications for patient care.

Clinical Implications

Patients with respiratory compromise, particularly CO₂ retention (e.g., cystic fibrosis) are at risk for experiencing a worsening of their pulmonary status if glucose provides a large proportion of their energy needs. The risk increases as energy intake surpasses REE. Malnourished patients may not manifest this response until they begin to be nutritionally rehabilitated. A hypometabolic patient will exhibit this reaction most quickly. Concerns about overfeeding have been addressed recently in a consensus statement on the care of the adult intensive care unit patient (55).

Intravenous Fat Emulsion

Unless otherwise noted, the term intravenous fat emulsion refers to the currently available (in the United States) soy- or soy/safflower-based emulsions. A key role for intravenous fat emulsion is the prevention of essential fatty acid deficiency. The usual preterm infant (< 2 kg birthweight) on PN without intravenous fat emulsion or on enteral feedings begins to demonstrate biochemical evidence of essential fatty acid deficiency (increased triene/tetraene ratio) within seven days of birth if not provided with adequate intravenous fat emulsion (56). In the absence of intravenous fat emulsion, endogenous adipose tissue and the liver are probably the source of essential fatty acids (57). In order to prevent the mobilization of fatty acids for energy, essential fatty acids must be provided in amounts necessary to both replace deficits and supply ongoing needs for metabolism and growth. In other words, essential fatty acid deficiencies are cumulative (58,59). Given that intravenous fat emulsions contain approximately 50% essential fatty acids by weight, about 0.5 g · kg⁻¹ · d⁻¹ of intravenous fat emulsion is required to prevent essential fatty acid deficiency in patients on total PN (56,60). However, there is controversy regarding this figure, particularly in adults (and presumably adolescents) with some investigators suggesting the recommendation is more than adequate (e.g., 1.5 g/kg twice weekly) and others stating it is too low (61–64). There appears to be a fair amount of inter-individual variation in essential fatty acid requirements based upon age, disease, and nutritional status (56,61,62,65). Thus, one should not presume that giving the smallest recommended amount of essential fatty acid, such as 1.5 g/kg (approximately 500 mL of 20% intravenous fat emulsion) twice a week in an adolescent, would be adequate for all such patients. In patients receiving no intravenous fat emulsion, some studies suggest that fatty acid deficiency develops faster when total energy intake is low than it does when total energy intake is high (66,67).

It often is suggested that intravenous fat emulsion be administered over less than 24 hours (e.g., 20 hours) to allow time for the fat to clear from the blood. In fact, studies suggest that it is better to administer the daily dose over 24 hours in patients who have difficulty tolerating the infusion. Preterm infants should receive the infusion over 24 hours to avoid hypertriglyceridemia. For patients without hypertriglyceridemia or other evidence of intolerance to intravenous fat emulsion, a less than 24-hour infusion schedule may be tolerated well. One of the major determinants of the rate of clearance of fat from the blood is the amount of intravenous fat emulsion infused per unit time (68). The longer the infusion time, the less likely the patient will develop hypertriglyceridemia (68,69). Intravenous fat emulsions with high concentrations of phospholipids (i.e., 10% emulsions) should be avoided as they carry a higher risk of producing high serum levels of triglycerides, cholesterol, and phospholipids than other emulsions (i.e., 20% and 30% emulsions) (70–72).

A number of other factors decrease the rate of clearance of intravenous fat emulsions. The more malnourished the patient, the slower the rate of clearance will be. Slower clearance in malnourished patients is a result of lower levels of lipoprotein lipase. This enzyme, which is responsible for releasing fatty acids from the fat emulsion, resides within the capillary system. The lower the capillary tissue mass (a situation found in preterm infants and malnourished patients), the slower the rate of intravenous fat emulsion clearance. Studies in adult volunteers have shown that the muscle, splanchnic, myocardial, and subcutaneous fat capillary systems clear 47%, 25%, 14%, and 13% of the total amount of lipid infused, respectively (73). Under normal circumstances the liver clears less than 1% of infused lipid (73).

Another factor that alters the tolerance to intravenous fat emulsion is the concurrent administration of drugs. Because of their lipolytic effect, steroids are the prototype. Patients simultaneously receiving steroids and intravenous fat emulsions are prone to hypertriglyceridemia (74). Additionally, a number of medications contain lipid or are microosomal formulations. Drugs such as propofol and amphotericin B may contribute significant amounts of (fat) energy to the total daily intake and which should be taken into account in nutritional calculations.

Patients who are metabolically stressed (i.e., sepsis, trauma) or who have organ dysfunction (e.g., liver and/or renal disease) also are likely to develop hypertriglyceridemia during intravenous fat emulsion infusion. These
patients have an outpouring of cortisol, catecholamines, and cytokines that promote the lipolysis of endogenous lipid stores (75–77). Liver and renal disease themselves are associated with hypertriglyceridemia. However, adult (and presumably pediatric) patients with sepsis and liver disease can tolerate and utilize intravenous fat emulsions (78,79). Infants with ventricular septal defects or transposition of the great vessels (i.e., cyanotic heart disease) do not have inordinate increases in serum triglycerides in response to intravenous fat emulsion (80).

Serum triglyceride levels should be measured four hours after starting an intravenous fat infusion or four hours after any increase in infusion rate. It is at this time that hypertriglyceridemia is most likely to occur (81–83). Ideally the triglyceride level should be ≤100 mg/dL (84). However, this upper limit varies depending on the method used to measure serum triglycerides. For example, some common methods of measuring triglycerides measure the free glycerol released from the triglyceride molecule (85). Given that intravenous fat emulsions contain free glycerol in addition to triglycerides, the serum triglyceride level measured by evaluating glycerol will be an overestimation of the true serum triglyceride level. A value of 150 mg/dL may correspond to an actual triglyceride level of only 100 mg/dL (Buffone and Shulman, unpublished data). Nephelometry should not be used to monitor serum triglyceride levels as it is unreliable (85,86). Heparin administration lowers serum triglyceride levels but does not affect the rate of fatty acid oxidation (83,87,88).

Clinicians frequently ask what level of hypertriglyceridemia is acceptable in a patient receiving PN. Given the need to provide essential fatty acids to patients who may have hypertriglyceridemia for prolonged periods (e.g., the critically ill patient), at what serum level do the triglycerides start having an adverse impact on the patient? Unfortunately, to our knowledge, there are no data defining the level at which one should be concerned.

Many investigators have studied the impact of intravenous fat emulsion on pulmonary function. Although an in depth review of this topic is beyond the scope of this article, a few points can be touched upon and the reader is referred to two reviews (89,90).

After a fatty meal, the serum triglyceride of normal adults may transiently approach 500 mg/dL (91). Even values above 1500 mg/dL do not appear to decrease the carbon monoxide diffusing capacity in healthy adults (91). This begs the question as to whether elevated triglycerides cause some of the adverse oxygenation effects reported with intravenous fat emulsions that when severe is referred to as the “fat overload syndrome” (92). It was first believed that the sometimes seen adverse effects of intravenous fat emulsions on pulmonary function (e.g., decreased diffusion capacity, oxygenation, intrapulmonary shunting) were related to the serum triglyceride level (89,90,93). It appears more likely that these changes, when seen, are due to the conversion of the polyunsaturated fatty acids in the emulsions to prostaglandins, which then can cause vasoconstriction or vasodilatation depending on the rate of infusion and the clinical state of the lungs (85,86,93). Peroxides are another contaminant that can be found in the fat emulsion (94). Evidence suggests that they also promote increased prostaglandin levels (95).

Interpretation of the data linking intravenous fat emulsions and pulmonary dysfunction is complicated. The adverse effects appear to depend on the dose and rate of administration, presence of peroxides, and clinical state of the lungs (89,90,93–95). Are the effects clinically relevant? In preterm infants the balance of data suggests that administration of intravenous fat emulsion at normal rates does not affect oxygenation (72). Studies to the contrary have usually used inappropriately rapid rates of infusion (96–98). Because intravenous fat emulsion can induce vasoconstriction that is not limited to the pulmonary vasculature, observed decreases in transcutaneous pO2 may be related to local declines in subcutaneous perfusion and not reflect systemic oxygenation (95,99). The effects of intravenous fat emulsion on the development of chronic lung disease have been reviewed recently (72). The balance of the data suggests no adverse impact and possibly a beneficial effect (72,100). However, much more work is needed in this area before we can be certain that there are no clinically significant adverse effects.

Even more confusing than the issue of pulmonary function is the controversy regarding the effect of intravenous fat (101–105) emulsions on immune function. Some studies show a beneficial effect, some no effect, and some an adverse effect. A complete discussion is beyond the scope of the present article and the reader is referred to the supplied references. It should be pointed out that reviews in this area sometimes give a prejudiced view in that only selected publications are quoted. Interpretation of publications often is blurred by the use of inappropriate doses (both in vivo and in vitro), differences in patient groups or in vitro models (102). Similar to the situation in pulmonary function studies, many of the effects of intravenous fat emulsions on immune function appear to be related to the generation of leukotrienes and other polyunsaturates from the emulsions. There also is evidence the long chain fats may alter cellular function by changing membrane fluidity (104). Studies on pediatric patients and tissues have not revealed evidence suggesting an impairment of immune function by intravenous fat emulsions (106–113).

Do intravenous fat emulsions promote infections? Data are limited. A study in adult and pediatric bone marrow transplant patients found no increase in the risk of bacteremia or fungemia in patients receiving intravenous fat emulsions (114). In contrast, a retrospective study of preterm infants identified intravenous fat emulsion as potentially contributing to the development of coagulase-negative staphylococcal infection (115). However,
the lack of a temporal relationship between intravenous lipid administration and infection weakens the conclusions of this study (115). The lack of knowledge on this important issue underscores the importance of monitoring and using intravenous fat emulsions judiciously. Newer intravenous fat emulsions not yet available in the United States using olive oil or structured lipids may obviate some of these immune-related concerns (116).

The use of intravenous fat emulsions in patients with coagulation abnormalities requires comment. In rare cases, intravenous fat emulsion has been associated with thrombocytopenia. However, prospective and retrospective reports suggest that under normal circumstances they do not induce thrombocytopenia (117,118). It should be kept in mind that essential fatty acid deficiency itself is a cause of hematologic abnormalities (119).

Clinical Implications

There is debate as to the appropriate amount of intravenous fat emulsion required to prevent essential fatty acid deficiency. In infants (including preterms) who are most susceptible, at least 0.5 g · kg\(^{-1}\) · d\(^{-1}\) should be used. In older children and adolescents the minimum dose is probably in the range of 1.5 g/kg (approximately 500 mL of 20% intravenous fat emulsion) twice a week. For individuals on long term parenteral nutrition who either have little or no enteral intake of fat or who have severe fat malabsorption (e.g., severe short bowel) essential fatty acid status should be assessed after a few months of therapy. It has been suggested that measurement of n-6 and n-3 long chain polyunsaturated fatty acids is more reliable than the more commonly employed triene/tetraene ratio (57).

The American Gastroenterological Association Technical Review on Parenteral Nutrition states that intravenous fat emulsion should not be administered to patients whose serum triglyceride levels exceed 400 mg/dL (21). No data are provided to support this statement but the authors agree that serum triglyceride levels exceeding 400 are unlikely to cause clinically relevant problems. How the duration hypertriglyceridemia might affect the complication rate is unclear. In preterm infants pulmonary vascular lipid deposition was more common in infants who received intravenous fat emulsion and correlated with the duration of lipid therapy although some infants who never received intravenous fat emulsion also demonstrated lipid deposition (120). Liver or pancreatic diseases are not in themselves contraindications to the use of intravenous fat emulsion. It is helpful to measure serum triglyceride levels prior to starting intravenous fat emulsion in patients who are likely to be hypertriglyceremic and when their clinical status deteriorates significantly.

Amino Acids

Use of amino acids in pediatric PN has recently been reviewed and the reader is referred to these references for more details (121,122). Amino acid requirements vary from ≥ 2.5 g · kg\(^{-1}\) · d\(^{-1}\) for preterm infants to 0.75 g · kg\(^{-1}\) · d\(^{-1}\) for adolescents (123,124). Similar to energy requirements, amino acid requirements vary from individual to individual under normal circumstances. The immunodeficiency associated with malnutrition is to a great extent related to protein malnutrition as opposed to energy malnutrition. Consequently, amino acid requirements should be attended to first in prescribing parenteral nutrition. The intake of energy and amino acids in combination result in the greatest protein gain. Amino acid intake is the main determinant of protein gain (Figure 2). That is, there is a much larger gain in protein accretion with increases in amino acid intake than with increases in energy intake (Fig. 2).

Since amino acids are generally not metabolized to supply energy but to provide structural and visceral proteins and enzymes, some clinicians do not include them in the total energy calculation. In practice, to include them or not usually does not make much difference. For example, a term infant who weighs 4 kg requires about 8 g/d of amino acids, which is equivalent to 32 kcal (8 g x 4 kcal/g). The total energy requirement is about 400 kcal/d (4 kg x 100 kcal/d). Thus, adding the calories from protein changes the total energy calculation by less than 10%. Interindividual energy requirements easily can vary by this much. The bottom line is that both amino acids and energy need to be titrated to the patient’s requirements.

Although serum prealbumin (transthyretin) and transferrin are often used as short-term (1–2 day) measures of the response to amino acid intake, the blood urea nitrogen (BUN) can be also be used in many cases. If renal function and hydration are normal, a low BUN (< 5) reflects inadequate amino acid intake and conversely, a high BUN (> 20) suggests that the amino acid intake may be too great. For many patients a BUN between 10 and 15 mg/dL is a good target and reflects an amino acid intake that is adequate for protein anabolism (Laine and Shulman, unpublished).

Although it has been stated in the literature that the amino acid intake should be gradually increased over the first few days of PN administration, we know of no good scientific documentation for this view. For example, we use intakes of 2.5 mg · kg\(^{-1}\) · d\(^{-1}\) even in 25-week gestation infants without complications starting within a couple days after birth. A recent review of the literature on the use of early amino acid introduction found no metabolic abnormalities (elevated BUN, serum pH, ammonia, serum amiogram) associated with this practice even in preterm infants (123). Gradually increasing the amino acid concentration or volume only postpones the time at which the patient receives adequate intake.
Evidence suggests that amino acids contribute to the development of PN-associated cholestasis (125,126). Even enteral protein intake can decrease bile flow (127). If amino acids are removed from the PN when the patient develops cholestasis and no other source of protein is provided, one then is faced with a patient who in addition to having liver disease has hypoproteinemia or even kwashiorkor. There are some data to support the idea that provision of protein enterally while other nutrients (primarily carbohydrate) are provided intravenously can reduce the risk of or lessen the severity of PN-associated cholestasis (125). Protein is usually well digested and absorbed, even in patients with short bowel syndrome (128). Consequently, this is an option for many patients receiving PN. Of course, whenever possible other nutrients should be provided enterally as well.

There are very limited data in pediatric patients regarding the use of specialized amino acid solutions for specific conditions such as critical illness and liver or renal failure. A crossover trial in children with end stage liver disease suggested a benefit to a branched chain supplemented enteral formulation in that the special formula promoted more rapid nutritional rehabilitation (129). Studies in adults with liver disease have been in-
consistent. Most studies indicate that if used at all, branched chain formulae should be reserved for patients who are malnourished and/or who are encephalopathic (130,131). The benefit of specialized amino acid solutions for patients with renal disease also is not clear (132,133). Similarly, the nutritional benefit of parenteral nutrition given during dialysis requires further study (134,229). The two commercially available (in the United States) pediatric amino acid solutions have concentrations of essential amino acids, including branched chain amino acids, which are fairly close to those in the specialized amino acids solutions.

Clinical Implications

Provision of amino acids should be a priority in calculation of PN requirements. In situations where fluid intake is significantly restricted, energy intake should be sacrificed at the expense of maintaining a greater amino acid intake, particularly when more than resting energy expenditure can be provided. The PN concentration of amino acids can be increased to 4%–8% (g/dL) depending on the amino acid brand used (concentration of the stock amino acid solutions range from 10%–20%). The BUN is a readily accessible and cheap method of titrating amino acid intake if renal function and hydration are normal. Consideration of enteral (as much as possible) rather than parenteral administration of protein should be considered, particularly in patients at risk for cholestasis. If not limited by intolerance (e.g., enteral carbohydrate in a patient with short bowel syndrome) other nutrients should be provided enterally as well.

CYCLIC PARENTERAL NUTRITION

The term cyclic PN refers to the administration of intravenous fluids intermittently with regular breaks from infusion. Cyclic PN offers the advantage of increasing the mobility of the patient and family. Much has been written regarding its other presumed advantages but there are scant scientific data (135,136). One of the proposed benefits is a lower risk for the development of liver disease although reports have been anecdotal (137). Recently, Hwang et al. carried out a prospective study in adults on PN exhibiting various degrees of presumed PN-associated liver disease (138). Patients who developed hyperbilirubinemia were randomized to either remain on continuous PN or were placed on cyclic PN. Patients with initial serum bilirubin less than 20 mg/dL, who remained on continuous PN, had a significant rise in serum bilirubin compared with the cyclic PN groups (138). There was no apparent advantage of cyclic PN in patients with serum bilirubin greater than 20 mg/dL (138). These results are intriguing and beg for similar studies in pediatric patients. For information on PN-associated cholestasis the reader is referred to recent reviews (139–141).

REFEEDING SYNDROME

Refeeding syndrome is a potentially lethal condition characterized by severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing refeeding orally, enterally, or parenterally (139). Clinical features include fluid-balance abnormalities, abnormal glucose metabolism, hypophosphatemia, hypomagnesemia, hypokalemia, and sometimes thiamine deficiency (142).

Refeeding syndrome can occur with either parenteral or enteral feeding. Because it is a preventable condition, patients who are at risk should receive a PN prescription from the outset that will decrease the likelihood of its occurrence. A detailed review of the condition is beyond the scope of this article but the reader is referred to comprehensive reviews (142,143). The syndrome can be prevented by adequate provision of phosphorus, and to a lesser extent magnesium and potassium at the time the patient begins to become anabolic. A common misconception is that additional magnesium and potassium provided at the onset of PN will prevent the syndrome. This is true only if adequate nutrition is being provided to the patient so that they are actually regaining lost tissue mass (i.e., muscle and viscera). If the amount of nutrition (energy) being provided is less than that required to maintain weight or promote catch-up weight gain, the syndrome will not develop. Consequently, the patient may be at risk for hypophosphatemia and hypokalemia weeks after the initiation of PN (or whenever nutrient intake allows for catch-up weight gain).

Refeeding syndrome can be prevented by providing additional phosphorus and potassium (usually as K₂PO₄) at the time PN is started. The amount of additional phosphorus and potassium required depends on the degree of malnutrition and the adequacy of total energy intake. A general rule of thumb in the authors’ experience is that twice the recommended daily allowance (RDA) of phosphorus is a reasonable starting point. Usually the risk for clinically significant declines in these minerals lasts for 7–10 days. During this period, it is important to follow serum phosphorus and potassium closely (e.g., every other day or more often if serum levels are tenuous). After this time, supplementation above the RDA can gradually be reduced. Calcium and phosphorus should not be given independently as administering one without the other leads to renal wasting of the infused mineral (144).

A rate-limiting factor in providing additional phosphorus is the risk of calcium/phosphorus precipitation. Table 3 provides guidelines for the maximal amounts of calcium and phosphorus that can be administered in PN (145–147). Note that the addition of cysteine (HCl) be-
cause of its low pH enhances the solubility of the minerals. Computer software is available to assist in assuring that calcium and phosphorus solubilities are not exceeded (148). In preterm infants and possibly other patients prone to acidosis, the addition of cysteine may require that the patient be supplemented with a source of base (e.g., acetate) (149). Calcium and phosphorus requirements for preterm infants have been fairly well delineated in contrast to older children (150,151).

PARENTERAL NUTRITION ADMIXTURES

PN admixtures (also called Total Nutrient Admixtures or TNA, Three-in-One solutions, or All-in-One solutions) make use of the fact that under certain conditions the glucose/amino acid solution may be mixed with intravenous fat emulsion and administered to the patient in one bag. There are a number of potential advantages to PN admixtures but also some drawbacks (Table 4; see below) (152).

In addition to reducing cost, use of a PN admixture simplifies the patient’s life in that only a single infusion pump with less tubing and other accessories are needed (153). There also is evidence that it reduces the risk of bacterial growth in intravenous fat emulsion even after 24 hours (154). In a randomized trial in which adult patients (N = 96) received either PN admixtures or traditional (two-in-one) PN there was no difference in the rate of infection between the two groups (155).

Recently, a bag has been developed that allows the solution to be made with the three components (amino acids, glucose, fat) stored in separate compartments separated by inner seals (Kabiven Multichamber Paren-

teral Nutrition Packaging System, Fresenius Kabi, Uppsala, Sweden). The bag and components can be stored up to 24 months with the seals between the chambers intact. Seals are opened just before use. PN admixtures find their greatest usefulness in older patients, particularly those on cyclic PN and those at home (see below).

Because the admixture is a physical mix of naturally incompatible substances (oil and water, calcium and phosphorus), their utilization requires strict attention to pharmaceutical guidelines for preparation, storage, and use (156). Particulate matter (mobile, undissolved substances that are unintentionally present in products) resulting from inappropriate preparation or storage can be life threatening. For example, deaths have been reported presumably as a result of precipitation of calcium and phosphorus in admixtures (157,158). Table 5 lists potential areas of concern in the preparation and storage of PN admixtures.

There have been multiple publications regarding how PN admixtures should be prepared and their stability. Preparation of an admixture requires exquisite attention to detail. The commercial product used, the sequence of mixing, the type and concentration of additives, and storage conditions are critical for maintaining lipid droplet size and distribution and preventing the development of particulate matter (159). For example, ideally all water-soluble additions should be mixed together whereas lipophilic additives (e.g., fat soluble vitamins) should be added to the intravenous fat emulsion (159). The last step should be mixing the intravenous fat emulsion (and its components) with the water-soluble components (159). Undiluted hypertonic glucose solution should not be

| TABLE 3. Maximal calcium and phosphorus concentrations in parenteral nutrition solutions |
|---------------------------------|-----------------|-----------------|
| g/dL (%)                         | Without cysteine | With cysteine*  |
| Calcium mEq/L                    | Phosphorus mmol/L | Calcium mEq/L   | Phosphorus mmol/L |
| 1.0                              | 50              | 12              | 50              | 23              |
| 1.5                              | 2               | 50              | 2               | 50              |
| 2.0                              | 5               | 50              | 12              | 50              |
| 2.5                              | 7               | 50              | 12              | 50              |
| 1.0                              | 50              | 12              | 50              | 23              |
| 1.5                              | 2               | 50              | 2               | 50              |
| 2.0                              | 5               | 50              | 12              | 50              |
| 2.5                              | 7               | 50              | 12              | 50              |

* Presumes the base amino acid solution has a pH of $\leq 5.5$.

Administration of intravenous fat emulsion into the same intravenous catheter may reduce solubility by 10%–20% (145,146). Addition of acetate without the addition of cysteine also may reduce solubility by 5–10% (147). # 40 mg/g of amino acids.

Note: This table is intended as a general guideline and is not to be used in lieu of pharmacist verification of the compatibility of the PN solution. Modifications to the formulation and alterations in the method and order of preparation may result in different calcium/phosphorus solubilities.

| TABLE 4. Advantages and disadvantages of parenteral nutrition admixtures |
|-----------------------------|-----------------------------|
| Advantages                  | Disadvantages               |
| Nursing time for administration of PN is decreased | Particulate matter is difficult to see prohibiting visual inspection of solution |
| Rate of extrinsic touch contamination potentially reduced | Filtration must be performed with a larger filter (1.2 micron vs. 0.22 micron) |
| Pharmacy preparation time decreased | Support the growth of microorganisms better than glucose-amino acid solutions |
| Admixtures support microbial growth less than fat emulsion alone | Computer interfaced automated compounder expensive |
| A two pump system is eliminated | Emulsion instability can be disrupted with high concentrations of electrolytes or when base solution component amounts exceed compatibility limits |
| Increased compliance of administering fat emulsion in the home patient population | The cost of ‘Y’-site tubing and additional supplies is saved |

From (152).
added to intravenous fat emulsion (160). Solutions may be stable when refrigerated and become unstable at room temperature. Another example, heparin stability, has been a subject of great debate. Contradictions regarding its risk of precipitating with calcium probably are related to differences in the studied heparin preparations and the other additives and their concentrations in the admixtures (159). The reader is referred to comprehensive reviews regarding the factors related to PN admixture stability as well as methodologies used to test stability (159–163). In general, final concentrations range from 2% to 5% for amino acids, 5% to 23% for glucose, and 1.5% to 5% for intravenous fat emulsion (161).

In order to see through the morass of information it is best to follow a simple rule: after identifying a PN admixture whose stability has been well documented, use them exactly as described. Unlike standard PN solutions, alterations of components, volumes, and/or concentrations should not be made. A case in point is a recent report of episodes of respiratory distress and death possibly related to changing from one commercial amino acid brand to another despite (or it should be said, because of) not modifying any other aspect of the admixture (164). A Food and Drug Administration (FDA) alert was issued in 1994 regarding the hazards of precipitation (165). It is recommended that information on the proper preparation of a PN admixture be obtained directly from the manufacturer(s) of the amino acids and intravenous fat emulsion that are to be used. As a general rule, the amino acids, glucose, and intravenous lipid are added in fixed ratios by volume (e.g., 2:1:1, 1:1:1, 1:1:0.5, etc.) (166). To reduce the risk of precipitates reaching the patient an inline filter should be used. This should be a 1.2 micron air-eliminating filter (in contrast to the 0.22 micron air-eliminating filter recommended for nonlipid-containing PN) (165). The importance of filtration recently has been reviewed and revalidated (167,168). A PN admixture is considered inappropriate for administration if > 0.4% of the total fat contains particles > 5 microns in size (162,163).

What patients are candidates for PN admixtures? It may be more important to ask whether there are PN mixtures that are inappropriate for certain patients. Because of the limitations in the amount of calcium and phosphorus that can be used in PN admixtures (even more severe than in non-admixture PN), their use may be inappropriate in young infants. One report has suggested that PN admixtures can be used in former preterm infants and newborns, however, in this study it was not clear that the PN admixtures had been validated as stable nor was there stability testing reported after the admixtures were prepared (169). Because the emulsion is opaque (as a result of fat emulsion) a precipitate may be invisible to the naked eye. The calcium and phosphorus requirements for neonates is 3–4 mEq · kg\(^{-1}\) · d\(^{-1}\) and 1–2 mmol · kg\(^{-1}\) · d\(^{-1}\), respectively (162). Based upon studies using a commonly employed pediatric amino acid solution (TrophAmine, B. Braun Medical, Inc., Melsungen, Germany) the PN admixture would provide inadequate amounts of these minerals (170). As an infant approached 4–6 months of age it is conceivable that their calcium and phosphorus needs could be met using a PN admixture (161,162,170). However, it must be stressed that this is dependent upon the amino acid, glucose, intravenous fat emulsion, calcium, and phosphorus products (as well as the other components) used as well as the mixing protocol. If a PN admixture is to be used in an infant less than a year of age, it should be done with particularly careful consideration regarding mineral requirements.

PN admixtures only should be used in patients who are clinically stable. Changes in the formulation of PN admixtures are more costly than changes in traditional (two-in-one) PN because of the wastage of both the dextrose/amino acid and its components, and the intravenous fat emulsion.

A number of questions remain about PN admixtures. These include the appropriate dosing of some vitamins, the true risks related to particulate matter and fat droplet size, and drug compatibilities. For example, there is less loss of fat-soluble vitamins such as vitamin A than in traditional (two-in-one) PN because the intravenous fat emulsion is protective (see below) (171). Some drugs are compatible with PN admixtures but not with traditional PN and visa versa.

---

**Table 5. Three potential issues in the use of PN admixtures and contributing factors**

<table>
<thead>
<tr>
<th>Chemical precipitation</th>
<th>Intravenous fat stability</th>
<th>Vitamin stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium and phosphorus</td>
<td>Low pH</td>
<td>Thiamine reduction by metabisulphite</td>
</tr>
<tr>
<td>Sulphur-containing amino acids and copper</td>
<td>Intravenous fat concentration</td>
<td>Lack of exclusion of oxygen during compounding</td>
</tr>
<tr>
<td>Sulphur-containing amino acids and calcium</td>
<td>Formation of peroxides</td>
<td>Lack of use of oxygen-impermeable containers during storage</td>
</tr>
<tr>
<td>Ascorbic acid and selenium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron and phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Order of Mixing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From (159).
VITAMINS

Guidelines for pediatric parenteral vitamin and mineral supplementation have been previously reviewed, albeit quite some time ago (173). Despite subsequent publications that have provided additional support for these recommendations, there has not been a recent significant evaluation or reformulation of parenteral vitamin products for premature infants, infants, or children (less than 11 years of age) (174,175).

Recommendations from the 1998 National Advisory Group on Standards and Practice Guidelines emphasized the need for establishing optimal trace element and vitamin formulations for both adult and pediatric patients (162). In April 2000, the Food and Drug Administration amended the adult multivitamin formulation to bring it into accordance with the 1988 recommendations of the American Medical Association-FDA Public Workshop Committee (Table 6) (176). To date, the optimal parenteral vitamin and mineral requirements for children and neonates have not been determined and a parenteral multivitamin formulation specifically for preterm infants has not been developed.

While there are several parenteral vitamin preparations available for older children (> 11 years) and adults (Table 6), few are available for neonates and children. Infuvite Pediatric™ (Sabex, Inc., Boucherville, Canada) and M.V.I. Pediatric™ (aaiPharma, Inc., Wilmington, NC) are approved for use in prematures, infants, and children < 11 years (Table 7). The adult formulations are not recommended for use in low birth weight infants less than 1500 grams because of concerns about the toxicity of the propylene glycol and polysorbate additives (177,178). Limitations in the availability of the pediatric products have made children vulnerable to shortages (179). Table 7 gives the doses of vitamins recommended for infants by the American Society of Clinical Nutrition Subcommittee on Pediatric Parenteral Nutrient Requirements (). This recommendation differs from the package inserts (180).

Clearly, there are patients whose needs do not fit the current vitamin formulations. For example, preterm infants, children with liver or renal disease or short bowel syndrome, or who are severely malnourished require close attention to vitamin nutriture. Some adult parenteral vitamin products that are used for children >11 years of age may put younger patients on long term PN at risk for excessive vitamin intakes (see Table 6).

| TABLE 6. Adult and children (>11 years of age) parenteral multivitamin preparations |
|-----------------|-----------------|-----------------|
| Vitamin         | Infuvite™* (Sabex) | M.V.I.-12™ (aaiPharma) |
| A (IU)          | 3300 IU          | 3300 IU          |
| D IU (µg)       | 200 (5)          | 200 (5)          |
| E (IU)          | 10               | 10               |
| K (µg)          | 150              |                  |
| C (mg)          | 200              | 200              |
| Thiamin (mg)    | 6                | 3                |
| Riboflavin (mg) | 3.6              | 3.6              |
| Niacin (mg)     | 40               | 40               |
| Pyridoxine (mg) | 6                | 4                |
| Folate (µg)     | 600              | 400              |
| B12 (µg)        | 5                | 5                |
| Pantothenic Acid (mg) | 15 | 15 |
| Biotin (µg)     | 60               | 60               |

* Conforms to the FDA amended formula for adult multivitamin preparations (165).

| TABLE 7. Infant and child parenteral multivitamin requirements and commercial preparations* |
|----------------------------------------|----------------|----------------|----------------|
| Vitamin (amount/d) | Best estimate# preterm infant | Pediatric parenteral multivitamins# <2.5 kg 40% of the vial (2 ml) | Pediatric parenteral multivitamins* >2.5 kg–11 yrs 100% of the vial (5 ml) |
| A (µg)** | 500 | 280 | 700 |
| C (mg) | 25 | 32 | 80 |
| D (IU) | 160 | 160 | 400 |
| E (mg)## | 2.8 | 2.8 | 7 |
| K (µg) | 80 | 80 | 200 |
| Thiamin (mg) | 0.35 | 0.48 | 1.2 |
| Riboflavin (mg) | 0.15 | 0.56 | 1.4 |
| Niacin (mg) | 6.8 | 6.8 | 17 |
| Pyridoxine (mg) | 0.18 | 0.40 | 1 |
| Folate (µg) | 56 | 56 | 140 |
| B12 (µg) | 0.3 | 0.4 | 1 |
| Pantothenic Acid (mg) | 2.0 | 2.0 | 5 |
| Biotin (µg) | 6 | 8 | 20 |

* Infuvite Pediatric™/MVI-Pediatric™.
# See reference (180).
** 500 µg = 1643 IU.
## 1 µg = 1 IU.
Vitamin K

One potential problem with the introduction of vitamin K into the new adult formulations is the possible interference with anticoagulants such as warfarin. Additionally, intravenous fat emulsions contain vitamin K in varying amounts (approximately 13–70 μg/mL) that can make titrating anticoagulant therapy even more problematic (181,182).

Vitamin A

A recent Cochrane review suggests that an increased vitamin A intake (via the intramuscular route) is beneficial in the preterm infant (183). Whether dosing of vitamin A in PN will provide a similar benefit is unclear. Dosing of vitamin A is complicated by its adherence to the bags and tubing and from photodegradation (184). Evidence suggests that when administered in the glucose/amino acid solution the current recommendation for vitamin A is too low (162,185,186).

Loss of several lipid soluble (and water-soluble) vitamins occurs during their delivery in PN (187,188). Evidence suggests that using dark tubing and placing fat-soluble vitamins into the intravenous fat emulsion (see PN Admixtures, above) mitigates the losses of these vitamins (189–192,230). However, multivitamin manufacturers in the US do not recommend mixing vitamins in lipid emulsions (see package inserts). Obviously it is commonly done in the case of PN admixtures (see above). More research in this area is vital.

Clinical Implications

Our knowledge regarding the appropriateness of current vitamin preparations and intake levels is less than optimal. Prudence would suggest checking vitamin levels (especially vitamin A and possibly riboflavin) in patients on long term PN because of potential losses in the administration set, particularly when enteral intake and/or absorption is poor (191). Consideration also should be given to monitoring fat-soluble vitamin levels in patients whose vitamins are placed into the lipid emulsion.

Carnitine

The use of carnitine in PN for preterm infants recently has been the subject of a Cochrane Database review (193). Using weight gain as a primary outcome, there was no apparent effect of carnitine supplementation (193). However, the studies available did not assess the use of carnitine in long term PN, a situation that is more likely to result in carnitine deficiency. Tissue carnitine levels decline in infants receiving carnitine-free PN (194). An adult patient who received PN for over a year has been described with symptomatic carnitine deficiency although the level of enteral intake was not described (195). It is possible that the effects of carnitine deficiency in patients on long term PN may be too subtle to be identified easily but are still metabolically relevant given the central role of carnitine in metabolism (196). Addition of carnitine does enhance intravenous fat emulsion oxidation although it has been argued that the increase may not be clinically relevant (193). In long term PN patients it may be reasonable to follow the suggestion that carnitine (as pure L-carnitine) be added at a dose of 2 to 5 mg · kg⁻¹ · d⁻¹ and that plasma and red blood cell concentrations be measured at baseline and at 4-month intervals until levels have stabilized, then yearly thereafter (196). Too high a carnitine dose may be detrimental (196).

Iron

Parenteral nutrition patients at risk for iron deficiency are premature infants, long-term PN patients with little or no enteral intake, and patients with significant malabsorption or fluid losses. Iron may be administered orally, intramuscularly, or parenterally. Parenteral iron can be infused as an intermittent intravenous infusion or as a diluted total dose infusion. Iron dextran has been used in children (197–200). Despite its fairly widespread use, total dose infusion is not approved by the Food and Drug Administration.

The use of iron dextran can be complicated by adverse reactions including a small but real risk of anaphylaxis. A test dose is recommended prior to administration of the required amount (see package insert). Iron dextran in PN can be efficacious (201,202). Although often employed in PN, the stability of iron dextran and its potential interaction with other nutrients remain as concerns (202). Its use in PN admixtures should be undertaken with extreme caution if at all (163).

Until recently, iron dextran was the only formulation available for parenteral iron therapy. Two new iron products free of dextran have recently been approved for use in the United States. Sodium ferric gluconate complex in sucrose (Ferrlecit, Watson, Inc., Morristown, NJ) has been used extensively in Europe and became available for use in the United States in 1999. Iron sucrose (Veenofer, Luitpold Pharmaceuticals, Inc., Shirley, NY) also previously available in Europe was introduced in late 2000. These products appear to be safe and have fewer side effects than those of iron dextran, although like iron dextran, they can cause hypotension (203,204). While the safety and efficacy of these products has not been extensively studied nor are they approved by the FDA for use in children, there is evidence that they are safe and effective in children (205).
Trace Minerals

Trace mineral requirements and metabolism in general, including concerns regarding aluminum contamination and toxicity, recently have been reviewed elsewhere (180,206–209). We briefly will touch on current issues regarding specific trace minerals in PN. First, it should be remembered that PN solutions usually contain some of the various trace minerals due to contamination of the components (e.g., amino acids, calcium gluconate, multivitamins) with trace metals (210). In one report Zn, Cu, Mn, and Se were found in greatest concentration but contamination will vary depending on the commercial products used to prepare the PN (210). Heat and storage time can modestly reduce the levels of some trace elements as well (210).

The importance of Se as an antioxidant is well known. A recent report suggests that the recommended intake of Se for preterm infants (N = 29, gestational age 26 weeks) may not be adequate for all infants (211). In contrast, a study of children and adults on long term PN suggested Se status is well maintained even with low or no Se intake (212). However, in this study there was great variability in Se serum levels as well as glutathione peroxidase activity with some patients actually showing deficiency (212). Given the reports of heart failure because of Se deficiency and our limited knowledge regarding adequacy of intake, it is prudent to check serum Se levels in the short term (particularly in preterm infants) and serum Se levels and glutathione peroxidase activity in older infants and adolescents (207,211–213).

Some studies have suggested that chromium toxicity may be a concern. Mouser et al. noted in infants and children (up to 12 years of age) on long term PN that serum Cr levels were elevated despite following the recommended intake (180,214). These data are consistent with other studies and imply that the addition of Cr to PN at recommended levels in combination with Cr contamination in the PN fluids raises serum Cr levels above that desired (210,215–217). Again, patients on long term PN should be closely observed. Whether the impaired glomerular filtration rate noted in children on long term PN is related to Cr excess requires further investigation (217).

Zn has the widest range of functions of all the trace minerals and is particularly important in wound healing and immune function. Despite its intentional and non-intentional addition to PN, many patients are at risk for Zn deficiency because of the number of predisposing clinical situations (206,207). For example, patients with gastrointestinal losses due to diarrhea, ileostomies, or even nasogastric suction are at risk for Zn deficiency because of the high Zn content of gastrointestinal fluids (218). Serum Zn levels, although not entirely reliable, are easily obtained and Zn intake can be titrated appropriately.

Of great concern are the numerous observations regarding Mn retention. This essential trace mineral normally is excreted in bile and has a special affinity for the extrapyramidal system (206,207). Mn often contaminates PN solution components in amounts sufficient for daily requirements (206,207,219). Manganese intoxication causes parkinsonian-like symptoms with muscular weakness, stiffness, tremors, ataxia, abnormal gait, asthenia, and difficulty with speech (220). Psychological changes have been reported including mental irritability, headaches, nervousness, compulsive actions, and hallucinations (220). Manganese accumulation can be detected in the basal ganglia as symmetric, increased signal intensity on T-1 weighted magnetic resonance images (220,221). These changes are reversible when Mn is removed from the PN (222,223). Clinical symptoms are usually but not always reversible (224).

It is not surprising that Mn accumulates in individuals with cholestatic liver disease given its hepatobiliary secretion (220). Of particular concern for pediatric patients is the widely held suspicion that Mn accumulation in patients on PN may cause cholestasis. A recent study randomized 244 children on PN to receive either 1.0 (Group 1) or 0.0182 μmol · kg⁻¹ · d⁻¹ (Group 2) of Mn (224). When all patients were considered, those in Group 1 showed a trend towards higher peak manganese and direct bilirubin levels. The two groups did not differ in the occurrence of cholestasis but Group 1 patients showed a trend towards increased incidence and severity of hyperbilirubinemia (225). Of the 160 children who received >75% of their daily fluid intake from PN for >14 days, peak whole blood manganese and peak serum direct bilirubin concentrations were significantly higher in Group 1. Significantly more infants in Group 1 developed a more severe degree of direct hyperbilirubinemia (225). These data implicate Mn as a contributor to the development and/or the severity of PN-associated cholestasis (225). Based on these and other data, it is suggested that patients with any cholestasis (some would say any liver disease) should not receive Mn in their PN (220,225,226). Others would go so far as to say that Mn should not be given to individuals on PN for <30 days and that levels should be monitored in patients receiving PN with Mn for >30 days (207,226).

There is disagreement regarding the best measure of Mn status (220). Whole blood Mn appears to correlate (in adults) with MRI-documented Mn deposition (226). Most investigators use whole blood Mn, red blood cell Mn, or Mn superoxide dismutase as measures of tissue deposition (220).

SUMMARY

Our knowledge regarding PN reflects the same pattern we find in all of medicine: what we do is based part upon science and part upon best judgment. It turns out that
practices that seem clear (i.e., based on science), often turn out to be wrong or not so clear. We now realize that aggressive nutritional support carries risks. The risk of infection may be related more to hyperglycemia (or hypertriglyceridemia) than to PN per se, and essential fatty acid requirements may not be as well defined as previously thought. When it seems as if knowledge is for naught, the following quote comes to mind: "I reserve the right to be smarter tomorrow than I am today" (227,228).

In a way, we are victims of our own success. PN can provide effective nutritional support but, as is evident from this review, there are large holes in our knowledge and little likelihood of abundant future research to fill them. For the most part, these deficiencies in knowledge are more problematic for pediatric patients than for adults. Unfortunately, because pediatric PN makes up such a small share of the market, manufacturers are reluctant to spend the resources to carry out the studies needed to define the child-specific impact of new lipid emulsions, reformulated vitamins, etc. Money spent on these questions would not be recouped quickly. The responsibility for improving PN safety and efficacy lies with all concerned: industry, funding agencies, physicians, pharmacists, nurses, and nutritionists.

PN is still the life-saving, far-from-perfect therapy it has been for over 40 years. Like all therapies it must be used and monitored appropriately. Using it means more than just checking the patient’s weight, and monitoring now means more than checking the serum electrolytes. Checking the box on the order sheet will never be enough.

Acknowledgments: The authors thank Dr. W.C. Heird for his very helpful comments. This study was supported by the National Institute of Child Health and Human Development, Grant No. ROI NR05337-01A2, the Daffy’s and Henrikres Foundations, and the USDA/ARS under Cooperative Agreement No. 58-6250-1-003. This work is a publication of the USDA/ARS Children’s Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine and Texas Children’s Hospital, Houston, TX. The contents of this publication do not necessarily reflect the views or policies of the USDA, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

REFERENCES

115. Avila-Figueroa C, Goldmann DA, Richardson DK, Gray JE, Fer...


158. Driscoll DF, Baptista RJ, Bistrian BR, Blackburn GL. Practical


228. C. Garza, personal communication, 1980.
