Clinical experience has demonstrated the value of optimal nutritional status in resisting the effects of trauma and disease as well as in improving response to medical and surgical therapy. The metabolic demands of rapid growth and the low nutritional reserves in infancy make the potential benefit of good nutrition to critically ill pediatric patients even greater.

This statement is not meant to be a comprehensive review of parenteral nutrition nor a guideline for specific techniques. It is intended to provide an update on the "state of the art" of parenteral alimentation. Details concerning the physiology, techniques for approach, and efficacy of parenteral nutrition are given elsewhere.1,2

In spite of the many formulas and feeding techniques available, several gastrointestinal and medical problems arise in infants that preclude or severely limit the use of the intestine for nutritional support. Since the first successful use of total parenteral nutrition in a malnourished infant in 1944, the use of total or supplemental parenteral nutrition has become a common practice. Premature infants with severe respiratory disease, congenital anomalies of the gastrointestinal tract, or inflammatory disease of the intestinal mucosa (necrotizing enterocolitis) are frequently candidates for this form of nutritional support. Older infants with intractable diarrhea, short bowel syndrome, severe malnutrition, or inflammatory bowel disease also have been successfully rehabilitated with parenteral feedings. Extensive body surface burns, malignancies, cardiac failure, and renal failure are examples of disorders outside the gastrointestinal tract in which parenteral nutritional support has been useful. Specific formulations and procedures are available for these latter situations and have been reviewed elsewhere.3

In certain settings, particularly larger hospitals with increased numbers of more complicated pa-

CATHETERS

Parenteral nutrition can be carried out via peripheral veins using standard peripheral intravenous catheters and solutions with an osmolarity of 300 to 900 mosm/L. When solutions of higher osmolarity are used, larger veins with a high blood flow volume must be used to avoid sclerosis and inflammation of the wall of the vein.

Strict asepsis is always mandatory during catheter placement. The catheters are made of a flexible material such as silicone elastomer, polyurethane, or stiffer polyethylene. They are generally placed, under anesthesia, in the subclavian or internal jugular vein and advanced toward the right atrium. Certain of these catheters can be introduced percutaneously into the subclavian vein. The more flexible catheters must be introduced through a hollow needle, or be placed by incising the skin and subcutaneous tissue to expose the vein or by creating a subcutaneous tunnel into a superficial neck vein and advancing the catheter toward the right atrium. The placement of flexible catheters in the premature infant has a lower incidence of vein perforation and thrombosis.4 On occasion when jugular or subclavian sites have been unavailable, veins that run toward the inferior vena cava, such as the inferior epigastric veins, are alternate choices.5 Regardless of the site, roentgenographic confirmation of the intravascular placement of the catheter is mandatory before parenteral nutrition solutions are infused.

A number of complications that are directly related to the catheter may occur. Malposition of a central venous catheter outside the vein, with in-
fusion of hypertonic solutions into the pleural or pericardial space, may be life threatening. A rapid decrease in serum glucose or the acute onset of circulatory or respiratory compromise should signal this complication. Hemorrhage, associated with erosion of central veins or of the wall of the right atrium, also has been reported. Pneumothorax and brachial plexus injuries are relatively common complications of percutaneous subclavian line insertion. Air embolus may occur. Air-eliminating filters and properly secured tubing junctions may help prevent this. Catheter emboli have occurred from rupture of silicone elastomer catheters perfused under extremely high pressures or from the tips of polyethylene catheters sheared off when the catheter was pulled back through the hub of the needle used to insert it. Thrombophlebitis may be observed in peripheral veins receiving hypertonic solutions. Skin slough is a rare but serious complication of extravasation of the parenteral solution into the interstitial space.

A major complication is catheter-related sepsis. Fever alone is not an indication for removal of a parenteral nutrition catheter. Other sources of infection should be searched for; if none are found, removal of the catheter should then be considered. Signs of sepsis in the neonate include lethargy, hyperbilirubinemia, temperature instability, and intolerance to previously tolerated glucose and lipid loads. Careful placement of the central catheter and strict adherence to established guidelines for catheter care and maintenance considerably decrease the incidence of catheter-related complications.

Metabolic complications caused by the composition and administration of the infusate will be considered as the various caloric sources are discussed. A suggested schedule for monitoring parenteral nutrition is shown in Table 1.

**COMPOSITION OF SOLUTIONS FOR INFANTS AND CHILDREN**

**Protein**

Current solutions supply nitrogen requirements as crystalline amino acids. Infants have demonstrated adequate growth with this source of protein. Commercial preparations are available as concentrated 3.5% to 10% mixtures of crystalline amino acids which can be diluted to meet nutritional requirements of infants at different ages. None of the solutions available in the United States has a composition that is qualitatively identical with that of the amino acid composition of breast milk, which has been used as the standard for the formulation of enteral mixtures promoting optimal growth in healthy infants. Also, the commercial solutions do not contain cysteine, although separate preparations of cysteine, which can be added to the solutions, are available. Cysteine may be an essential amino acid in premature infants with low activity of hepatic cystathionase, which converts methionine to cysteine. Taurine, which is formed from cysteine and is present in human milk, may also be important for these premature infants and is absent from commercial solutions. None of the available solutions contains carnitine, which is required for the optimal oxidation of fatty acids.

In spite of the recently recognized potential deficiencies, infants have tolerated the available solutions and have grown well while using them. Most metabolic complications related to amino acids in the solutions, including azotemia and acidosis, have occurred when the infants received more than 4 g/kg/d of protein equivalent. Complications are rarely encountered with the recommended intake of 2 to 3 g/kg/d of protein equivalent. Hyperammonemia, seen with earlier solutions, now rarely occurs with the increased amounts of arginine and decreased quantities of glycine in the formulations. Hyperchloremic metabolic acidosis, another problem...
noted with earlier crystalline amino acid solutions, has been ameliorated by the substitution of acetate for chloride in the salts of lysine and the use of basic salts of histidine.

**Carbohydrate**

Glucose (dextrose), fructose, galactose, sorbitol, glycerol, and ethanol all have been used as a source of carbohydrate calories in infants. Presently, nearly all centers use glucose as the principal carbohydrate. A small amount of glycerol present in lipid solutions contributes to carbohydrate calories. The other carbohydrate sources have fallen out of favor because they have no advantage over glucose and can produce serious complications in premature infants.

The quantity of glucose in the infusate that premature infants will tolerate is variable. Infusing glucose at 5 mg/kg/min and advancing to 15 mg/kg/min over a two-day period may reduce the intolerance seen when large amounts of glucose are infused initially. This is accomplished by increasing the concentration of glucose in the solution while keeping the volume of infusate constant at between 100 to 150 mL/kg/d, depending on the infant’s fluid requirements. A suggested protocol to gradually increase the amount of glucose given the infant is shown in Table 2. Acute consequences of glucose intolerance are serum hyperosmolality and osmotic diuresis. Both of these situations can be avoided by careful serum monitoring. Hypoglycemia is generally related to the sudden cessation of the total parenteral nutrition solution. In adult postsurgical patients, there appears to be no correlation between glucose clearance and the rate of oxidation of glucose. An increase in the glucose infusion rate from 4 to 7 mg/kg/min is associated with an increased rate of glucose oxidation; but, at higher infusion rates, fat is synthesized from the glucose without a further increase in glucose oxidation or energy derived therefrom. Although similar studies have not been completed in infants, this suggests that higher glucose loads delivered by solutions containing more than 20% glucose at 150 mL/kg/d may not be beneficial to infants and may contribute to the fatty infiltration of the liver seen with prolonged parenteral nutrition. The use of added insulin is difficult because of unpredictable responses to this hormone.

**Lipids**

The composition, use, and complications of intravenously infused fat emulsions have been discussed. Briefly, in addition to being a concentrated source of energy and providing essential fatty acids, parenteral lipid solutions are iso-osmolar.

### Table 2. Suggested Protocol for a 3-Kilogram Infant on Central Parenteral Nutrition

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Volume (mL/kg/d)</th>
<th>Calories/24 h</th>
<th>Calories/kg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric 10% dextrose solution</td>
<td>100</td>
<td>126</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>(122)†</td>
<td>(40.6)</td>
<td></td>
</tr>
<tr>
<td>Pediatric 10% dextrose solution</td>
<td>150</td>
<td>189</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>(153)</td>
<td>(51)</td>
<td></td>
</tr>
<tr>
<td>Pediatric solution 15% dextrose (central)</td>
<td>150</td>
<td>266</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>(230)</td>
<td>(77)</td>
<td></td>
</tr>
<tr>
<td>Pediatric solution 20% dextrose (central)</td>
<td>150</td>
<td>342</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>(306)</td>
<td>(102)</td>
<td></td>
</tr>
<tr>
<td>Pediatric solution 25% dextrose (central)</td>
<td>150</td>
<td>419</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>(383)</td>
<td>(128)</td>
<td></td>
</tr>
</tbody>
</table>

* From *Pediatric Parenteral Nutrition Manual.* If glucose intolerance develops: (1) the rate of infusion can be lowered, then increased slowly over several hours; (2) intravenous fat emulsion can be started. Ten percent fat emulsion supplies 1.1 kcal/mL (0.122 g/mL) and will allow use of lower glucose loads while maintaining adequate fluid volumes. Fat emulsion contains 87% wt/vol water, and this should be counted in total daily fluid intake. Twenty percent fat emulsion provides 0.222 g fat per milliliter, 2 kcal/mL, and is 77% wt/vol of water (30% fat emulsions should be used with care). Note: Begin intravenous fat emulsion at 0.5 g/kg/d, given over 20 to 24 hours, and increase volume over 96 hours to a maximum of 4 g/kg/d or 45% of total calories, whichever is reached first. Essential fatty acid requirements can be met by 0.5 g/kg/d once to twice a week. All caloric calculations use 3.4 calories/g of intravenous dextrose, due to water of hydration. Weight gain of more than 50 g/d more likely represents edema than cell growth and suggests need for a more concentrated solution to provide adequate calories while limiting fluid intake.

*† Values in parentheses are nonprotein calories.*

When lipid and amino acid-glucose solutions are infused simultaneously into the same vein, the patient receives a higher calorie, lower osmolar solution than with a glucose-amino acid solution alone. The use of "Y" connector tubing proximal to the Micropore filter to infuse lipids simultaneously with, but separately from, the glucose-amino acid solution (containing vitamins, minerals, electrolytes, and trace elements) has greatly improved the effectiveness of peripheral intravenous nutrition and increased its use substantially in nutritional support.

The requirement for linoleic acid (essential fatty acid requirement) can be achieved by supplying 0.5 to 1 g/kg/d of intravenous lipid. Premature infants have adequate lipoprotein lipase to metabolize serum triglyceride concentrations of 100 mg/dL. When triglyceride levels exceed 100 mg/dL, deposition of lipid may occur in reticuloendothelial cells.
or along vascular endothelial surfaces. The easier ways of determining lipid tolerance, visual inspection and nephelometry, correlate well with serum chylomicron concentration, but do not correlate well with the glyceride or free fatty acid concentrations. Unfortunately, the latter chemical determinations are costly, require relatively large volumes of blood, or may not be readily available. The slow infusions are costly, require relatively large volumes of intravenous lipid should minimize the chances of lipid intolerance. Under certain circumstances (eg, sepsis, hyperbilirubinemia, pulmonary hypertension), the lowest dose that meets essential fatty acid requirements should be used.

Vitamins, Minerals, and Trace Elements

Vitamins, minerals, and trace elements must be supplied in parenteral solutions. Metabolic complications have been described for deficiencies and excesses of some of these nutrients. Intravenous dose requirements are not fully known. Current recommendations are derived from oral requirements and knowledge of enteric absorption. Suggested amounts for use in parenteral alimentation solutions are given in Table 3. Guidelines for multivitamin and essential trace element preparations for parenteral use have been established.\textsuperscript{,14,15}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Component & Infants Aged 0.0 to 1.0 yr & Children Aged <11 yr \\
\hline
Fat-soluble vitamins & & \\
Vitamin A (\mu g retinol equivalents) & 400–420 & 400–700 \\
Vitamin D (\mu g) & 10 & 10 \\
Vitamin E (mg \alpha-tocopherol) & 3–4 & 5–8 \\
Vitamin K (\mu g) & 12–20 & 15–60 \\
Water-soluble vitamins & & \\
Ascorbic acid (mg) & 35 & 45 \\
Thiamine (mg) & 0.3–0.5 & 0.7–1.2 \\
Riboflavin (mg) & 0.4–0.6 & 0.8–1.4 \\
Pyridoxine (mg) & 0.3–0.6 & 0.9–1.6 \\
Niacin (mg nicotinamide) & 6–8 & 9–16 \\
Folacin (\mu g) & 30–45 & 100–300 \\
B\textsubscript{12} (\mu g) & 0.5–1.5 & 2–3 \\
Biotin (\mu g) & 35–50 & 65–120 \\
Pantothenic acid (mg) & 2–3 & 3–5 \\
Minerals & & \\
Zinc (mg) & 3–5 & 10 \\
Iodine (\mu g) & 40–50 & 70–120 \\
Iron (mg) & 10–15 & 10–15 \\
Magnesium (mg) & 50–70 & 150–250 \\
Trace elements & & \\
Copper (mg) & 0.5–1.0 & 1.0–2.0 \\
Fluoride (mg) & 0.1–1.0 & 0.5–2.5 \\
Manganese (mg) & 0.5–1.0 & 1.0–3.0 \\
Chromium (mg) & 0.01–0.06 & 0.02–0.2 \\
Selenium (mg) & 0.01–0.06 & 0.02–0.2 \\
\hline
\end{tabular}
\caption{Recommended Safe and Adequate Intakes of Vitamins, Minerals, and Trace Elements*}
\end{table}

GASTROINTESTINAL EFFECTS OF PARENTERAL NUTRITION

The single most problematic gastrointestinal complication of total parenteral nutrition is the development of liver disease, presenting clinically as hepatomegaly and jaundice and histologically as cholestasis, hepatocellular necrosis, and, in far advanced cases, as cirrhosis or hepatic failure.\textsuperscript{16} Since 1971, liver disease has been recognized in approximately one third of premature infants receiving total parenteral nutrition. The etiology remains obscure.\textsuperscript{17} Toxic effects of the amino acid and lipid solutions have been proposed, although not corroborated on further study. The appearance of liver disease with elevations in levels of transaminases, bilirubin, and alkaline phosphatase usually occurs after 2 weeks of total parenteral nutrition; it frequently is progressive and leads to fibrosis and, in a few infants, hepatic failure. These infants frequently are compromised by a number of intercurrent illnesses, including sepsis and severe respiratory distress. It has been difficult to separate these factors from the effects of parenteral nutrition on the development of hepatic dysfunction. The longer the infusions are administered, the greater the risk of cholestasis.

Much less is known about the long-term effects of total parenteral nutrition on gastric, pancreatic, and small bowel structure and function. Studies in animals have documented pancreatic hyposecretion and intestinal mucosal atrophy, which are reversible on resumption of enteral feeding.\textsuperscript{18} The few studies from human subjects\textsuperscript{19} suggest that exocrine pancreatic secretion and gastric parietal cell mass are decreased and the mucosa of the small intestine atrophies during total parenteral nutrition. However, amino acids infused intravenously stimulate gastric acid secretion, but much less than if amino acids are infused into the stomach. These effects disappear over a variable period of time after a return to enteral nutrition. Although similar studies have not been done in premature infants, clinical experience suggests that enteric functions in premature infants also return to normal with time.
ENTRAL FEEDINGS

Initiation of enteral feedings should begin as soon as the gastrointestinal tract is functional. Initially, enteral feedings may be a supplement to parenteral nutritional support, which should not be discontinued until the patient is tolerating enteral feedings well enough to meet nutritional requirements.

SUMMARY

Nutritional requirements of young infants, both premature and full-term, can be met better by recognizing the absorptive and digestive limitations present. When gastrointestinal disease is superimposed on an immature digestive system, special support frequently is needed to maintain adequate growth. This support can be offered as parenteral nutrition or with specialized enteral feeding techniques and formulations.

Because parenteral solutions are formulated to provide complete nutritional support, they may be used for short as well as extended periods of time. Recommendations for use include:

1. Careful catheter placement and confirmation of position by roentgenogram; strict adherence to aseptic techniques and established guidelines of catheter care; and laboratory and clinical monitoring of patients for intolerance.

2. Protein, in the form of crystalline amino acids, should be provided at a rate of 2 to 3 g/kg/d. The concentration of carbohydrate, as glucose (dextrose), should be advanced in a methodical manner to ensure tolerance. Essential fatty acid requirements can be met by infusing 0.5 to 1 g/kg/d of intravenous lipid. The slow infusion of up to 4 g/kg/d of intravenous lipid should maximize tolerance. Vitamins, minerals, and trace elements are essential nutrients and should be contained in parenteral nutrition solutions.

3. The transition to enteral nutrition should begin as soon as possible, with continuation of parenteral nutrition until full nutritional support is achieved via the gastrointestinal tract.

4. Continuous monitoring of nutritional status is mandatory to assure the adequacy of nutritional support. In some settings, a nutritional support team with expertise in parenteral nutrition can help provide optimal care.

ACKNOWLEDGMENTS

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AMERICAN ACADEMY OF PEDIATRICS
A MAJOR PROBLEM

Two years after benoxaprofen (Opren) was launched in a blaze of publicity its product licence [was suspended in Britain] on the grounds of concern about serious side effects. . . . The public has been alarmed by the total of 61 deaths in patients, mostly elderly, taking benoxaprofen and by the admission of the Committee on Safety of Medicines that it has received 3500 reports of adverse reactions. . . . What are the lessons to be learnt?. . . A major unexpected side effect (cholestatic jaundice) was first reported through a medical journal. Yet benoxaprofen had full, careful clinical trials on over 3000 patients and was monitored. . . on 5000 patients after marketing with no mention of jaundice. The problem remains one of numbers. Even if 20,000 patients had been monitored nothing untoward might have been detected. Among the classic side effects that would evade detection by such a programme are the marrow aplasia associated with chloramphenicol, the slow development of chloroquine retinopathy, and the association between unopposed postmenopausal oestrogens and endometrial carcinoma.

Submitted by Student


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