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PARENTERAL NUTRITION IN LOW-BIRTH-WEIGHT INFANTS

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ABSTRACT

Parenteral nutrition has been used in the nutritional management of low-birth-weight infants for the past 25 years. Nonetheless, many aspects of the technique still are not completely understood. Further, other aspects that are reasonably well understood frequently are not applied in clinical practice. As a result, infants requiring this therapy frequently do not benefit maximally from it. Some of the important issues concerning this technique are discussed, and some of the important questions that need to be addressed are identified. Answers to many of these important questions are necessary to further enhance the benefits and diminish the undesired consequences of this therapy for infants who require it.

CONTENTS

INTRODUCTION 471
TECHNIQUES OF PARENTERAL NUTRIENT DELIVERY 473
INFUSATE COMPOSITION 474
Amino Acid Needs 477
Energy Intake 481
Lipid Intake 483
Electrolyte and Mineral Intakes 486
Trace Mineral Intakes 487
Vitamin Needs 487
COMPLICATIONS OF PARENTERAL NUTRITION 488
OTHER CONSIDERATIONS 492
CONCLUSIONS 494

INTRODUCTION

The modern era of parenteral nutrition began in the late 1960s with the demonstration that animals could be maintained successfully for long periods

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of time while receiving only parenterally delivered nutrients (23). This demonstration was followed shortly by a report of successful use of essentially the same technique to produce normal growth and development in an infant who had virtually no remaining small intestine (109). The single previous report of at least semi-successful use of parenteral nutrition in the clinical management of a pediatric patient was described approximately 25 years earlier (51). The subject of this report was a 5-month-old male with severe marasmus who received alternate peripheral vein infusions of a 50% glucose/10% casein hydrolysate mixture and a noncommercial homogenate of olive oil and lecithin, providing a total energy intake of 130 kcal/(kg • day) and a fluid intake of 150 ml/(kg • day). The therapy was terminated after five days, with some improvement in general nutritional status.

By the early 1970s, parenteral nutrition was being used extensively in management of infants and children with congenital or acquired surgically correctable lesions of the gastrointestinal tract (29, 46) and in infants with intractable diarrhea (46, 59). Use of the technique in nutritional management of low-birth-weight (LBW) infants soon followed (22, 80). Currently, most infants who weigh less than 1500 g at birth—at least 1% of all newborns in the United States—receive parenterally delivered nutrients as their major source of nutrition for the first several days to weeks of life. In one multicenter report (39), 81% of such infants received parenteral nutrients for a mean duration of 19 days (range, 12–26 days).

Limited endogenous nutrient stores coupled with relatively high rates of ongoing energy expenditure place LBW infants at great risk for rapid development of malnutrition, if not actual starvation. Theoretically, the total endogenous nutrient stores of the 1000-g infant are sufficient to support survival without exogenous nutrients for only about five days (50). However, despite this theoretical consideration, it is not clear that the increasing use of parenteral nutrition in LBW infants over the past two decades has contributed to the concurrent dramatic improvement in survival. During this time, there have been improvements in many other aspects of neonatal care, and it is impossible to attribute the improved survival to parenteral nutrition alone.

Regardless of the contribution of parenteral nutrition to the current high rate of survival of LBW infants, this therapy has become a firmly established part of neonatal care. However, a number of aspects of the technique as used in any population remain poorly understood, and use of the technique in LBW infants raises yet additional issues. In this review, both the general aspects of the technique that remain poorly understood and those aspects that may be particularly problematical for the LBW infant are discussed, but emphasis is placed on the latter.

TECHNIQUES OF PARENTERAL NUTRIENT DELIVERY

Parenteral nutrition therapy is simply the infusion of a nutrient solution into the circulation. Initially, a hypertonic nutrient mixture was infused at a constant rate through an indwelling catheter placed through a surgical cutdown into either the internal or external jugular vein; it was recommended that the tip of the catheter be in the superior vena cava just above the right atrium and that the distal end be tunneled subcutaneously to exit at a site some distance from the site of insertion (109). Subsequently, it was realized that some of the complications of the technique might be related to the central vein catheter. Thus, infusion of parenteral nutrition regimens by peripheral vein became, and remains, very popular.

By necessity, the glucose concentration of regimens delivered by peripheral vein cannot be much greater than 10%; thus, the nutrient intake that can be delivered by this route without excessive fluid intake is limited. Use of parenteral lipid emulsions helps compensate for this drawback. Nonetheless, if fluid intake is limited to a total volume of 150 ml/(kg • day) and intravenous lipid intake is limited to 3 g/(kg • day), the maximum energy intake that can be delivered is approximately 80 kcal/(kg • day) (44). Although the growth achievable with this intake is less than that achievable with conventional central vein infusions of up to 120–125 kcal/(kg • day), it probably is adequate over the short term. Moreover, few LBW infants are able to tolerate the maximal energy intake that can be delivered by central vein.

Part of the popularity of peripheral vein infusion is based on the concept that this route of delivery is easier and less time-consuming than successful delivery by central vein. This concept, however, is not necessarily valid. The nursing supervision required for successful peripheral vein delivery is at least equal to that required for successful central vein delivery. In addition, considerable time and effort are required to maintain peripheral vein infusions. Although the complications associated with the two routes of delivery are different in nature and severity, the overall incidence of complications with the two routes of delivery appears to be similar (55). Thus, the choice of peripheral versus central vein delivery of nutrients is best based on an individual infant's clinical condition and nutritional needs rather than on the perceived ease or difficulty of a particular technique.

Over the past few years, use of small silastic or polyurethane catheters inserted into the superior vena cava through a needle placed percutaneously via a peripheral vein has become quite popular. Although the technique was described initially some 20 years ago (74, 91), its advantages and/or disadvantages versus those of conventional central and/or peripheral vein techniques of nutrient delivery have not been evaluated extensively. Available data sug-

gest that these catheters do not remain functional as long as central catheters placed in the conventional manner but that they remain functional for a much longer period than does a single peripheral vein site (76, 95). They also appear to be as safe as conventional central vein catheters (10, 95).

Whether delivered by peripheral or central vein, the nutrient infusate should be infused at a constant rate with a constant infusion pump. Placement of a 0.22–μ membrane filter between the catheter and the administration tubing is often considered optional; however, use of a filter prevents infusion of any microscopic particulate matter and/or bacteria that may be present in the infusate.

Many infants tolerate the same infusate for the total duration of parenteral nutrition, but others, particularly more immature and clinically unstable infants, require frequent adjustment of the intake of one or more nutrients. For this reason, it is important to be able to change the composition or volume of the infusate in response to clinical and chemical monitoring or to an increase or decrease in fluid needs.

INFUSATE COMPOSITION

Regardless of route of delivery, the parenteral nutrition infusate must include adequate amounts of amino acids, energy, electrolytes, minerals, and vitamins. However, the amount of each the infusate should contain varies considerably depending on the infant's age, maturity, and clinical condition, as well as on the results to be achieved with the parenteral nutrition regimen. Suitable central vein and peripheral vein infusates for LBW infants are shown in Table 1. In general, the peripheral vein infusate is appropriate for the first several days of life and for infants likely to require parenteral nutrients for only a short time. The central vein infusate, on the other hand, is more appropriate for depleted infants or infants likely to be dependent on parenterally delivered nutrients for more than 7–10 days. Typically, the peripheral vein infusate is started and later changed to the central vein infusate if enteral feedings must be further delayed.

Several crystalline amino acid mixtures (Table 2) are available for use as the nitrogen source of parenteral nutrition infusates. The amount provided usually ranges from 2 to 4 g/(kg • day); an intake of 2–2.5 g/(kg • day) results in nitrogen retention comparable to that observed in normal, enterally fed term infants, but a higher intake is required to achieve a rate of nitrogen retention equal to the intrauterine rate.

Glucose is the predominant energy source of most parenteral nutrition regimens. An intake greater than 15 g/(kg • day) rarely is tolerated by any infant on the first day of therapy, and the amount tolerated by most LBW infants frequently is much less. However, intake usually can be increased by at least 2 g/(kg • day) until the desired intake is achieved. Although larger amounts

Table 1 Composition of typical nutrient infusates used for central and peripheral vein infusion

Component	Vein [amount/(kg · day)]	
	Central	Peripheral
Amino acids	3–4 g	2.5–3.0 g
Glucose	15–25 g	10–15 g
Lipid emulsion	0.5–3.0 g	0.5–3.0 g
Sodium	2–3 mEq	2–3 mEq
Potassium[a]	2–4 mEq	2–4 mEq
Calcium	80–100 mg	40–80 mg
Magnesium	3–6 mg	3–6 mg
Chloride	2–3 mEq	2–3 mEq
Phosphorus[a]	43–62 mg	43–62 mg
Zinc[b]	200–400 μg	200–400 μg
Copper[b]	20 μg	20 μg
Other trace minerals[b]		
Iron[b]		
Vitamins (MVI-Pediatric®)[c]		
Total volume	120–130 ml	150 ml

[a]With a lower calcium intake [40–60 mg/(kg · day)], a phosphorus intake in excess of 1.4 mmol/(kg · day) or 43 mg/(kg · day), the amount given with a daily potassium intake of 2 mEq/(kg · day) as a mixture of KH_2PO_4 and K_2HPO_4, frequently results in hyperphosphatemia. Although this may not be true with the calcium intakes suggested here, a potassium intake of more than 2 mEq/(kg · day) should be given initially as KCl, and the infant should be monitored carefully to assess the adequacy of phosphorus intake.

[b]See text and Table 4. Iron Dextran (Imferon®, Fisons Corp., Bedford, MA) can be added to the infusate of patients requiring parenteral nutrition, but the dose should be limited to 0.1 mg/(kg · day). Alternatively, the indicated intramuscular dose can be used intermittently, either as the sole source of iron or as an additional dose.

[c]MVI-Pediatric® (Armour Pharmaceutical Co., Chicago, IL) is a lypholized product. When reconstituted as directed, 2 ml added to the daily infusate provides 280 μg of vitamin A, 2.8 mg of vitamin E, 80 μg of vitamin K, 4 μg (64 IU) of vitamin D, 32 mg of ascorbic acid, 520 μg of thiamine, 560 μg of riboflavin, 400 μg of pyridoxine, 6.8 mg of niacin, 2 mg of pantothenic acid, 8 μg of biotin, 56 μg of folic acid, and 0.4 μg of vitamin B_{12}. See Table 5.

are often given, it is usually recommended that parenteral lipid intake not exceed 3 g/(kg • day) (17).

Convenient additive preparations of electrolytes, minerals, and vitamins are available; however, the content of individual vitamins in the available multivitamin preparations are not necessarily optimal (see below). Because of the low solubility of calcium phosphate, inclusion of sufficient amounts of both calcium and phosphorus is virtually impossible. The amounts of these two

Table 2 Amino acid pattern (mg/g) of selected amino acid mixtures

Amino acid	Aminosyn®[a]	Aminosyn-PF®[a]	Travasol B®[b]	FreAmineIII®[c]	Trophamine®[c]	Novamine®[d]
Isoleucine	72	76	48	70	82	50
Leucine	94	119	62	91	140	70
Lysine	72	68	58	73	82	79
Methionine	40	18	58	53	33	50
Phenylalanine	44	43	62	56	48	70
Threonine	52	52	42	40	42	50
Tryptophan	16	18	18	15	20	16
Valine	80	64	46	66	78	65
Histidine	30	32	44	28	48	59
Cystine	0	0	0	<3	<3	<5
Tyrosine	4.4	6	4	0	23[e]	4
Taurine	0	7	0	0	2	0
Alanine	128	70	207		53	141
Aspartate	0	53	0	0	32	30
Glutamate	0	82	0	0	50	50
Glycine	128	38	207	71	37	70
Proline	86	82	42	112	68	59
Serine	42	50	0	59	38	40
Arginine	98	123	103	95	122	99

[a]Abbott Laboratories, N. Chicago, IL.
[b]Clintec, Morton Grove, IL.
[c]McGaw Laboratories, Irvine, CA.
[d]Kabi-Vitrum, Inc, Franklin, OH.
[e]Mixture of L-tyrosine and *N*-acetyl-L-tyrosine.

minerals suggested in Table 1 usually are compatible, but the amount of calcium is not sufficient to support optimal skeletal mineralization. Any infant likely to require parenteral nutrients for more than a few days should receive zinc. If exclusive parenteral nutrition is required for more than two weeks, other trace minerals [e.g. copper, chromium (56), selenium (60), molybdenum (1)] also should be provided.

The amounts of various nutrients to be provided parenterally depend, in large part, on the endpoints to be achieved with the therapy. For example, the requirements for normal growth are considerably greater than are the requirements for merely preserving existing body composition, and the requirements for maintaining normal growth and also supporting catch-up growth are even greater. Although the requirements for achieving any specific goal remain poorly defined, considerable information is available concerning the amounts of some nutrients needed, particularly protein and energy. However, less information is available concerning special requirements imposed by immaturity or by differences in metabolism incident to parenteral versus enteral delivery. The sections that follow summarize what is known about the parenteral requirements for various nutrients, as well as some of the issues concerning requirements that have yet to be resolved.

Amino Acid Needs

Some years ago, Anderson et al (2) reported that LBW infants who received a peripheral vein regimen providing an energy intake of 60 kcal/(kg • day) with an amino acid intake of 2.5 g/(kg • day) during the first week of life were in positive nitrogen balance [178 mg/(kg • day)] but did not gain weight, whereas infants who received the same energy intake with no amino acids were in negative nitrogen balance [−132 mg/(kg • day)]. More recently, these general findings have been confirmed in smaller, sicker, more immature infants (48, 87, 89, 106). On average, infants who receive no amino acid intake lose at least 100 mg/(kg • day) and up to 180 mg/(kg • day) of nitrogen. Because these losses reflect net tissue breakdown, infants who receive no nitrogen intake for the first few days of life experience a daily protein loss of from 0.6 to 1.2 g/kg, or about 1% of endogenous protein stores. This can be prevented by provision of an amino acid intake at least equal to endogenous losses. Recent studies in small, sick, LBW infants suggest that a parenteral amino acid intake of 2 g/(kg • day) with an energy intake as low as 35–50 kcal/(kg • day) consistently results in positive nitrogen retention without significant metabolic abnormalities (48, 88). Based on these findings, it seems desirable to provide an amino acid intake of at least 2 g/(kg • day) as soon after birth as feasible, preferably within the first 24–48 h of life.

The factorial approach is commonly used to estimate the protein requirement

of any population. This approach sets the requirement as the amount needed for growth (corrected for the less than 100% efficiency of conversion of dietary protein to body protein) plus the amount needed to replace excretory and skin losses. Assuming that parenterally administered amino acids are converted to body protein with an efficiency of 75% and that endogenous nitrogen losses are about 160 mg/(kg • day), equivalent to 1 g/(kg • day) of protein, the parenteral amino acid intake required to produce the intrauterine rate of nitrogen retention [i.e. 300 mg/(kg • day), or 1.875 g/(kg • day) of protein (113)] is about 3.5 g/(kg • day).

This estimate is 15–20% higher than the intake of 3 g/(kg • day) that Zlotkin et al (115) found was necessary to produce the intrauterine rate of nitrogen retention. Explanations for this small difference include the possibility that the previously reported nitrogen retentions were overestimates of the amount actually retained as body protein, that parenterally administered amino acids are converted to body protein with greater than 75% efficiency, or that inevitable nitrogen losses, particularly after the first week of life, are less than assumed.

The amino acid requirement will be even greater if catch-up growth also is to be produced. This additional requirement can be estimated in the same way as the amino acid requirement for growth, i.e. the amount of catch up desired corrected for the inefficiency of converting intake to body protein. For example, if a 10-day-old infant's parenteral amino acid intake has been sufficient to match endogenous nitrogen losses but insufficient to result in deposition of new body protein, he/she is 10 days behind the fetus of comparable age with respect to protein deposition. Since the intrauterine rate of protein deposition is 1.875 g/(kg • day), this infant must deposit an additional 18.75 g of protein per kg to catch up with the fetus of comparable age. If the efficiency of conversion of parenteral amino acid intake to body protein is 75%, the infant must receive an additional 25 g of protein per kg. If this is provided over a 10-day period, the daily intake required for catch-up growth alone is 2.5 g/(kg • day). If provided over a longer period, which is probably more reasonable, the daily intake, of course, will be less.

The quality of the parenteral amino acid intake also appears to be important. Duffy et al (24) found that infants who received a regimen containing a crystalline amino acid mixture retained more of the nitrogen intake than those who received a regimen containing casein hydrolysate; protein synthesis also accounted for a greater percentage of total nitrogen flux in those who received the crystalline amino acid regimen. Helms et al (52) observed that infants who received a regimen containing a parenteral amino acid mixture designed to result in normal plasma amino acid concentrations retained 78% of the amino acid intake, whereas infants who received an isocaloric regimen containing an older, general-purpose parenteral amino acid mixture designed for adults re-

tained only 66% of intake. However, the specific reason for better utilization of one regimen over the other remains unclear. Helms et al (52) suggested that provision of more optimal intakes of cyst(e)ine and tyrosine, both of which are considered indispensable for the infant (99), was responsible for the better nitrogen retention of the infants who received the newer amino acid mixture. While perhaps not entirely valid, this certainly is a logical suggestion.

Cystine and tyrosine are virtually insoluble, and cysteine is unstable in aqueous solution; hence, no currently available parenteral amino acid mixture contains appreciable amounts of either. Moreover, plasma cyst(e)ine and tyrosine concentrations of infants receiving cyst(e)ine- and tyrosine-free amino acid mixtures are quite low, and greater intakes of methionine and phenylalanine do not result in greater plasma concentrations, respectively, of cyst(e)ine and tyrosine (110). The hepatic activity of cystathionase, a key enzyme in endogenous conversion of methionine to cysteine, is absent or low throughout gestation and for some time postnatally (32, 103). Thus, this developmental delay is an acceptable explanation for the low plasma cyst(e)ine concentration of infants receiving cyst(e)ine-free parenteral nutrition regimens. Because there appears to be no developmental delay in the hepatic activity of enzymes involved in conversion of phenylalanine to tyrosine (85), and because conversion of phenylalanine to tyrosine has been demonstrated in LBW infants (61), it is difficult to explain the low plasma tyrosine concentration of infants receiving tyrosine-free parenteral nutrition regimens on this basis.

Plasma cyst(e)ine and tyrosine concentrations of adults receiving cyst(e)ine- and tyrosine-free parenteral nutrition regimens also are low in comparison to those receiving either the same parenteral regimen by intragastric infusion (102) or a cyst(e)ine- and tyrosine-free elemental enteral diet (11). In one study, patients who received the parenteral regimen also had lower plasma concentrations of carnitine, creatine, and choline (11). Since endogenous synthesis of these compounds requires a methyl group from *S*-adenosylmethionine, the first intermediate in the usual pathway of conversion of methionine to cyst(e)ine, the investigators suggested that parenterally delivered methionine may be metabolized by an alternative pathway, perhaps immediate transamination. The specific reason for the apparent requirement for tyrosine is less clear, but a similar mechanism seems reasonable.

Cysteine hydrochloride is soluble and also is reasonably stable for short periods in aqueous solutions; thus, it is possible to supplement parenteral nutrition infusates with cysteine hydrochloride. However, early trials of cysteine supplementation (68, 114) did not show a beneficial effect of parenteral cysteine intake on nitrogen retention, perhaps because the tyrosine content of the control regimens of these studies also was low, and any beneficial effect of cysteine intake on nitrogen retention was masked by concurrent tyrosine deficiency. One of the newer parenteral amino acid mixtures contains *N*-ace-

tyl-L-tyrosine (Table 2), which is soluble, and infants receiving this amino acid mixture also have higher plasma tyrosine concentrations than do infants receiving mixtures without it (45, 47). Also, infants receiving this parenteral amino acid mixture with cyst(e)ine hydrochloride retain about 35% more nitrogen than do infants receiving an isonitrogenous amino acid intake without cysteine hydrochloride (58).

Rivera et al (87), studying cysteine supplementation of a parenteral nutrition regimen containing an amino acid mixture without *N*-acetyl-L-tyrosine, also found that the nitrogen retention of infants who received cysteine was higher than those who did not. Cyst(e)ine, in addition to being a component of protein, is a component of the important antioxidant tripeptide, glutathione. Because the plasma concentration of glutathione is low in LBW infants (98), it is tempting to speculate that cysteine supplementation will raise plasma glutathione concentration. However, the available data raise as many questions as answers. For example, Mendoza et al (72) found that whole blood glutathione concentration increased by ~80% in infants who received parenteral nutrition regimens supplemented with cysteine, whereas it decreased by 35% in infants who received no cysteine supplementation. In contrast, Kashyap et al (58) found that cysteine supplementation had no effect on plasma glutathione concentration. These seemingly conflicting findings should precipitate further studies of the role of plasma versus erythrocyte glutathione, particularly in protection against oxidant stress.

Definitive data showing that inclusion of *N*-acetyl-L-tyrosine improves nitrogen retention of infants receiving parenteral nutrition are lacking. However, Wykes et al (111) have shown that piglets receiving *N*-acetyl-L-tyrosine retain nitrogen somewhat better than do piglets receiving a tyrosine-free parenteral nutrition regimen but not as well as piglets receiving the same amount of tyrosine as a dipeptide. This probably is related to the fact that *N*-acetyl-L-tyrosine is metabolized only very slowly by both infants and piglets. In infants, for example, ~40% of *N*-acetyl-L-tyrosine intake is excreted in the urine, and the plasma concentration of this tyrosine derivative is as high or higher than the concentration of tyrosine (45, 47).

The inability to provide adequate tyrosine to infants requiring parenteral nutrition, particularly those who are infected or experiencing other forms of stress, may limit the efficacy of this form of nutritional management. For example, a successful response to stress includes synthesis of a variety of acute-phase proteins. Waterlow (107), using data of others (15, 64), has estimated that the septic adult synthesizes about 1.2 g of these proteins per kg daily. If the septic infant responds similarly, the amino acid needs for synthesis of acute-phase proteins approximately doubles the intake necessary to maintain nitrogen equilibrium, and in the absence of sufficient intake, endogenous protein breakdown must increase in order to support a successful acute-phase

protein response. However, as pointed out by Reeds et al (86), the amino acid pattern of most acute-phase proteins is considerably different from that of the body proteins; for example, the aromatic amino acid content of the mixed acute-phase protein response as estimated by Waterlow (107) is roughly double the aromatic amino acid content of mixed body proteins. Thus, the endogenous protein breakdown required to support the acute-phase protein response is roughly double the amount of acute-phase proteins synthesized.

Energy Intake

Theoretically, if amino acid intake is adequate, an energy intake approximating energy expenditure [i.e. 55–65 kcal/(kg • day)] is sufficient to maintain body weight, but an energy intake in excess of energy expenditure is necessary for achievement of weight gain. Although this theoretical consideration has been confirmed by a number of investigators, the marked variability in resting energy requirements among infants makes it difficult to predict the total energy intake necessary to produce a specific rate of weight gain. For example, the resting energy expenditure of infants with bronchopulmonary dysplasia is 10–30% greater than that of infants without bronchopulmonary dysplasia (108). Hence, infants with bronchopulmonary dysplasia require a greater energy intake to produce a specific rate of weight gain than do infants without this condition. The same is likely to be true for infants with other chronic or acute clinical conditions, but definitive data are not available.

Zlotkin et al (115) have shown that LBW infants who receive an energy intake of 80 kcal/(kg • day) with a concomitant amino acid intake of 3 g/(kg • day) gain weight, on average, at a rate approximating the intrauterine rate. Those who receive a greater energy intake, theoretically, will experience an even greater rate of weight gain. However, the greater rate of weight gain incident to a greater energy intake is likely to result entirely from a greater rate of deposition of adipose tissue. Hence, if the rate of weight gain of an infant receiving 80 kcal/(kg • day) is acceptable, it is unlikely that a greater energy intake will be particularly desirable unless it is accompanied by a greater amino acid intake. Such intakes, theoretically, should support greater rates of deposition of both protein and adipose tissue, but there are few data concerning this theoretical possibility.

The relationship between energy intake and nitrogen utilization also must be considered. The usual concept is that utilization of any adequate protein intake will improve if energy intake is increased (8, 75). Zlotkin et al (115) have documented greater retention of amino acid intakes of both 3 and 4 g/(kg • day) with a concomitant energy intake of 80 versus 50 kcal/(kg • day). However, Pineault et al (83) observed only minimal differences in nitrogen retention of LBW infants receiving an amino acid intake of 2.7 g/(kg • day)

with an energy intake of 80 versus 60 kcal/(kg • day). These two sets of data suggest that a parenteral energy intake of about 22 kcal/g of concomitant amino acid intake will result in reasonable, although perhaps not maximal, amino acid utilization. This suggestion, of course, requires confirmation by actual clinical studies. If correct, an infant who can tolerate an energy intake of 30 kcal/(kg • day) should easily tolerate an amino acid intake of 1.35 g/(kg • day). Since this amino acid intake is at least as much as the expected urinary nitrogen losses, it should result in nitrogen equilibrium or, perhaps, a minimally positive nitrogen balance.

The distribution of energy intake between glucose and lipid also may be important with respect to amino acid utilization. In general, the nitrogen-sparing effect of carbohydrate in the absence of nitrogen intake is not shared by fat, but differences between the effects of parenterally administered glucose versus lipid on utilization of concomitantly administered amino acids appear to be minimal. Pineault et al (83), studying the effects of parenteral lipid intakes of 3 versus 1 g/(kg • day) at total energy intakes of both 60 and 80 kcal/(kg • day), found that the higher carbohydrate regimens, regardless of total energy intake, resulted in somewhat lower plasma concentrations of most amino acids. Although this finding suggests that the amino acid intake was used more efficiently by infants who received the greater carbohydrate intakes, the rates of nitrogen retention did not differ. A more recent study in larger infants suggests that inclusion of lipid may be preferable (7).

Unfortunately, many LBW infants, particularly smaller infants and infants with a variety of medical problems, are unable to tolerate an energy intake that even approaches the amount necessary for normal growth. However, even during the first several days of life, most will tolerate a glucose intake of at least 5 g/(kg • day) and a lipid intake of at least 1 g/(kg • day). This combination provides a non-protein energy intake of only about 30 kcal/(kg • day), considerably less than that required for energy balance but sufficient to support reasonable utilization of an amino acid intake of up to 1.5 g/(kg • day). Thus, this combination of intakes should result in nitrogen equilibrium, perhaps even a slightly positive nitrogen balance, without either marked hyperaminoacidemia or azotemia.

Collins et al (16) have shown that glucose intolerance, the more common reason for being unable to provide energy needs, can be alleviated by careful administration of insulin. In these investigators' hands, insulin administration permitted delivery of considerably greater glucose intakes and achievement of greater rates of weight gain. Moreover, it did not result in hypoglycemia or other problems. Nonetheless, some question the advisability of using insulin routinely to circumvent what can best be described as physiologic insulin resistance rather than insulin deficiency.

Table 3 Composition (amount/liter) of parenteral lipid emulsions

Component	Soybean oil emulsion[a]	Soybean/safflower oil emulsion[b]
Soybean oil (g)	100	50 or 100
Safflower oil (g)	–	50 or 100
Egg yolk phospholipid (g)	12	up to 12
Glycerol (g)	22.5	25
Fatty acids (% of total):		
16:0	10	8.8
18:0	3.5	3.4
18:1	26	17.7
18:2	50	65.8
18:3	9	4.2
Particle size (microns)	0.5	0.4

[a]Intralipid®, Kabi-Vitrum, Sweden.
[b]Liposyn II®, Abbott Laboratories, N. Chicago, IL.

Lipid Intake

Parenteral emulsions of soybean oil and a mixture of safflower and soybean oils are currently available (Table 3). The emulsifying agent of both is egg yolk phospholipid, and the emulsion particles of both are roughly the size of chylomicrons or very-low-density lipoproteins. After infusion, the triglyceride portion of these particles is hydrolyzed by endothelial lipoprotein lipase, and the free fatty acids and glycerol released are metabolized by the usual pathways (43). The ability to hydrolyze the infused emulsion particles increases with increasing gestational age, and at any gestational age, the capacity for hydrolysis is greater in the infant whose size is appropriate for gestational age versus the infant who is small for gestational age (3, 20). A number of clinical conditions (e.g. infection, surgical stress, malnutrition) adversely affect the hydrolysis step (26), but little information is available concerning the factors that affect metabolism of free fatty acids and glycerol.

If the lipid emulsion is infused at the same or lower rate than the rate of hydrolysis, it is unlikely that plasma triglyceride concentration, a reflection of the accumulation of the infused triglyceride emulsion, will change appreciably. However, if the rate of infusion exceeds the rate of hydrolysis, plasma triglyceride concentration will increase. Moreover, if this increase in triglyceride concentration is of sufficient magnitude, it is likely to exert adverse effects on pulmonary diffusion (36, 82) and polymorphonuclear leukocyte function (14, 66). Conversely, if the rate of triglyceride hydrolysis exceeds the rate at which the released free fatty acids are oxidized (and/or stored), the plasma concen-

tration of free fatty acids will increase. Since free fatty acids displace bound bilirubin from albumin (77), this possibility is of some concern in infants with hyperbilirubinemia. Unfortunately, the concentration of free fatty acids likely to result in displacement of albumin-bound bilirubin in vivo is not known. Extrapolations from in vitro data (101) suggest that the concentration of free fatty acids is unlikely to be of sufficient magnitude to cause displacement of albumin-bound bilirubin if total bilirubin concentration is below 10 mg/dl (43).

Hypertriglyceridemia as well as hypercholesterolemia and hyperphospholipidemia appear to be less problematic with infusion of 20 versus 10% lipid emulsions (41, 42). The mechanism is thought to be related to the lower phospholipid/triglyceride ratio of the 20 versus the 10% emulsion and, hence, to less inhibition of lipoprotein lipase activity secondary to infused phospholipid (28). Emulsions containing medium chain triglycerides are being used with increasing frequency in Europe. The triglycerides of these emulsions are hydrolyzed more rapidly (19), and the medium chain fatty acids released are oxidized more rapidly (79); thus, these emulsions may permit safe administration of larger parenteral doses of lipid than is possible with conventional emulsions. To date, these emulsions are not available in the United States.

Low plasma carnitine concentrations are commonly observed in infants and adults (see above) receiving carnitine-free parenteral nutrition regimens (81), and it has been suggested that this may inhibit fatty acid oxidation. However, few trials have shown a clear effect of carnitine supplementation on fatty acid oxidation (78, 90). One exception is a study in which carnitine supplementation following a prolonged period of carnitine-free parenteral nutrition improved fatty acid oxidation (53).

The amount of the soybean oil emulsion necessary to prevent linoleic acid deficiency is approximately 0.5 g/(kg • day), a dose likely to be tolerated by any infant. Since the linoleic acid content of safflower oil is approximately 50% higher than that of soybean oil, an even smaller dose of the safflower plus soybean oil emulsion should provide the linoleic acid requirement. A previously available parenteral emulsion of safflower oil, which contains little or no α-linolenic acid, was associated with α-linolenic acid deficiency (54); however, both emulsions currently available in the United States appear to contain an adequate amount of α-linolenic as well as linoleic acid.

A prudent approach to use of the currently available lipid emulsions in LBW infants is to limit intake initially to 0.5 g/(kg • day), particularly in infants who are likely to experience difficulties hydrolyzing the emulsions and in infants with hyperbilirubinemia. Subsequently, as tolerance of the emulsion is demonstrated and/or hyperbilirubinemia resolves, the amount can be increased. This approach is common in clinical practice, but it appears to be based on the mistaken assumption that slowly increasing intake of the lipid emulsion increases the recipient infant's ability to utilize the infused lipid in the same

way that slowly increasing glucose intake increases ability to utilize glucose. The available data show, instead, that plasma triglyceride and free fatty acid concentrations of LBW infants receiving parenteral lipid emulsions, regardless of the method or duration of lipid infusion, are a function of the amount of emulsion administered over a specific time (6). Plasma triglyceride and free fatty acid concentrations appear to remain within an acceptable range so long as the dose of emulsion does not exceed 0.08–0.12 g/(kg • h), or 2–3 g/(kg • day). Despite the lack of a physiologic reason to gradually increase the dose of lipid emulsion over several days, gradual introduction seems more prudent for smaller infants, small-for-gestational-age infants, and infants who are infected or experiencing other complications associated with delayed triglyceride hydrolysis. In such infants, the graded introduction permits assessment of lipid tolerance before the next increase in dose.

A major theoretical concern with the available parenteral lipid emulsions is that neither contains either n-6 or n-3 fatty acids with a chain length greater than 18 carbons (Table 3). This concern arises from the fact that infants appear to have a limited ability to convert the parent fatty acids of the two series, linoleic (n-6) and α-linolenic acid (n-3), to longer-chain, polyunsaturated fatty acids. Moreover, the fatty acids of the two series compete for the same desaturases and elongases, which appear to prefer the n-3 fatty acids. Thus, the ratio of linoleic to linolenic acid in available parenteral lipid emulsions also is of some concern.

Because appreciable amounts of the longer-chain, more unsaturated members of both the ω-3 and ω-6 fatty acid families rather than the parent fatty acids accumulate during development (12, 13), particularly in the developing central nervous system, the possibility that the infant cannot convert the parent fatty acids to longer-chain, more unsaturated derivatives gives rise to concern regarding the fatty acid pattern of tissue lipids. Indeed, the long-chain, polyunsaturated fatty acid content of both the liver and brain of infants who succumb after receiving only parenteral nutrition is low compared to that of normal infants (69). Further, recent studies in enterally fed infants (9, 105) show that development of retinal function is slower in infants fed formulas containing only vegetable oils than in infants fed the same formula supplemented with long-chain polyunsaturated ω-3 fatty acids or human milk, which contains long-chain polyunsaturated ω–3 and ω–6 fatty acids.

Some of the elongated, desaturated derivatives of both linoleic and linolenic acid are precursors of the various eicosanoids. Thus, if the precursors cannot be formed or are formed in inappropriate ratios to each other, infants receiving available lipid emulsions, theoretically, may develop derangements in eicosanoid metabolism secondary to specific long-chain polyunsaturated fatty acid deficiencies. Indeed, the arachidonic acid content of serum lipids has been shown to decrease in infants receiving the available soybean oil emulsion (30).

Moreover, these infants' urinary excretion of a stable metabolite of prostaglandin E, which is synthesized from arachidonic acid, is very low (31).

Electrolyte and Mineral Intakes

From the early days of parenteral nutrition, the electrolyte content of parenteral infusates has been the same as that of maintenance parenteral fluids (i.e. approximately 3 mmol of sodium and chloride per kg per day and approximately 2 mmol of potassium per kg per day). These intakes seem appropriate for most stable, growing infants (50), but very small LBW infants may require lesser or greater intakes of sodium to maintain a normal plasma sodium concentration, and nutritionally depleted infants may require greater potassium intakes to maintain a normal plasma potassium concentration. Frequent monitoring of plasma electrolyte concentrations and appropriate reformulation of the infusate in response to deranged plasma electrolyte concentrations is recommended, particularly during the first few days of parenteral nutrition.

The parenteral intakes of phosphorus [1.4–2.0 mmol/(kg • day) and magnesium (3–6 mg/(kg • day)] that are usually recommended were established in the same manner as the recommended electrolyte intakes. These intakes, too, appear to maintain normal plasma phosphorus and magnesium concentrations in most infants. However, frequent monitoring of the plasma concentration of both and appropriate reformulation of the infusate in response to monitoring data are recommended.

Most commonly used parenteral nutrition regimens maintain a normal plasma calcium concentration but, because of the insolubility of calcium phosphate, do not provide an adequate calcium intake. Hence, osteopenia, fractures, rickets, and collapsed vertebra have been reported in both LBW and term infants who require parenteral nutrition as their sole source of nutrient intake for prolonged periods (62, 63). The probable requirement for calcium, based on the accretion rate of the fetus during the last trimester of gestation (113), is about 100 mg/(kg • day). Until recently, it was impossible to provide more than half this amount unless the phosphorus intake was lowered sufficiently to result in hypophosphatemia. The lower pH of some of the newer amino acid mixtures permits administration of up to 80 mg of calcium per dl without sacrificing phosphorus intake. Such intakes have been shown to result in more optimal skeletal mineralization (84).

Calcium phosphate, interestingly, is more soluble at cooler versus warmer temperatures. This peculiarity raises serious concerns about the overall safety of recently advocated three-in-one or complete parenteral nutrition infusates (i.e. mixtures of glucose, amino acids, lipid emulsion, electrolytes, minerals, and vitamins in the same bag or bottle). Because the presence of the lipid in the infusate obscures any precipitate of calcium phosphate that may occur upon

removal of the infusate from refrigeration and warming prior to administration or during the time of infusion, and because such infusates must be administered without an in-line filter, their use in LBW infants seems unwise. This is particularly true for infants in whom efforts are being made to maximize calcium and phosphate intakes.

Trace Mineral Intakes

During the early years of parenteral nutrition, frequent plasma and/or blood transfusions were given to provide needed trace minerals. Reports of zinc and copper deficiencies, even in infants who had received these transfusions, demonstrated the inadequacy of this approach and led to the availability of zinc and copper additives. More recently, additives of all trace minerals for which a deficiency has been demonstrated have become available. However, little definitive information is available concerning the parenteral requirements of any of the trace minerals. In large part, this is because research concerning the parenteral requirements of these nutrients by infants is hindered by the difficulties of measuring plasma concentrations with small volumes of plasma, of interpreting the physiologic significance of plasma concentrations, and of performing accurate retention studies. The current recommendations for parenteral trace mineral intakes (35), summarized in Table 4, are based on the most reliable information available. Data from randomized trials of various intakes are scarce.

Vitamin Needs

The current recommendations for parenteral vitamin intakes are summarized in Table 5. Infants receiving these intakes do not develop obvious vitamin deficiencies or symptoms of excessive intake of any vitamin. However, these recommendations, like those for trace mineral intakes, although based on the best information available are not based on data from randomized trials of different intakes. These intakes also differ somewhat from the consensus recommendations of the authors of a recent textbook concerning nutritional needs of preterm infants (40). The latter recommendations include much greater intakes of vitamin A, particularly for infants with lung disease [700–1500 g/(kg • day) for infants without lung disease and 1500–2800 g/(kg • day) for those with lung disease], greater intakes of vitamin K during the early days of life [300 g/(kg • day)], much lesser intakes of vitamin K for stable growing infants [8–10 g/(kg • day)] and somewhat greater intakes of vitamin E (3.5 g). The recommendation for greater intakes of vitamin A is based on studies showing that this vitamin is important in lung development as well as for recovery from injury (100), that cord plasma concentration is lower in preterm than in term (92) infants, and that greater intakes may decrease the incidence

Table 4 Suggested parenteral intakes of trace minerals[a]

Trace mineral	Preterm infants [μg/(kg · day)]
Zinc	400
Iron	200
Copper	15–20
Selenium	1.5–2
Mangane	1.0
Iodide	1.0
Molybdenum	0.25
Chromium	0.20

[a]If parenteral nutrients are used as a supplement to tolerated enteral feedings or as the sole source of nutrients for <2 weeks, only zinc is needed. From Reference 35.

of chronic lung disease (93, 94). In addition, some is known to be lost into intravenous administration sets, resulting in low plasma levels (38). The consensus recommendations for the parenteral intake of other vitamins are similar to those shown in Table 5 but include a range with the amounts shown in Table 5 being near the upper end of the range.

Clearly, much more research is needed before the parenteral vitamin needs can be clarified further. Unfortunately, this research, like that concerning trace mineral requirements, is difficult. Further, there seems to be little interest in development of additional multivitamin preparations, probably because LBW infants and other pediatric patients requiring parenteral nutrition, although quite numerous, do not constitute a sufficiently large percentage of the patients requiring parenteral nutrition to make development of specialized pediatric and/or LBW infant products profitable.

COMPLICATIONS OF PARENTERAL NUTRITION

The complications of total parenteral nutrition can be classified into two general categories—those related to the technique, particularly the presence of an indwelling catheter (infusion-related complications), and those related to composition of the infusate (metabolic complications).

The major infusion-related complication is infection. Although many of the infusate components support growth of various microorganisms (34, 70), a contaminated infusate is a rare cause of infection. Rather, most infections appear to result either from improper care of the catheter, particularly failure to follow meticulously the requirement for frequent changes of the catheter exit-site dressing, or frequent use of the catheter for purposes other than delivery of the nutrient infusate. Other complications related to central vein infusion include malposition, dislodgment, and thrombosis, including superior

Table 5 Suggested parenteral intakes of vitamins[a]

Vitamin	Amount/(kg · day)
Vitamin A (μg)	280–500
Vitamin E (mg)	2.8
Vitamin K (μg)	100
Vitamim D (μg)	4
(IU)	160
Ascorbic acid (mg)	25
Thiamin (μg)	350
Riboflavin (μg)	150
Pyridoxine (μg)	180
Niacin (mg)	6.8
Pantothenate (mg)	2
Biotin (μg)	6
Folate (μg)	56
Vitamin B_{12} (μg)	0.3

[a]Total daily dose should not exceed the amounts provided by 5 ml of reconstituted MVI-Pediatric® (Armour Pharmaceutical Co., Chicago, IL): 700 μg of vitamin A, 7 μg of vitamin E, 200 μg of vitamin K, 10 μg of vitamin D, 80 mg of ascorbic acid, 1.2 mg of thiamin, 1.4 mg of riboflavin, 1.0 mg of pyridoxine, 17 mg of niacin, 5 mg of pantothenic acid, 20 μg of biotin,140 μg of folic acid, 1 μg of vitamin B_{12}. From Reference 35.

(or inferior) vena cava thrombosis. Malposition can be avoided by radiographic confirmation of the location of the catheter tip prior to infusion of the hypertonic nutrient infusate and reconfirmation as indicated thereafter. The other complications in this category cannot be completely avoided; however, careful attention to all procedures involving the catheter appears to reduce their incidence to an acceptable level.

Infusion-related complications associated with peripheral vein delivery of nutrients include thrombophlebitis, as well as skin and subcutaneous sloughs secondary to infiltration of the hypertonic infusate. Infection appears to be much less common with peripheral than with central vein delivery, probably because infusion sites must be changed so frequently.

The metabolic complications of parenteral nutrition can be subdivided into three categories, i.e. those related to the patient's limited metabolic capacity for the various components of the infusate, those related to the infusate per se, and those related to the fact that nutrients are administered by vein rather than by the gastrointestinal tract. These are summarized in Table 6. The metabolic complications related to the patient's metabolic tolerance of the infusate are likely to be less with the less-concentrated peripheral vein regimens. Certainly,

Table 6 Metabolic complications of parenteral nutrition and their most common cause(s)

Disorder	Most common cause(s)
Related to metabolic capacity of patient	
Hyperglycemia	Excessive concentration or excessive infusion rate (e.g. pump dysfunction) relative to infant's metabolic capacity; sudden change in metabolic state (e.g. infection).
Hypoglycemia	Sudden cessation of infusion; inappropriate use of insulin
Azotemia	Excessive amino acid intake
Electrolyte, mineral and vitamin disorders	Excessive or inadequate intake relative to needs
Hypertriglyceridemia; elevated free fatty acid concentration	Excessive lipid emulsion relative to metabolic capacity (see text)
Related to infusate composition	
Abnormal plasma aminograms	Pattern of parenteral amino acid mixture or its route of metabolism
Hypercholesterolemia/phospholipidemia	Characteristics of lipid emulsion (see text)
Abnormal fatty acid pattern	Characteristics of lipid emulsion or its
Related to parenteral delivery	
GI tract development	See text
Hepatic disorders	See text

glucose intolerance is less frequent with peripheral vein delivery, which limits glucose intake to about 15 g/(kg • day). Electrolyte and mineral disorders usually result from provision of either too much or too little of the particular nutrient relative to the infant's needs, but electrolyte disorders also can result from hyperglycemia and attendant osmotic diuresis. These complications can be controlled by appropriate monitoring of plasma electrolyte and mineral concentrations and reformulation of the infusate in response to the monitoring data.

Since the infusates delivered by central vein and peripheral vein are qualitatively similar, the metabolic complications related to the infusate are similar with the two routes of delivery. One of the major concerns in this category is the fact that few, if any, of the currently available amino acid mixtures result in a completely normal plasma amino acid pattern (110). Some of the reasons for this are discussed above. In part, concern about abnormal plasma amino acid pattern is based on the long-recognized coexistence of mental retardation and elevated plasma concentrations of specific amino acids in patients with inborn errors of metabolism (e.g. hyperphenylalaninemia in patients with phe-

nylketonuria). However, the plasma concentration of many amino acids is low in patients receiving parenteral nutrition, which suggests that the intake of these amino acids may be inadequate. As discussed above, plasma concentrations of the possibly indispensable amino acids cyst(e)ine and tyrosine are quite low unless soluble/stable forms of these amino acids are provided. Plasma concentrations of the branched-chain amino acids also tend to be low with use of most parenteral amino acid mixtures. Plasma concentrations of other amino acids may be low or high, depending on the amino acid pattern of the parenteral amino acid mixture used.

In animals, the abnormal plasma amino acid pattern associated with administration of parenteral nutrition regimens is accompanied by an abnormal tissue amino acid pattern (49). Although this relationship is not necessarily a direct one, the abnormal plasma and tissue amino acid patterns are of concern with respect to possible adverse effects on ongoing protein synthesis. They also raise theoretical concerns regarding the relationship between plasma concentrations of specific amino acids and concentration of various neurotransmitters within the central nervous system (CNS), e.g. plasma tryptophan concentration and CNS serotonin, plasma tyrosine concentration and CNS catecholamines, and plasma concentrations of amino acids that may function as neurotransmitters and CNS concentrations of these amino acids. Unfortunately, this latter area has not been studied sufficiently to warrant major concern or to allay fears.

The final subcategory of metabolic problems resulting from parenteral nutrition probably is related to the fact that the gastrointestinal tract is bypassed. In normal animals, parenteral nutrition, like starvation, results in an appreciable decrease in enteric mucosal mass (27, 57, 65). However, clinical studies of the effects of parenteral nutrition on intestinal tract structure and function do not demonstrate morphologic involution (37, 96). The effect of parenteral nutrition on mucosal enzyme activities is unclear. Some studies show that the specific activity of some disaccharidases decreases relative to that of control animals (65); others show no differences in specific activity between control animals and animals receiving parenteral nutrition (57). These discrepancies may be related to the nature of the diet consumed by the control animals of the different studies. The clinical studies suggest that disaccharidase activities, which usually are low when parenteral nutrition begins, are not fully restored until enteral intake is reinstituted (37).

Many infants maintained solely on parenteral nutrition develop a typical clinical and histologic picture of cholestasis (5, 73). Whether this results from a toxic effect of some component of the parenteral nutrition infusate or simply from bypassing the gastrointestinal tract is not clear. A number of studies, none rigorously controlled, have suggested a number of etiologies, including parenteral amino acid intake. In an uncontrolled study, infants receiving one of

the newer parenteral amino acid mixtures had a lower-than-expected incidence of cholestasis (45). A randomized trial of the effects of isonitrogenous intakes with and without taurine revealed no effects of taurine on liver function during the first 10 days of life (18); however, none of the infants in either group developed hepatic dysfunction. The results of another trial (25) suggested that cholestasis could be reduced by minimal enteral feeding. Since the release of a number of gastrointestinal hormones appears to be delayed by exclusive parenteral nutrition (67), it might be particularly informative to determine if parenteral nutrition affects the release of cholecystokinin, which stimulates contraction of the gall bladder, and if development of cholestasis is related to the pattern of cholecystokinin release.

OTHER CONSIDERATIONS

Some of the questions most commonly asked concerning parenteral nutrition include: When should the therapy be started? How long should it be continued? When should enterally delivered nutrients be introduced? Unfortunately, there are few definitive data on which to base an answer to any of these questions. Thus, it is not surprising that some nurseries routinely start parenteral nutrition soon after birth and continue this form of nutritional management exclusively for several days to weeks, whereas others start parenteral nutrition much later, with or without enterally delivered nutrients, and discontinue it as soon as possible.

As discussed above, the question of when to start parenteral nutrients is more easily addressed than the others. Since infants who receive only glucose lose at least 1% of endogenous protein stores daily whereas those who receive an isocaloric infusate containing amino acids are in positive nitrogen balance without marked hyperaminoacidemia or azotemia, it is difficult to argue against a policy of starting a parenteral nutrition regimen containing amino acids as soon after birth as feasible, preferably within the first 24–48 h.

Whether or not a policy of exclusive parenteral nutrition for some arbitrary period is advantageous is not clear. The issue has been addressed by two controlled trials (33, 112). In one (33), very-low-birth-weight infants (<1200 g) who survived the first 24 h of life were assigned randomly to receive either total parenteral nutrition or intermittent gavage feedings for a two-week period. In the other (112), infants were assigned alternately within the first 24 h of life to receive either total parenteral nutrition or continuous transpyloric infusion of either human milk or a formula. Based on the results of these two trials, exclusive parenteral nutrition for the first one to two weeks of life versus enteral feeding with parenteral feeding backup was not advantageous with respect to acute survival but might reduce the incidence of necrotizing enterocolitis. However, conjugated hyperbilirubinemia, the usual biochemical marker

of cholestasis, was more common in infants assigned to the exclusive parenteral nutrition groups.

Because of the concern that lack of enteral nutrients decreases secretion of gastrointestinal hormones and might impair intestinal tract development (see above), the practice of minimal enteral feeding, i.e. infusion of 1–2 ml of human milk or a standard formula per kg per h during the early days to weeks of life when the bulk of nutrient intake is supplied by parenteral nutrients, has become quite popular. The effects of this strategy have been tested in several randomized trials (4, 25, 71, 97, 104). Provision of 1–2 ml of a standard infant formula or human milk per kg per h results in earlier tolerance of full enteral intakes, better tolerance of enteral intake, shorter duration of parenteral nutrition, more rapid rates of weight gain, and/or a more rapid rate of maturation of intestinal motility. This practice versus parenteral nutrition alone does not appreciably affect the incidence of necrotizing enterocolitis or hyperbilirubinemia.

The information currently available is inadequate to warrant recommendation of a single strategy for use of parenteral nutrition in LBW neonates. Rather, the early nutritional management of each infant should be individualized. For example, infants with a number of predisposing factors for development of necrotizing enterocolitis might receive only parenteral nutrients until some of these factors resolve, whereas those deemed less likely to develop this disease might be started on enteral feedings much earlier. Although many nurseries have standard policies for increasing the enteral intake of all infants, this aspect of feeding also is one that might best be determined on an individual basis.

When to stop parenteral nutrition also is frequently debated. Usually, this is done when sufficient enteral intake to supply fluid requirements is tolerated. This practice may result in nutrient intake being less than optimal for a few days, but it seems reasonable, particularly if nutrient intake prior to this time has been adequate.

Current methods of management at individual institutions range from those that are very tightly controlled, i.e. only a few individuals supervise the parenteral nutrition program for all patients, to those in which any physician is allowed to order any regimen desired for any patient, with or without an assessment of the patient's need for parenteral nutrition and with or without requirements for monitoring either the efficacy or the safety of the regimen ordered. A system in which one of a few standard parenteral nutrition infusates can be ordered by any physician represents a common intermediate system for management of parenteral feeding. The advantages, disadvantages, and costs of these various approaches have been addressed by a single randomized controlled study (21). In this study, neonates requiring parenteral feeding were assigned alternately to receive either a standardized formulation or an individualized formulation monitored by a pharmacist. The group assigned to the

latter strategy received higher intakes of amino acid and energy intakes [2.2 versus 1.9 g/(kg • day) and 63 versus 53 kcal/(kg • day)] and also exhibited a greater rate of weight gain (11.8 versus 4.9 g/day). The total cost of the two strategies was deemed to be roughly equal. The results of this one study confirm earlier impressions that a centralized system of managing parenteral nutrition is most likely to both maximize benefits and minimize risks of the technique (50). Nonetheless, more such studies are needed.

CONCLUSIONS

For the past quarter century, parenteral nutrition has been an established part of neonatal care. However, despite the nutritional advantages of this method of nutritional management, many problems remain. Some of these result from inadequate attention to all aspects of the technique and, hence, are sufficiently controllable that, in most institutions, the benefits of the technique far outweigh its risks. Controlling these problems requires recognition that the technique is deceptively simple and that it should not be used indiscriminately without careful consideration of indications as well as of alternative strategies for nutritional management. Resolution of other problems will require further research. For example, the available parenteral amino acid mixtures and lipid emulsions, although considerably improved over earlier versions, remain far from optimal. Unfortunately, the required research is impeded by the attitude that parenteral nutrition as practiced today, while perhaps not perfect, is preferable to the situation prior to its widespread use. To stimulate the needed research, this attitude must be replaced by one recognizing that the technique undoubtedly can be further perfected, thereby increasing its benefits for infants who require this form of nutritional management.

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