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Introduction

Nutrition support by the parenteral and/or enteral route is freely available in any neonatal intensive care unit (NICU) and plays an important role in the management of sick neonates and infants. It can reduce metabolic complications and minimize the interruption to normal growth. However, nutrition support is frequently applied inappropriately — that is, “too little too late” or “too much too quickly.” The former often occurs when the infant is considered “too sick” or “too immature,” and the latter often occurs when there is an unreasonable expectation that the effects of prior prolonged periods of inadequate nutritional support can be dramatically reversed. This overview, therefore, aims to provide a practical basis upon which optimal nutrition support can be provided to patients in the NICU, taking into account the unique challenges posed by the sick infant.

- I. Special Considerations
- II. Parenteral Nutrition
- III. Enteral Nutrition
- IV. Nutrition Support for Sick Infants With Specific Disorders

I. Special Considerations.

Nutrition support of sick infants, especially preterm infants, in the NICU must take into consideration the following issues:

- A. Tissue stores of nutrients are rapidly depleted if exogenous nutrient intake is not begun immediately. The critical role of early complete nutrition support in minimizing potential problems is shown in Table 26-1.

Table 26-1. Nutritional Issues in the NICU*

Problem**	Potential Solutions
Low tissue energy store	Multiple sources of energy (carbohydrate, fat, protein) from PN or EN
Obligatory tissue (protein) catabolism = 0.5 g/kg/d	Adequate protein and energy intake from PN or EN
Essential fatty acid deficiency	Essential fatty acids and adequate energy intake from PN or EN
Disturbance to circulating concentrations of electrolytes (sodium, potassium, chloride) and minerals (calcium, magnesium, phosphorus) and hydrogen ion	PN or EN with some modifications as necessary
Hyperbilirubinemia	EN to decrease enterohepatic circulation of bilirubin
Glucose intolerance	Complete nutrition support, including nutrients such as thiamine and chromium from PN or EN
Delayed tolerance to full enteral feeding	PN plus trophic feeding
Incomplete catch-up growth and development	Early complete nutrition support

EN, enteral nutrition; NICU, neonatal intensive care unit; PN, parenteral nutrition
*For neonates unable to receive adequate enteral feeding, the use of parenteral dextrose (+/- electrolytes) and water should be limited to the brief period pending the routine availability of PN.
**Pathogenesis begins at birth.

- B. The capacity of enzyme and organ systems is limited.
1. Gastric capacity and intestinal motility may be limiting factors for the delivery, digestion, and absorption of nutrients.
 2. The limited capacity of enzyme systems can result in diminished tolerance of nutrients such as glucose and lipids.
 3. Limited organ function, for example, decreased renal capacity is associated with lower renal tubular glucose absorption and contributes to glucose intolerance.
 4. Neurobehavioral and neuromotor immaturity can impede normal nipple feeding.
 5. There is an increased risk for disease conditions associated with premature birth (e.g., respiratory distress syndrome, necrotizing enterocolitis).
- C. Different problems are associated with underlying illnesses.
1. Nutrient delivery needs to be tailored to the clinical situation and biochemical parameters. For example, if nipple feeding is unsuccessful, a different route of delivery for enteral nutrients or the use of parenteral nutrition (PN) may be needed. Different amounts or combinations of nutrients may be needed in renal or hepatic failure.
 2. Therapies for the illness may interfere with nutritional status.

- a) Long-term diuretic therapy results in increased loss of minerals and trace metals, nephrocalcinosis, and metabolic bone disease.
 - b) Corticosteroid therapy to shorten the duration of mechanical ventilator support can result in negative nitrogen balance, delayed growth, glucose intolerance, and possibly bone demineralization and neurodevelopment impairment.
 - c) Bowel resection decreases the mucosal area for digestion and absorption of nutrients and fluid.
3. After resolution of the acute illness, catch-up growth needs to occur.

D. Nutrition support has several phases (Table 26-2).

Table 26-2. Phases of Nutrition Support for Critically Ill Infants

Phase	Duration*	Primary Source of Nutrient	Goal
Immediate newborn period and during acute illness	Days to weeks	Parenteral nutrition**	Minimize catabolism. Begin nutrition support within 24 hours after birth. Aim to maintain normal biochemical status and some somatic growth, if possible.
Later neonatal period and during hospitalization	Weeks to months	Enteral nutrition***	“Catch-up” growth. Aim to reach normal centile channel for gestation and postnatal age.
Post-hospital discharge	Months to years	Enteral nutrition****	Slower growth rate than phase 2 but still may require additional nutrients. Aim to achieve growth rate comparable to postmenstrual age-matched infants born at term.

*May vary somewhat depending on the extent of functional immaturity and the course of underlying illness.

**Most critically ill infants require a period of PN during the transition to full enteral feeding.

***Term infants require human (own mother’s) milk or standard infant formula. Preterm infants require human milk with fortifier or specifically designed preterm formulas.

****Ad libitum breast-feeding or standard formula. Preterm infants may require additional supplementation or use of specific postdischarge infant formula.

Metabolic response in the critically ill infant is proportional to the degree of stress and involves an increase in the turnover of proteins, fats, and carbohydrates. The resting energy expenditure is high, with protein degradation rates elevated out of proportion to synthetic rates, and resultant negative protein balance. Appropriately designed nutritional support that has a mixed fuel system and is replete in protein does not quell this metabolic response. However, it can minimize the morbidity and mortality associated with depletion of the limited body stores of nutrients and may result in anabolism and continued growth at a rate appropriate to the gender and gestational and postnatal age. Therefore, no infant is too sick to receive nutrition support. It is a matter of whether the nutrients are delivered parenterally or enterally and the composition of the formulation.

II. Parenteral Nutrition

A. Indications. PN can be used as the sole source of complete nutrition support for infants who cannot be fed enterally or as an adjunct to enteral feeding. In sick infants, PN allows prompt

resumption of growth and expedites the transition to full-volume enteral feeding by providing supplemental nutrition while enteral tolerance is reduced. Any infant unable to tolerate adequate enteral feeding for more than 2 or 3 days should receive PN support. However, to optimize nutritional support and minimize complications, PN and/or enteral nutrition (EN) should begin within 24 hours after birth. (1-4) ¹⁻⁴

- B. Preparation. Because of stability and sterility issues (5) ⁵ and the need for adjustments to various nutrient components during the initial phase of nutrition support, PN solutions are usually prepared daily for infants in the NICU. See Table 26-3 for PN macronutrient recommendations for neonates. Major groups of nutrients include the following:

Table 26-3. Recommendations for Parenteral Nutrition Macronutrients for Neonates

Source	Initiation	Advancement	Goal	Neonate	Blood or plasma monitoring
Amino acids	1.5–2 g/kg/d	0.5–1 g/kg/d	2-3 g/kg/d	Term	BUN, ammonia, arterial pH
	1.5–2 g/kg/d	0.5–1 g/kg/d	3.5-4 g/kg/d	ELBW	
	1 g/kg/d	0.25–0.5 g/kg/d	3-4 g/kg/d	Septic, hypoxic	
Dextrose	8 mg/kg/min	1–3 mg/kg/min	12-14 mg/kg/min*	≥1 kg	Lactate concentration Glucose <150 mg/dL
	6 mg/kg/min	1–3 mg/kg/min	12-14 mg/kg/min	<1 kg	Glucose <125 mg/dL
Fat	1–2 g/kg/d	0.5–1 g/kg/d	3 g/kg/d**	Term	Triglycerides <200 mg/dL*** Bilirubin, glucose Bilirubin*****
	0.5–1 g/kg/d	0.25–1 g/kg/d	3 g/kg/d	Preterm	
	0.5 g/kg/d***	0–0.5 g/kg/d	1-2 g/kg/d	Hyperbilirubinemic***** Sepsis Severe respiratory distress	
Energy			90-108 kcal/kg/d	Term	
			100-120 kcal/kg/d	Preterm	
Fluid			130-150 mL/kg/d	Term	
			130-180 mL/kg/d	Preterm	

BUN, blood urea nitrogen; ELBW, extremely low birth weight; FFA, free fatty acids

*Maximum recommended upper limit for glucose intake.

**May consider slightly higher dose in growth failure.

***Heparin 1 unit per milliliter parenteral nutrition solution improves lipid clearance.

****IV fat emulsion infusion over 24 hours maximizes clearance.

*****Minimum fat needed to prevent essential fatty acid deficiency.

*****Bilirubin approaching exchange transfusion levels.

*****IV lipid dose can be increased to normal range when bilirubin is below 50% of exchange level and when sepsis and respiratory distress is under adequate control

Adapted from: A.S.P.E.N. Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *J Parenter Enteral Nutr.* 2002;26(1 suppl):1SA–138SA with permission.

Nash MA. The management of fluid and electrolyte disorders in the neonate. *Clin Perinatol.* 1981;8:251–262 with permission.

Table 26-3 adapted from work contributed by Gordon Sacks, Susan Mayhew, and Debbie Johnson.

1. Protein

- a) During the immediate newborn period, sick infants, especially preterm infants, may not tolerate standard amounts of nutrients normally delivered to clinically stable infants and may not tolerate adequate energy intakes for optimal utilization of amino acids. The administration of glucose alone may result in hyperglycemia and cannot fully prevent tissue catabolism. Early administration of protein as amino acids may decrease the risk for hyperglycemia and promote nitrogen retention. The usual starting dose for amino acids is 1 to 2 g/kg/day. The dose is increased by similar amounts each day to the desired goal, depending on the weight of the infant. Generally, the extremely low birth weight (ELBW, birth weight up to 1 kg) infant may require up to 3.5 to 4g/kg/day, the very low birth weight (VLBW, birth weight up to 1.5 kg) infant may require up to 3 to 3.5 g/kg/day, and the term infant may require up to 2-3 g/kg/day. (1-4,6) ^{1-4,6} Once EN is started, the volume (and therefore the amount) of nutrients from PN is correspondingly decreased.
- b) Commercial amino acid solutions used for infants are formulated to result in plasma amino acid profiles comparable to those of breast-fed infants. Like human milk, these “pediatric” amino acid formulations contain taurine, tyrosine, histidine, aspartic acid, and glutamic acid. They contain lower concentrations of glycine, methionine, and phenylalanine than the amino acid preparations intended for older patients. Preparations with other sources of nitrogen, including dipeptides, are under study.
- c) Cysteine (a conditional essential amino acid for infants that also enhances calcium and phosphorus solubility), glutamine (a primary fuel for enterocytes, lymphocytes, and macrophages as well as a precursor for nucleotides and glutathione), and carnitine (required for optimal metabolism of fatty acids) are not currently included in commercial pediatric amino acid formulations because of problems with short shelf life and uncertain efficacy. Cysteine hydrochloride can be added to PN infusate at a dose of 40 mg/g of amino acids.
- d) Carnitine can be added to PN infusate in varying amounts depending on institutional practice (see Section II.B.2.b).
- e) Glutamine supplement to PN is not recommended. Glutamine at a dose of 20% of total amino acids of PN had no effect on decreasing mortality, late-onset sepsis or necrotizing enterocolitis, or improving tolerance of enteral feeds or growth in ELBW infants. (7) ⁷

2. Energy. Carbohydrate and lipid emulsion are the major sources of energy used in PN. Provision of adequate energy is essential for optimal use of other nutrients for tissue synthesis and growth. Energy requirements are influenced by many factors. Factors that increase energy requirements include prematurity (increased absorptive loss and heat loss), preexisting nutritional status (small for gestational age versus

appropriately grown infants), physiologic stress (fever, sepsis, respiratory failure, etc), type (enteral (versus parenteral) nutrients have absorptive loss) and method of feeding (nipple versus gavage feeding), and rate of growth (tissue synthesis). (8) ⁸ Preterm infants receiving an energy intake as low as 70 kcal/kg/d can achieve positive nitrogen balance⁹ because there is no absorptive or digestive loss of energy with PN. In the presence of adequate protein intake, adequate weight gain occurs at a parenteral energy intake of 80 to 130 kcal/kg/day. Excessive energy intake is associated with increased fat deposition and greater carbon dioxide production, which further complicates any underlying respiratory illness. (10,11) ^{10,11}

a) Carbohydrate

- 1) Dextrose, hydrated glucose solution, is the standard source of carbohydrate used in PN. It may be initiated at a rate of about 4 to 8 mg/kg/min. This is comparable to the range of endogenous glucose production rate in clinically stable infants. (12,13) ^{12,13} Normally, dextrose can be started at 10% concentration, which delivers a glucose load of ~7 mg/kg/min at 100 mL/kg/d. However, immediately after birth or during acute stress events such as sepsis or corticosteroid therapy, the sick or preterm infant may tolerate <5% dextrose solution, which provides a much lower glucose infusion rate. Dextrose concentration can be increased gradually at about 2.5g/100 mL per day to deliver a load of 12 to 14 mg/kg/min. For infants who need PN after a period of adequate enteral feeding, a PN infusate containing 10% or 12.5% dextrose can be used from the onset, provided the blood glucose is normal.
 - 2) A trace amount of glucosuria is not uncommon in critically ill infants, although glucosuria of >1% is of concern and the rate of glucose infusion may need to be decreased. The use of insulin to treat hyperglycemia and promote growth in infants is not well established. Insulin infusion at 0.05 unit/kg/hr (14) ¹⁴ has been associated with the development of lactic acidosis. However, bolus doses of crystalline insulin may be useful to treat persistent hyperglycemia (blood glucose >200 mg/dL) after lowering the dextrose concentration. In our experience, 0.05 to 0.1 unit/kg of crystalline insulin as an intravenous bolus may be effective as an initial dose. Repeated monitoring of blood glucose and acid-base status at 1- to 4-hour intervals is needed to determine whether there is a further need for insulin. Insulin administration should be discontinued when the blood glucose is <100 mg/dL. It is important to monitor for and manage other conditions (e.g., sepsis) that could contribute to hyperglycemia.
- b) Fat emulsions. Available commercial fat emulsions provide a source of concentrated calories and prevent essential fatty acid deficiency (EFAD). Fat emulsions are isotonic. When fat and amino acid–dextrose solutions are infused simultaneously into the same vessel, the patient receives a higher energy and lower osmolar solution (which helps spare peripheral veins from thrombophlebitis) than with amino acid–dextrose alone. Commercial fat emulsion is available as 10% (1.1 kcal/mL) and 20% (2 kcal/mL) soy or soy-safflower oil. These preparations contain >40% by weight linoleic acid and >4% by weight linolenic acid. The use of 20% emulsion is preferred since it is more energy-dense and contains the same amount of phospholipids (1.2% by weight) and same osmolarity as the 10% emulsion. Phospholipid is believed to inhibit

lipoprotein lipase, the main enzyme for intravenous lipid clearance. Newer lipid preparations not available in North America include those containing structured triglycerides (mixture of long- and medium-chain fatty acids on a glycerol backbone) and water-soluble short-chain triglycerides, which may have some metabolic advantages compared with the available lipid emulsions with long-chain triglycerides. However, none of the fat preparations appear to be able to support the normal rate of intrauterine accumulation of very long chain polyunsaturated fatty acids of the n-3 and n-6 families in developing infant tissues. Administration of fat emulsion in an energy-deficient state may not adequately prevent development of EFAD because EFAs can be oxidized to meet energy needs. However, in the presence of adequate energy intake, a minimum of 0.5 to 1 g/kg/d of commercial fat emulsion containing the C18 fatty acids, linoleic acid, and linolenic acid is needed to prevent clinical EFA deficiency. Fat emulsion can be started on the first day of PN at 0.5 to 1 g/kg/d and increased by a similar amount daily up to 3 g/kg/d. To maximize lipid clearance, the daily amount of fat emulsion is generally infused over 18 to 24 hours. Smaller increments and lower total dose may be prudent for acutely ill or ELBW infants. Jaundice and sepsis are not absolute contraindications to the use of fat emulsions. The dose probably should be in the range of 1 to 2 g/kg/d if serum bilirubin is near the exchange level (15)¹⁵ and during the acute phase of sepsis. Parenteral fat can be increased to the normal dose once the serum bilirubin or sepsis is controlled. Carnitine plays an essential role in the metabolism of long-chain fatty acids. However, no convincing evidence of clinical benefit has been demonstrated in infants receiving carnitine-supplemented PN; specifically, there was no evidence of effect on weight gain, lipid utilization, or ketogenesis. (16)¹⁶ Nevertheless, since both breast milk and infant formulas contain carnitine, infants who received PN without carnitine have very low tissue levels of carnitine. Since fatty acid oxidation is impaired when the tissue carnitine levels fall below 10% of normal, it seems reasonable to provide L-carnitine at 2 to 10 mg/kg/d. This approximates the amount provided in human milk and the in utero rates of tissue carnitine accretion. There is no evidence that pharmacological concentrations of carnitine provide greater benefit in infants in the absence of (rare) metabolic defects of carnitine metabolism.

3. Electrolytes and minerals

- a) Sodium and potassium are available as chloride, acetate, and phosphate salts. During the first one to two days after birth, parenteral nutrition for small preterm infants need not contain potassium until regular urine output is assured; and sodium phosphate can be used as the only source of sodium. The latter practice allows the flexibility to use small amounts of sodium bicarbonate as needed and minimizes the risk of hypernatremia if there is high insensible loss of water. The normal range of maintenance intake for sodium and potassium is 2 to 4 mEq/kg/d.
- b) Calcium is usually delivered as 10% calcium gluconate. Phosphorus is added as either a sodium or a potassium salt. During the first one to two days after birth, the parenteral nutrition for small preterm infants may contain about half the maintenance phosphorus content to minimize the risk for hyperphosphatemia. Sodium phosphate is preferred unless there is a risk for hypernatremia. Potassium phosphate can be used in the presence of adequate urine output. Maintenance calcium and phosphorus are usually added at 500 to 600 mg of elemental calcium per L and 350 to 500 mg of elemental phosphorus per L of PN at a weight ratio

of ~1.3 to 1.7:1 (or 1 to 1.3:1 by molar ratio). The ability to maintain calcium and phosphorus solubility in PN solution depends on a number of factors, particularly the type and amount of amino acid and the presence of cysteine. The amount of calcium and phosphorus delivered in PN is several times greater than that absorbed from human milk.

- c) Magnesium is usually added to PN at 25 to 50 mg/L of elemental magnesium. The amount of magnesium may need to be decreased in sick infants with impaired renal function or transiently withheld or provided in a lower amount for infants whose mothers received intrapartum magnesium sulfate infusion.
 - d) Chloride and other anions are normally provided in sufficient quantities if the minerals or cations are given in the recommended amounts. Current commercial amino acid preparations for infants contained minimal amount of chloride at 0.46 to 0.97 mEq per gram of amino acid. Some clinicians also use small amounts of acetate (10–20 mEq/L PN solution) as part of anion intake and as a source of base to lower the risk of metabolic acidosis.
 - e) Supplemental iron usually is not provided with PN for patients in the NICU. However, if PN is provided exclusively for >2 months after birth or if iron deficiency develops, parenteral iron can be administered at 0.1 to 0.2 mg/kg/d, up to as high as 10 mg/kg/d. (17) ¹⁷ Three parenteral products are currently available in the United States: iron dextran, sodium ferric gluconate complex in sucrose, and iron sucrose. Except for iron dextran, the experience with use of iron products in children is extremely limited.
4. Trace minerals. Trace mineral preparations are commercially available as single agents or as combinations of various trace minerals. There is no compelling reason to avoid providing trace minerals for infants requiring short-term PN, and they probably should be provided from initiation of PN. Recommended normal daily trace mineral intakes are the same for preterm and term infants, except for zinc. Recommended intakes are as follows: chromium 0.2 mcg/kg; copper 20 mcg/kg; iodide 1 mcg/kg; manganese 1mcg/kg; molybdenum 0.25 mcg/kg; and selenium 2 mcg/kg. (4) ⁴ Zinc dosing for preterm infants is 400 mcg/kg; for term infants <3 months, 250 mcg/kg; and at >3 months, 100 mcg/kg. The use of both single and combination trace mineral preparations is usually needed to provide the recommended doses. Most institutions provide PN solutions containing chromium, copper, manganese, selenium, and zinc.
 5. Multivitamins. Two commercial multivitamin products are available for use in infants. Both products have the same contents in the same concentration. Neither provides the exact range of estimated needs for all vitamins,⁴ and none of the several recommended dosages has been demonstrated to be superior for sick infants. The manufacturers recommended that for infants weighing <1 kg, 1 to 3 kg, and >3 kg, the intake should be 30%, 65%, and 100% of a 5-mL vial. The American Academy of Pediatrics⁴ recommends 2mL/kg/day up to one vial (5 mL) of multivitamins. The American Society of Clinical Nutrition¹⁸ recommends 40% of a 5-mL vial (2 mL) to patients less than 2.5 kg, and one vial (5 mL) to patients >2.5 kg up to 11 years.

C. Delivery

1. Peripheral or central catheters

- a) Peripheral catheter. To minimize thrombophlebitis, only PN solutions with amino acids and a <12.5% concentration of dextrose are delivered via a peripheral intravenous catheter. (4) ⁴ Coinfusion of fat emulsions reduces the degree of venous irritation.
- b) Central catheter. Higher dextrose concentrations (>12.5%) can be delivered through the central catheter to a large vessel with high blood flow. Insertion of

the catheter into the central venous system by cutdown, percutaneously, or through the umbilical artery or vein is widely used in neonates. Central catheter placement must be confirmed by x-ray before infusion of PN solution.

2. Volume. The delivery of adequate amounts of nutrients parenterally often is limited by the amount of fluid that the sick infant needs or can tolerate. In situations of severe fluid restriction, the concentration of all nutrients must be increased, resulting in extremely high osmolarity and possibly exceeding the limits of solubility of calcium and phosphorus salts. In contrast, in situations of high fluid requirements (>200 mL/kg/d) in preterm infants with low renal thresholds for many nutrients, a diluted infusate must be provided to prevent delivery of excessive nutrients, particularly dextrose. Normally, adequate amounts of parenteral nutrients can be delivered in a total volume of 120 to 160 mL/kg/d. Some flexibility in the tolerance to the volume infused can be achieved by manipulating environmental factors. For example, caring for the neonate under a radiant warmer results in greater insensible fluid loss, thus allowing delivery of a larger volume of PN (Table 26-4).

Table 26-4. Factors Affecting Water Requirements (19) ¹⁹

Factors Increasing Water Requirements	
Environmental Factors	Infant Factors
Radiant warmers Conventional single-walled isolette Phototherapy Ambient temperature above the neutral thermal range	Physiologic Increased permeability of the skin Larger body surface area relative to body weight Increased blood flow to the skin Pathologic Increased respiratory distress Elevated body temperature Glycosuria with osmotic diuresis Gastric or intestinal losses
Factors Decreasing Water Requirements	
Environmental Factors	Infant Factors
Thermal blankets Double-walled isolette Above-ambient humidity	Physiologic Increasing gestation and postmenstrual age Pathologic Renal oliguria

Adapted from Doyle LW, Sinclair JC. Insensible water loss in newborn infants. *Clin Perinatol*. 1982;9:453–482, with permission from Elsevier.

3. Infusion rate. In the NICU, amino acid–dextrose solution is infused continuously over 24 hours to improve tolerance, particularly if higher concentrations of dextrose are used. Fat emulsion is also better tolerated if infused over 18 to 24 hours each day. Infusing fat emulsion over about 18 hours allows the measurement of plasma triglyceride level immediately prior to the next day’s infusion, which makes it possible to determine tolerance to fat emulsion without concern about interference from the triglyceride content of the lipid emulsion.
4. A 2-in-1 versus a 3-in-1 solution. The amino acid–dextrose solution and lipid emulsion can be provided separately as a 2-in-1 solution and delivered together through a Y connector to the peripheral or central venous catheter or through umbilical venous or arterial catheters. In some institutions, PN is delivered as a total nutrient admixture (TNA) or 3-in-1 solution (i.e., mixing all nutrient components in the same container). The

disadvantages of TNA in the NICU are that the stability of each component of TNA is not completely defined, it is impossible to determine whether there is a precipitation of nutrients in the admixture, and a 1.2 micron filter must be used instead of the standard 0.22 micron bacterial filter. TNA also may be a better bacteria growth medium than amino acid–dextrose solution.⁴

5. Light exposure. Amino acid–dextrose solution containing vitamins and other additives and lipid emulsion should be protected from direct exposure to phototherapy light to avoid photodegradation. Some NICUs routinely protect PN infusate from exposure to ambient light.

D. Monitoring (see Tables 26-3 and 26-5).

Table 26-5. Guidelines for Metabolic Monitoring During Parenteral Nutrition

Variable to Be Monitored	Initial Period*	Later Period**
Growth***		
Weight	Daily	Daily
Head circumference	Baseline	Twice weekly
Length	Baseline	Weekly
Intake and output	Every shift	Daily
Glucose reagent strips	1 to 3 times/day	As indicated
Serum electrolytes, urea nitrogen, creatinine	Baseline and every 1 to 3 days	Every 1 to 2 weeks
Serum calcium, magnesium, phosphorus	Baseline and every 2 to 3 days	Every 1 to 2 weeks
Serum triglycerides****	Daily during dose increase	Every 1 to 2 weeks
Serum glucose	As needed	As needed
Total and direct bilirubin	Baseline, as needed clinically	Every 1 to 2 weeks
Total protein and albumin	Baseline	Every 2 to 3 weeks
Alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase	Baseline	Every 2 to 3 weeks
Complete blood cell count	Baseline	Every 2 to 3 weeks
Vitamin and trace mineral status and other specific tests	As indicated	As indicated

*The period before reaching maximum doses of glucose, amino acids, and lipid emulsion, or during any period of metabolic instability. This period normally lasts 3 to 4 days.

**The period during which the patient is in a metabolic steady state. For clinically stable infants receiving the desired intake of nutrients, the interval between laboratory measurements may be increased beyond the above recommendations.

***All measurements should be plotted on growth charts appropriate for sex, gestation⁶² and postnatal⁶³ age. Growth charts based on postnatal growth of preterm infants are biased for nutritional management regimens and should not be used.

****Target level <200 mg/dL.

E. Complications. The potential complications of PN are all seen in the NICU patient.

A. Mechanical

- a) Kinking, compression, or tearing of the catheter can occur with all central catheters, but the thin-walled percutaneously inserted Silastic catheters used in neonates appear to be more prone to kinking and compression. Pneumothorax

and brachial plexus injury may complicate the percutaneous insertion of a subclavian catheter.

- b) Catheter occlusions presumed to be associated with thromboses are treated with 0.25 to 2 mg (0.25–2 mL) of tissue plasminogen activator (tPA) or 5000 units (1 mL) of urokinase instilled in the catheter for 30 to 60 minutes; then the blood and tPA or urokinase is aspirated from the catheter. This may be repeated once. For chemical (e.g., calcium phosphate) or medication precipitate, 0.1N hydrochloric acid (HCl) (1mL) or 0.1N sodium hydroxide (NaOH) (1 mL) may be used with the same technique. For lipid-related occlusion in TNA, 70% ethanol (1 mL) may be used with the same technique. Some clinicians flush tPA or urokinase through the catheter to gain patency of the catheter. In infants, experience with the use of these agents as therapy for catheter occlusion, particularly for the percutaneous Silastic catheter, is limited.
- c) Extravasation of nutrient infusate into interstitial space resulting in skin slough is a frequent complication associated with the use of peripheral intravenous catheters in infants. This complication can be reduced by meticulous observation of the catheter insertion site and removal of the catheter at the first sign of swelling or thrombophlebitis. Extravasation of nutrient infusate into the pleural or pericardial space occurs rarely but may be associated with acute metabolic (decreased plasma glucose), circulatory, or respiratory compromise requiring symptomatic support, including drainage of the fluid.

A. Sepsis

- a) Source identification. Sources of infection can be catheter related, involving the catheter insertion site, the subcutaneous tunnel, or line sepsis (see Chapter 8). Non-catheter-related sources of sepsis should also be considered.
- b) Diagnosis. Cultures of blood drawn from the catheter, a noncatheterized blood vessel, and obvious sites of septic foci are needed.
- c) Therapy. Empiric antibiotic therapy should be started whenever sepsis is suspected (e.g., sudden, unexpected glucose intolerance or temperature instability). Initial therapy should be based on the clinical status of the neonate and the antibiotic sensitivities of microbial organisms prevalent in the NICU. Antibiotics should be adjusted on the basis of culture results. Catheter removal is indicated if sepsis is not promptly resolved. Some clinicians recommend immediate catheter removal if there is evidence of a fungal infection or some gram-negative rods such as *Klebsiella*. Antibiotic lock and antimicrobial-impregnated central venous catheters are not routinely used in NICU patients.

B. Metabolic. Most metabolic complications are related to excessive, imbalanced, or inadequate intake. (1) ¹ A recent shortage of multivitamin preparations resulted in more than 30 cases of vitamin deficiency. (20) ²⁰

- a) Glucose disturbances. Hyperglycemia from excessive glucose load or during short-term stress such as sepsis may result in glucosuria, osmotic diuresis, and dehydration. Treatment of the underlying cause, a decrease in glucose load, and even the use of insulin for brief periods may be needed to correct hyperglycemia. Hypoglycemia may occur with abrupt discontinuation of lipid-free PN containing >12.5% dextrose.
- b) Hypertriglyceridemia. Plasma triglyceride >200 mg/dL may occur during lipid infusion. The infusion of lipids over 18 to 24 hours and the use of heparin in a dose of 1 unit/mL may increase lipid clearance. The latter increases lipoprotein lipase activity. The use of carnitine may be beneficial in clearing triglycerides.

- c) Mineral (calcium, phosphorus, magnesium), blood urea nitrogen (BUN), and acid-base disturbances. Hyper- or hypocalcemia and hyper- or hypophosphatemia can result from excessive or inadequate infusion of these minerals. In addition, phosphate deficiency with hypophosphatemia and secondary parathyroid hormone resistance can cause hypercalcemia even in the presence of low calcium intake. (21) ²¹ Phosphorus must be added to the PN if serum phosphorus is <4 mg/dL during infancy. Hyperphosphatemia (and secondary hypocalcemia) may occur in preterm infants receiving high phosphorus intake because of limited renal excretory capacity. Adjustments may be needed for one or both minerals. Hyper- or hypomagnesemia can result from excessive intake or inadequate renal excretory capacity, or inadequate intake or replacement of gastrointestinal losses. (22) ²²
- d) The potential for metabolic acidosis is higher during the immediate newborn period and during acute stress. Abnormal serum chloride levels from inappropriate intake or inadequate replacement of losses can be associated with metabolic acidosis or alkalosis.
- e) Increased BUN or plasma ammonia has been reported only in infants who received >4 g protein/kg/d and from the use of earlier amino acid preparations.⁴ Starvation and tissue catabolism is a more likely cause of raised BUN in the absence of documented renal failure. Underlying disease processes also may result in disturbances of acid-base status. Occasionally, symptomatic treatment of metabolic acidosis with sodium or potassium acetate and treatment of metabolic alkalosis with sodium or potassium chloride may be appropriate.
- f) Decreased nutrient availability. Decreased nutrient availability may result from adsorption to delivery systems (e.g., insulin, vitamin A), light (especially phototherapy) degradation (e.g., tryptophan, methionine, histidine, riboflavin, vitamin A), and increased nutrient loss (e.g., electrolyte, mineral, or trace metal loss from loop diuretics and to a lesser extent from thiazide diuretics; potassium and magnesium loss with amphotericin B).
- g) Toxic products. Toxic products in PN can be found as contaminants of nutrients or from exposure to the environment during preparation, storage, or delivery to the patient.
 - 1) Aluminum is the best-studied contaminant of parenteral nutrients. Aluminum has no known physiologic role, and preterm infants and infants with severe renal impairment are at risk for aluminum toxicity. Many nutrient components of PN are contaminated with aluminum, and the same nutrients from different manufacturers can have different degrees of aluminum contamination. (23) ²³ Calcium salts alone accounted for >80% of the total aluminum load from PN. (23) ²³ The Food and Drug Administration has labeling requirements concerning aluminum contents on all PN components, and efforts should be made to use products with the lowest aluminum contamination.
 - 2) Formation of toxic lipid peroxidation products is also of potential concern. Ambient and especially phototherapy light increase peroxidation of fatty acids lipid emulsion to form lipid hydroperoxides (24) ²⁴ and also increase hydrogen peroxide generation from multivitamins, in particular the riboflavin in amino acid–dextrose solutions. (25) ²⁵
- h) PN flush solutions and drug-nutrient interactions. All medications not compatible with PN infusate should be administered as close to the catheter entry site as

possible or via a separate catheter. Most, but not all, medications can be flushed with normal saline before and after infusion of medication to minimize any risk of drug-nutrient interaction. Normal saline flush solutions can result in significant sodium intake. Generally, this is well tolerated by many VLBW infants because of the greater sodium needs secondary to decreased renal tubular absorption of sodium or concurrent diuretic therapy. Glucose in the flushing solution can cause swings of blood sugar in VLBW infants. Only preservative-free flush solutions should be used.

- i) PN-associated cholestasis (26-28) [26-28](#)
 - 1) Risk factors. The incidence varies inversely with the degree of prematurity, the duration of PN (>2 weeks), excessive intake of calories and nutrients (e.g., glucose, lipids, amount and type of amino acids, copper, manganese), sepsis, and impaired intestinal function, including dysmotility, bowel rest, and lack of enteral feedings.
 - 2) Management. Enteral feedings should be initiated and continued if feasible. However, PN should not be discontinued if the infant is unable to tolerate enteral feeding. Excessive intake of nutrients, particularly the nutrients that require normal metabolic or excretory function of the liver, should be avoided. For example, protein intake should be the minimum that allows adequate growth and good nutritional status, and copper and manganese supplements may need to be held or reduced and their status monitored. Use of pediatric amino acids solutions and change from continuous infusion to cyclic PN may improve the cholestasis. Medications such as cholecystokinin, ursodeoxycholic acid, and henobarbital have been used with varying success to stimulate bile flow and lower the bilirubin level.
- j) Metabolic bone disease (21,29-31) [21,29-31](#)
 - 1) Risk factors. Metabolic bone disease incidence varies directly with degree of prematurity, duration of PN (>4 weeks), prolonged volume restriction, PN solutions with low mineral (calcium and phosphorus) content, secondary vitamin D deficiency from calcium and/or phosphorus deficiency, (29-31) [29,31](#) aluminum contamination of nutrients, delayed initiation and delay in achieving the full volume of appropriate enteral feeding, and prolonged excessive pharmacotherapy, in particular, with loop diuretics and corticosteroids. Excessive force (e.g., physical restraint during surgery) or during physical therapy has occasionally caused fractures in osteopenic patients.
 - 2) Management. Enteral feedings should be initiated and continued if feasible. However, PN should not be discontinued if the patient is unable to tolerate enteral feeding. The recommended minerals, vitamin D, and other nutrients should be maintained in the PN solution. Pharmacotherapy and physical therapy should be reassessed and modified if necessary. Supplementation with calcium and/or phosphorus alone is not recommended since a balanced intake of all nutrients is necessary for normal bone growth.
- k) Oral aversion. Oral aversion may occur in chronically ill infants who have not been fed for many months. Difficulty in achieving adequate nipple feeding is particularly notable in ELBW infants and those who have experienced hypoxic insults. Non-nutritive sucking during the course of illness does not appear to

improve the ability to nipple-feed; actual oral feeding is necessary for the development of sucking behavior. (32) ³²

III. Enteral Nutrition

A. Assessing readiness for enteral feeding. For the healthy neonate born at term, transition from the placental source of nutrients to enteral feeding usually occurs within a few hours after birth once physiologic adaptation to the extrauterine environment is achieved. For the sick and/or premature neonate, indicators of readiness for enteral feeding include the following:

1. Absence of gastrointestinal anomalies that interfere with adequate delivery, digestion, or absorption of enteral nutrients
2. Cardiorespiratory stability as indicated by the absence of respiratory distress and consistently normal vital signs. The prone or side-lying position with the head of the bed elevated generally improves respiratory gas exchange and decreases gastroesophageal reflux and aspiration.
3. Controversial issues. There are generally no contraindications to enteral feeding under the following conditions, provided the infant is clinically stable:
 - a) Mechanical ventilation or continuous positive airway pressure
 - b) Indwelling umbilical vein or arterial catheters
 - c) Perinatal asphyxia
 - d) Inotropic, sedative, or indomethacin therapy

B. Enteral preparations

1. Human milk. The advantages to the use of human milk include psychosocial benefits to the mother and easy digestibility, low formula and renal solute load, and potential benefits from immunologic and trophic factors for the infant. (33) ³³ Human milk contains long-chain polyunsaturated fatty acids (LCPUFA) of the n-3 and n-6 fatty acid families, and some data show possible neurological or visual developmental advantages in preterm infants fed human milk compared to those fed formulas without LCPUFA supplementation. (34) ³⁴ There are very few contradictions to feeding human milk. (33) ³³ These include the presence of certain maternal systemic infections such as tuberculosis and human immunodeficiency virus, and certain metabolic disorders affecting the infants, including galactosemia. A number of drugs may be secreted into human milk, but not all are thought to be of concern to the infant. (35) ³⁵ The mother should be encouraged to discuss any use of prescription drugs, over-the-counter drugs, or herbal medications with the physician. Presence of jaundice (if determined to be breast milk–associated jaundice) does not preclude continuation of breast-feeding, although a 24- to 48-hour substitution with infant formula may be useful as a diagnostic test and for management.

- a) Human milk can be the exclusive source of nutrition for all term infants for 4 to 6 months after birth. ³³ For small preterm infants, breast milk has insufficient amounts of protein, energy, sodium, calcium, phosphorus, vitamin D, zinc, and probably folic acid to for adequate growth. Commercial powder or liquid human milk fortifier containing multiple nutrients should be used to supplement all small preterm infants fed human milk, at least until ad libitum breast-feeding begins.
- b) Critically ill infants are usually unable to nipple-feed and may not tolerate enteral feeding, and mother’s milk is collected for delivery via gavage feeding or stored for later use. A lactation specialist may be helpful in teaching and assisting in breast-pumping techniques and for

support in maintaining lactation for the mother. Manual expression of breasts or mechanical aids can be used depending on the mother's preference. An electric breast pump that allows simultaneous emptying of both breasts shortens the duration of milk expression and tends to encourage the most milk production. Breast pumping should begin within 24 hours after delivery and should be done every 3 to 4 hours during the day and once or twice at night. A sterile bottle or plastic bag should be used for each collection. Maternal stress and fatigue can decrease milk production. Encouragement and support of the mother may be needed to maintain the milk supply. Routine use of oxytocin nasal spray to promote a let-down response or metoclopramide to stimulate prolactin secretion, and the use of herbal products to stimulate milk production, are not recommended.

- c) Plastic containers are preferred to glass containers for storage of breast milk. (36) ³⁶ Fresh breast milk can be refrigerated for 48 hours without significant microbial growth. During transport from the home to the hospital, fresh milk should be cooled or frozen by packing tightly in a cooler with freezer gel packs. Frozen milk can be stored for about 3 months in a home freezer at -20 degrees Celsius (-4 degrees Fahrenheit). (37) ³⁷ Frozen milk should be thawed in the storage container in a refrigerator or under cool running water. Boiling or microwave heating can affect the nutritional and immunologic properties of human milk. Thawed or refrigerated milk is often warmed under hot water and several drops of milk should be dripped onto the dorsum of the hand to confirm that it is not too hot prior to feeding the baby.
- d) The use of donated human milk is controversial, and the practice remains regional.

2. Commercial preparations

- a) Infant formulas are designed to substitute for human milk in the event that the mother decides not to breast-feed or in the presence of contraindications to breast-feeding. For infants born at term or small preterm infants beyond 6 to 12 months of postnatal age, standard cow milk-based infant formulas should be used. There are limited indications for soy formula (38) ³⁸ or partially hydrolyzed protein formulas. (39) ³⁹ Highly modified infant formulas based on extensive protein hydrolysates or amino acids are used in certain allergic or intestinal disorders (see Section IV).

For small preterm infants, only formulas designed specifically to meet the nutrient requirements of VLBW infants should be used. (40) ⁴⁰ The two commercially available iron-fortified preterm infant formulas contain whole protein with a whey-casein weight ratio of 60:40, long-chain and medium-chain triglycerides in an approximate weight ratio of 1:1, and lactose and glucose polymers in an approximate weight ratio of 1:1. All other nutrients, including LCPUFA, are added in amounts designed to meet the nutrient requirements of preterm infants when fed at about 150 mL/kg/d. Both commercial preterm infant formulas are available in 20 or 24 kcal/oz preparations and all are isotonic. The higher nutrient density preparation can be used as the initial feeding and there is no advantage in the use of the lower density preparation.

Soy protein-based formula should not be used because of uncertain mineral absorption and higher concentrations of some trace elements such as manganese and aluminum. Protein hydrolysate formulas with other highly modified macronutrients, including a high proportion of medium-chain triglycerides with glucose polymers as the sole source of carbohydrate, theoretically can improve absorption of these nutrients. However, VLBW infants who receive these formulas may have distortions of the plasma aminogram, lower total nitrogen absorption and retention, and lower phosphorus absorption compared with those fed formulas designed specifically for VLBW infants. Elemental formulas containing free amino acids are rarely needed and should be used only under the supervision of physicians with special knowledge of nutrition support in infants. It is important to note that commercial milk powder preparations are not sterile and are not recommended for in-hospital use for small preterm infants unless there is no suitable alternative. (41) ⁴¹

Careful preparation and handling of all infant formulas, particularly those prepared from powder, is warranted. All formulas should be fed immediately or refrigerated and fed within 24 hours of preparation. For infants requiring continuous infusion of milk feeding, the “hang time” of each feed type depends on institution practice. In any case, hang time of >4 hours is not recommended for enteral feeding. (42,43) ^{42,43} For human milk containing human milk fortifier, the maximum suggested hang time is 4 hours.

- b) Commercial human milk fortifiers are available from two manufacturers in North America. They provide additional energy and multiple nutrients when added to human milk. The contents of the two commercial fortifiers differ, and when the fortifiers are added to human milk in the recommended amounts, the final nutrient compositions tend to resemble the commercial preterm infant formulas from the respective manufacturers. The optimal level of iron content in human milk fortifier is controversial. In vitro studies indicated that a higher iron content may adversely affect the bacteriostatic properties of human milk against *Escherichia coli*, *Staphylococcus*, *Enterobacter sakazakii*, and group B streptococcus, (44) ⁴⁴ and results in greater generation of free radicals and lipid peroxidation products. (45) ⁴⁵ Thus, use of a low iron-containing human fortifier may be preferable. However, one report of short term (up to 28 days) use of human milk fortifier with 1.44 mg of iron added to 100 mL of human milk showed there was no increase in the incidence of sepsis or necrotizing enterocolitis. (46) ⁴⁶ The low-iron, insoluble calcium salt-containing human milk fortifier also resulted in better growth than the one with soluble calcium salts. (47) ⁴⁷ In terms of product sterility, there is no alternative to powdered human milk fortifier for in-hospital use. When mixed with human milk, the fortified milk should be used within 4 hours of preparation. A sterile liquid human milk fortifier is available, but when used according to the manufacturer’s directions, it reduces human milk intake by 50%.
- c) Vitamin D supplementation is recommended for all infants receiving human milk as an exclusive source of nutrition. (48) ⁴⁸ It is often part of commercial infant multivitamin preparations. Preterm infants, especially

ELBW infants, are often given additional multivitamin supplementation containing 400 international units of vitamin D early in their course, whether they are receiving fortified human milk or preterm infant formula. Anecdotal reports exist for hypercalcemia with or without hypervitaminosis D in VLBW infants receiving preterm formula or fortified human milk with additional vitamin D or multivitamin supplementation. In any case, vitamin supplementation is unnecessary when these infants reach about 2 kg and are receiving adequate feedings of fortified human milk or preterm infant formula.

- d) For term infants, adequate intake of iron during the first 6 months is <0.3 mg/d and can be met by breast-feeding alone. For the small preterm infant, the recommended daily iron intake is 1.7 to 2.5 mg elemental iron/100 kcal (2–4 mg/kg) during early infancy. Iron supplementation can be started once the infant achieves full enteral feeding and continues for the first year up to a maximum of 11 mg of elemental iron per day. (49) ⁴⁹ For infants receiving erythropoietin therapy, the iron requirement is substantially higher, and 10 mg/kg/d has been used. (17) ¹⁷ Prolonged contact of human milk with iron may impede bacteriostatic activities and increase generation of free radicals and peroxidation products. (44,45) ^{44,45} Medicinal iron given as once or twice daily supplementation is a proven effective therapy and may be preferably to the continuous contact of human milk to the high iron containing fortifier. No fluoride supplementation is recommended for infants in the first 6 months of life. Thereafter, daily supplementation of 0.25 mg of fluoride until 3 years of age is recommended if the drinking water contains <0.3 ppm of fluoride. (50) ⁵⁰
- e) Commercial modular nutrient components are available to meet the increased or altered dietary needs of infants in the NICU. These components include carbohydrate, fat, and protein modules. Modular protein products may be used to increase protein density (but are only available in powder), and emulsified fat products, medium-chain triglyceride, or glucose polymer may be used to increase caloric density. The use of modular nutrients may result in imbalanced intake of various nutrients. For example, increased protein density may result in an abnormal plasma aminogram, and increased caloric density may result in excessive fat deposition as adipose tissue and in various organs (including the liver), with adverse consequences. Thus, sick infants without significant gastrointestinal problems can have the infant formula concentrated. For those without the need for severe fluid restriction, the use of a greater volume of mother's milk or infant formula is preferred since the intake of all nutrients is proportionally increased. The experimental use of recombinant human lactoferrin, oligosaccharides, prebiotics, and probiotics in the diet holds promise to improve the gastrointestinal function and growth of sick and healthy infants.
- C. Feeding methods. Enteral feeding methods should be individualized on the basis of gestational age, clinical status, and expected tolerance to feeding. Before about 32 weeks postmenstrual age (PMA), most preterm infants require gavage feeding because the integration of sucking, swallowing, gastrointestinal motility, and breathing necessary for successful oral feeding is generally inadequate. Between 32 and 36 weeks PMA, the preterm infant may need a combination of gavage and bottle (or breast) feedings. Once a

coordinated suck and swallow are present, the change to full oral feedings usually can be established within 1 to 2 weeks. (51) ⁵¹ Avoidance of hypoxemia is critical to successful enteral feeding. Use of a pulse oximeter should be part of the management during the transition from gavage to oral feedings. Parameters that should be evaluated include heart rate, respiration, and oxygenation relative to baseline through sucking and the postfeed period. Illnesses, particularly those affecting the central nervous system— whether congenital or secondary to severe asphyxia insult — can affect the normal maturation of the physiologic actions needed for successful nipple feeding.

1. Gastric gavage

- a) Indications include infants with a poor suck-and-swallow reflex, such as extremely premature infants and infants with congenital or acquired neuromuscular disorders. Gavage feeding may be used during the transition from PN to EN or during the establishment of nipple feedings. Some infants with high respiratory rates may require gavage feeding, although enteral feeding probably should be withheld if the respiratory rate exceeds 80 breaths per minute to minimize the risk of aspiration.
- b) The appropriate size gavage tube, which ranges from a 5F to an 8F catheter for intermittent gavage feeding, or an anchored indwelling naso- or orogastric catheter, should be selected. For ELBW infants, the smaller catheter is preferred to minimize occlusion of the nares, although an anchored orogastric tube may result in less airway resistance and less impairment of minute ventilation than a nasogastric tube.
- c) Clinical verification of correct tube placement must be done immediately after insertion, at regular intervals during each nursing shift, and prior to each bolus feeding.
- d) Polyvinyl chloride catheters should be changed every 24 to 48 hours to prevent stiffening of the plastic and potential gut perforation. Silastic or polyurethane catheters are preferable if a feeding tube is to be left indwelling for more than 72 hours.
- e) For continuous gavage feedings, the amount of breast milk or formula placed on the constant-rate infusion pump should be only the amount that is to be delivered for a 3- to 4-hour period. Possible advantages compared with bolus feeding include less abdominal distention, improved intestinal absorption, better tolerance to feeding, and faster growth rates. Possible disadvantages may include increased risk of aspiration from the potential for increased gastroesophageal reflux (common in this population) or dislodgment of the feeding tube from the stomach to above the gastroesophageal junction. In addition, when breast milk is continuously infused, large amounts of fat may be lost with separation and layering of fat in the delivery system. This loss can be minimized by tilting the infusion pump so the fat is delivered before the water-soluble portion.
- f) For bolus gavage feeding, most infants weighing >1500 g will tolerate feedings every 3 hours. Each feeding can be delivered by gravity or infused over 15 to 20 minutes. Smaller infants may require delivery over 1 to 2 hours to improve tolerance to intermittent bolus feeding. Possible advantages compared with continuous gavage feedings include more complete delivery of nutrients. For example, there is less risk of mineral sedimentation from high-mineral preterm infant formula or separation of human milk fat during delivery. In addition, bolus gavage feeding is

- simple to administer and requires minimal equipment. Possible disadvantages may include an increased risk of gastric residuals, abdominal distention, and gastroesophageal reflux.
- g) Potential complications of gavage feedings
 - 1) Misplacement of the tube into the trachea
 - 2) Irritation or perforation of the pharynx, esophagus, or stomach
 - 3) Vagal stimulation resulting in apnea and bradycardia
 - 4) Gastroesophageal reflux and aspiration with subsequent pneumonia
 - h) Infants showed variable responses to non-nutritive sucking. Some studies reported benefits in weight gain, energy intake, heart rate, oxygen saturation, and intestinal transit time, and decreased time to full oral feeds. (52) ⁵² A pacifier may be offered to infants during gavage feedings, although actual oral feeding is necessary for the development of sucking behavior. (32) ³²
2. Transpyloric feeding. The transpyloric feeding route is rarely used because of multiple potential complications, including abdominal distention, diarrhea, fat malabsorption, bacterial overgrowth, necrotizing enterocolitis, malposition or dislodgment of the tube, and perforation of the intestine.
3. Gastrostomy tube
- a) Indications. Infants who have a functional stomach and intestine but a major impairment in swallowing or an esophageal obstruction are candidates for gastrostomy feeding. For example, a gastrostomy tube can be used as a long-term route for feeding infants with severe neurological deficits or as a temporary measure in infants with congenital esophageal atresia.
 - b) Placement method. Gastrostomy tubes are percutaneously placed by radiologists with skill in invasive procedures or by surgeons as a specific surgical procedure. Tubes can be easily replaced 2 to 3 weeks after the initial operative procedure.
 - c) Potential complications
 - 1) Risk of surgical and anesthesia procedures
 - 2) Local skin breakdown
 - 3) Leakage of gastric contents around the gastrostomy tube insertion site
 - 4) Accidental removal of tube or tube migration
 - 5) Gastroesophageal reflux worsening with gastrostomy without fundoplication
4. Nipple feeding
- a) Breast-feeding. General hygienic practice is essential. This includes hand washing and making sure the breast/nipple area is clean before feeding. A lactation consultant or clinician can teach and support the mother to help ensure effective breast-feeding. Postsurgical infants may need additional positioning supports to minimize stress on the surgical incision. The infant should be assessed for respiratory and gastrointestinal tolerance, sucking strength, and coordination. The feeding duration on each breast should start at 3 to 5 minutes, thereafter increasing daily by 1 to 2 minutes, up to a total of 10 to 12 minutes per breast per feeding. For some infants, supplemental gavage feedings after breast-feeding attempts may be needed during the transition to complete

breast-feeding. Continued support and education helps promote a let-down reflex and a positive breast-feeding experience for both the mother and the infant. Test weighing after breast-feeding to determine the volume of milk ingested is unnecessary. Observing the infant during breast-feeding, monitoring urine and stool patterns, and following daily and preferably weekly weight gains are better indicators of successful breast-feeding. If there is a local breast infection, milk should be expressed from the breast and discarded.

- b) Bottle feeding. Appropriate flow from the nipple is important. Too slow a flow requires excessive effort and may not allow adequate intake; excessive flow may result in choking or aspiration. Typically, more time is required to complete a feeding in the preterm or sick infant compared to the healthy term infant. The infant should be allowed to set the pace of bottle feeding so less energy is expended for feeding. Force-feeding or overstimulation of the infant may result in hypoxia or vomiting. It is important that the infant be held comfortably and securely during the feeding. The infant's head should be higher than the rest of the body to minimize the risk of gastroesophageal reflux. The bottle should be held so the infant sucks in only milk and not air through the nipple. The bottle should never be propped in the bed for feeding.

D. Transition from PN and initial feeding

1. Achieving adequate enteral intake may require considerable time depending on the infant's gestational age and clinical status. PN should be continued until about 70% of intended intake is provided through the enteral route. However, in extremely small preterm infants weighing <1 kg, PN should be continued even at 1 mL/hr since this is equivalent to as much as 50 mL/kg/d for infants with birth weight of <500g, a substantial source of nutrition support.
2. Full-strength feedings can be attempted whenever the infant is clinically stable. There is no advantage to the use of diluted milk for initial feedings. Human milk should never be diluted. Some clinicians prefer that infants first tolerate some enteral feeding, ~30 mL/kg/d, before adding human milk fortifier. Formula-fed preterm infants should start with 81 kcal/dL formulations since they are isotonic and there is no advantage in the use of 67 kcal/dL formulations. Some clinicians use protein hydrolysate formula with the aim of maximizing macronutrient absorption. However, this type of formulation was not designed to meet the nutrient needs of the preterm infant, and specific indications for the term infant are limited. Their use in small preterm infants has been associated with altered plasma amino acid patterns.

E. Feeding volume and energy. In contrast to PN, in which the content of multiple nutrients and fluid volume can be adjusted, EN support is limited to the type of milk and the volume provided to the infant. For the vast majority of infants in the NICU, the type of milk would be mother's milk or standard infant formula for those born at term, and mother's milk with fortifier or preterm infant formulas for those born prematurely. The fortified human milk and the preterm infant formula provide a caloric density of 24 kcal/oz, with fixed content of specific nutrients in the range to meet the estimated requirement. (40) ⁴⁰ The practice in most NICUs is to start with small volumes and advance slowly to allow for adaptation of the gastrointestinal tract (GIT) to avoid distention, emesis, and diarrhea.

1. A typical starting volume is 10 to 30 mL/kg/d, advanced daily in increments of similar amounts as tolerated until the fluid goal is reached. Smaller, sicker infants

- generally tolerate the smaller initial volume of feeds and a slower rate of increase.
2. The volume of feedings needs to be adjusted daily or on alternate days with increasing body weight to maintain the fluid and nutrient goals for growth. Consistent weight gain usually occurs with an intake between 150 and 200 mL/kg/d.
 3. Sick infants, particularly preterm infants, even if they are not expected to tolerate much milk feeding, may benefit from minimal enteral feeding (<10 mL/kg/d) soon after birth once clinically stable. This minimal enteral feeding is intended as trophic stimulus for gut growth and function. Trophic feeding alters gastrointestinal disaccharidase activity, hormone release, blood flow, motility, and microbial flora. The clinical benefits appear to include improved milk tolerance, greater postnatal growth, reduced systemic sepsis, and shorter hospital stay. (53)⁵³ There is no evidence of any adverse effects from trophic feeding.
 4. Energy requirements for enterally fed infants are generally 10% to 20% higher than for parenterally fed infants because of individual variability in digestion and absorption. Generally, an enteral intake of 110 to 130 kcal/kg/d (~136 to 160 mL/kg/d of 24 kcal/oz milk) should allow adequate growth in most sick infants, even those born prematurely.
- F. Complementary feeding. Additional foods or fluids are rarely needed. For patients in the NICU, the priority is to achieve adequate intake of mother's milk (with or without fortification, depending on the infant's weight, as discussed in Section III.B) or nutritionally complete infant formulas. There is no nutritional indication to add complementary foods before 4 to 6 months. Infants who are ready to receive complementary feeding for the purpose of adding variety in texture and taste to the diet normally would have been discharged from the NICU. In a few infants being prepared for home ventilator support, the use of complementary feeding should be similar to that for healthy infants, with one "single-ingredient" new food introduced at a time and at the consistency or texture appropriate for oral motor development. (54)⁵⁴
- G. In-hospital monitoring
1. Daily body weight in addition to intake and output, twice-weekly head circumference, and weekly body length should be measured. All measurements should be plotted on appropriate growth charts. See Chapter 1.
 2. The type and frequency of laboratory monitoring should be based on the individual needs of the infant and his or her tolerance of enteral feedings. Laboratory studies may be similar to those needed for PN but are oriented toward determining hematologic and biochemical homeostasis and improving nutritional status.
 3. If an infant has signs or symptoms such as lethargy, abdominal distention, increased gastric residuals, vomiting, bilious aspirate, diarrhea, or bloody stools, feedings should be stopped to allow for assessment of the cause and appropriate management instituted.
 4. Apnea, bradycardia, and desaturation may result in or be caused by feeding intolerance. Care should be taken to define the origin of these signs so the infant can be treated appropriately. Head up with prone or right lateral positions are best during gavage feeding to maximize gastric emptying and minimize respiratory impairment. After hospital discharge, the head-up feeding position can be maintained, but a supine sleep position is strongly recommended. (55)⁵⁵ Caution should be exercised with the prolonged use of antireflux medication.

5. Gastric residual is normally used as an indicator of feeding tolerance. There is no specific cutoff for the amount of residual as a predictor of additional complications such as necrotizing enterocolitis. (56) ⁵⁶
 - a) With gavage feedings, check for aspirates before each feeding.
 - b) The aspirate volume should be less than the volume infused over the previous hour if fed by continuous infusion, or 10% to 20% of the bolus volume. Refeed the aspirate, give the intended volume for the next feed, and continue with the same feeding schedule.
 - c) If the aspirate is >20% of the volume fed, assess the infant for other signs of intolerance such as abdominal distension. If no other signs are noted, reduce the feeding volume to the previously tolerated volume and adjust the PN intake accordingly. Continue to assess the infant for signs of intolerance.
 - d) If feeding intolerance continues or other signs of intolerance develop, stop feedings immediately and assess the infant for complications.

IV. Nutrition Support for Sick Infants With Specific Disorders.

The key to maintaining optimal nutritional status in the critically ill infant is to begin appropriate nutrition support via the enteral or parenteral route within 24 hours of admission. Nutrition support should include taking into account the influence of the underlying pathophysiology of the disease process and minimizing the use of therapeutic measures that might interfere with nutrient utilization and tolerance. Nutrition support of all infants depends on a number of factors. See Table 26-6.

Table 26-6. Nutrition Support for Critically Ill Infants

Nutrition Concerns	Nutritional Management
Impaired function of gastrointestinal tract from <ul style="list-style-type: none"> · Primary or secondary shortening · Motility or mucosal dysfunction 	<ul style="list-style-type: none"> · Modify protein (hydrolysate or amino acids), carbohydrate (glucose polymer), and fat (medium-chain triglyceride) components of milk. · Supplement other nutrients (eg, electrolytes, vitamins) as needed. · Give continuous infusion rather than bolus feeding. · Use total or supplementary parenteral nutrition.
Impaired function of other organ function	<ul style="list-style-type: none"> · Modify fluid goal and components of milk as needed. · Limit nutrients that require the metabolic or excretory capacity of the organ (eg, fluid and electrolyte restriction in renal impairment, copper and manganese restriction in hepatic impairment).
Underlying disease	<ul style="list-style-type: none"> · Modify route of delivery (eg, nasogastric or gastrostomy feeding in patients with impairment of sucking and swallowing). · Increase nutrient density of standard milk preparations (eg, small preterm infants, infants with poorly controlled cardiac failure). · Adjust nutrient (glucose and/or lipid) load in septic subjects. · Replace abnormal losses (eg, gastric, enterostomy, or diarrhea losses). · Provide specific formulation for cow milk protein or soy protein allergy, and inborn errors of metabolism.
Therapy for underlying illness	<ul style="list-style-type: none"> · Adjust glucose load in patients receiving systemic steroid therapy. · Minimize therapy that might increase nutrient losses or adversely affect nutrient digestion, absorption, metabolism, or excretion (eg, proton pump inhibitor, corticosteroids, phenobarbital, chronic diuretics). · Use appropriate analgesia and anesthesia to minimize tissue

- A. Functional capacity of the GIT and cardiorespiratory stability. If the GIT function is intact and the cardiorespiratory status is stable, then the use of enteral feeding with standard enteral preparations (see Section III.B) is appropriate, except in patients with inborn errors of metabolism. The route (see Section III.C) of feeding will vary depending on the neurodevelopmental maturity of the patient.

GIT function is significantly impaired in primary or secondary short-bowel syndrome or severe intractable diarrhea. The presence of enterostomy (especially at the upper small bowel), motility disorder, or bacterial overgrowth also may complicate the nutritional management. To improve digestion and absorption of nutrients, protein hydrolysate formula with modified fat and carbohydrate delivered by continuous infusion is usually used as the initial feeding. The amount can be increased slowly, depending on the volume of gastric residual and the quality and quantity of stool. Gastric residuals may be reduced by continuous gavage feeding, and the short-term use of a prokinetic agent may be helpful. There is no agreement on the amount of stool or enterostomy output that is acceptable. A decrease in enteral intake and supplemental PN is generally indicated if the volume of output is >20% to 30% of enteral intake and the infant fails to gain weight, head circumference, and length.

There are some differences in the contents of the two commercial protein hydrolysate formulations. The most convenient and important indicator of its adequacy would be clinical tolerance and adequate growth. An amino acid–based elemental formula containing modified fat and carbohydrate source can be used (57) ⁵⁷ if a protein hydrolysate formula is not tolerated. Supplementation of fluid and multiple nutrients such as electrolytes, minerals, trace minerals, and vitamins such as B₁₂ and fat-soluble vitamins are frequently needed. Pharmacotherapy to modulate intestinal motility, intestinal fluid loss, gastric acid production, and the use of growth hormone and other intestinal growth–enhancing agents in short-bowel syndrome (see Chapter 14) may be needed. Early provision of a central venous catheter is necessary in these infants to allow easy access for supplemental or total PN, including home PN, as necessary.

To optimize nutrition support, it is better to provide the infant a small volume of full-strength milk formula and employ supplemental PN rather than providing a high volume (but nutritionally insufficient) of diluted milk formula alone. Maintaining even a minimal amount of enteral feeding, if tolerated, may be helpful to intestinal growth and adaptation. The rate of intestinal adaptation to EN varies with the gestation of the infant (preterm infants may have better potential than term infants for compensatory intestinal growth), the site and length of residual bowel (upper or lower small bowel with or without the presence of ileocecal valve, or colon), the response to other medical and surgical therapy, and the ability to maintain or improve the nutritional status throughout the course of illness. In any case, meticulous attention to details of fluids and electrolytes, and all aspects of macro- and micronutrient status, is essential. If a small preterm infant with impaired GIT function has tolerated protein hydrolysate formula, cautious introduction of preterm formula with more appropriate nutrient composition for the infant’s needs should be attempted. Ultimately, functional adaptation of the intestine may allow gradual transition to a normal diet. Management of these infants by a small group of multidisciplinary professionals is strongly recommended.

- B. Functional capacity of organs other than the GIT system. This also is important to the tolerance and type of nutrients delivered. For example, with renal disorders, most infants can be fed human milk or “humanized” infant formulas, depending on the extent of renal impairment and the treatment for it. Close monitoring of serum electrolytes, minerals,

urea nitrogen, and albumin status is needed. Infants with biliary atresia often have reduced intake and impaired digestion and absorption of nutrients, particularly long-chain fats and fat-soluble vitamins. The use of protein hydrolysate formula rich in medium-chain triglycerides, supplementation of multivitamins, and continuous enteral feedings may be needed to maximize digestion and absorption of nutrients to promote growth until definitive treatment for the underlying disease can take place.

- C. Constraints imposed by the underlying disease state. Fluid restriction may limit the amount of nutrient that can be delivered in infants with acute renal failure or the syndrome of inappropriate antidiuretic hormone secretion. However, an increase in fluid intake may be feasible with manipulation of environmental factors (Table 26-4).

In other situations such as infants with poorly controlled cardiac failure, can be fed with standard infant formula concentrated to 80 to 100 kcal/dL as necessary. Infants receiving the highly concentrated formulas should be observed for gastrointestinal tolerance, and use of the concentrated formula should be terminated if the infant is having other problems such as gastroenteritis.

With surgical operation and sepsis, the increased metabolic demands return to normal upon resolution of the primary conditions. After most elective operations in otherwise normal infants, the increase in metabolic demand often lasts only 4 to 6 hours⁵⁸ and no change to standard nutrition support is needed. Septic infants frequently do not tolerate the increased amount of nutrients needed to compensate for their greater metabolic demands, and complications such as hyperglycemia may develop while they are receiving the previously tolerated PN infusate. Replacement of losses such as enterostomy losses of electrolytes is needed. The clinician also must be cognizant of the loss of minerals and trace minerals in addition to electrolytes, since the content of minerals such as magnesium²² or trace minerals such as zinc⁵⁹ and many other nutrients in the fecal or enterostomy fluid is rarely measured. Zinc status may be the limiting factor in immunologic and numerous other functions and growth.

Infants with demonstrated allergy to cow milk or soy protein may require protein hydrolysate formula. The use of elemental amino acid infant formula and even PN also may be needed. Infants with inborn errors of metabolism such as phenylketonuria have specific needs and therapy regardless of gestational age or birth weight. These groups of patients should be comanaged by a physician and a dietitian familiar with the management of these disorders.

- D. Alteration in the form of nutrients and adjunctive support. Changes in the form of nutrients are not necessary for many complications commonly found in patients in the NICU. For example, some conditions such as feeding difficulties associated with central nervous system complications require a change in the route of delivery rather than a change in the form of nutrients. Even gastrointestinal complications normally do not require modification of standard PN infusate or enteral feeding unless there is a significantly shortened intestinal tract or dysmotility problems. Infants requiring extracorporeal membrane oxygenation (ECMO) therapy generally have severe respiratory failure. Protein catabolism in these infants is markedly elevated, consistent with their severe illness. A surplus of dietary caloric intake does not improve protein catabolism and merely increases carbon dioxide production in the highly stressed neonates. (60)⁶⁰ Thus, excess nutrient intake, especially during the acute phase of illness, including the period on ECMO, is not warranted and may be detrimental. Some infants on ECMO show intolerance to nutrients such as carbohydrate load, as other sick infants do, and some develop hypercalcemia if they are receiving PN solutions high in calcium. Hyperglycemia and hypercalcemia are transient and resolved with temporary lowering of dextrose and calcium in PN. Occasionally, calcium may need to be withheld from PN for

2 or 3 days. Many infants who received ECMO therapy suffer from variable periods of hypoxia and are at risk for increased intestinal permeability with the potential for bacterial translocation and sepsis. However, neonates on ECMO have tolerated some enteral feeding without further clinical deterioration.⁶¹ The major complication with feeding is the poor nipple-feeding effort of many infants after discontinuation of ECMO therapy, and almost all infants require a period of gavage feeding. There are no data to indicate that the nutrient requirement for infants needing ECMO would differ from that of other sick infants with non-GIT problems, and there is no indication to use milks other than human milk or standard infant formula.

Infants with chronic disease states such as Bronchopulmonary Dysplasia (BPD) may require relative fluid restriction but possibly have increased energy needs because of increased respiratory effort. Increased energy intake in this situation should be managed with the understanding that excessive carbohydrate load also may increase the work of respiration and that balanced macronutrient content is needed.

All pharmacotherapy including but not limited to diuretics, corticosteroids, proton pump inhibitors, and phenobarbital must be regularly reassessed to determine its continuing need. This could minimize the adversely effect on nutrient digestion, absorption, metabolism and excretion. Adequate analgesia and anesthesia are proven means of reducing the catabolism associated with sick and stressed infants and are useful adjuncts to optimize the nutritional management.

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