Nutrition for Ill Neonates
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OBJECTIVES
After completing this article, readers should be able to:
1. List the factors on which the nutritional needs of the neonate depend.
2. Describe the factors that illnesses alter, thereby changing nutrient requirements.
3. Describe the levels of amino acids that can be initiated without causing intolerance or toxicity in most ill infants.
4. Delineate the adverse effects of protein malnutrition following an acute or prolonged illness or insult.

Introduction
From early in this century, investigators have attempted to determine the optimal nutrient delivery for term infants to promote normal growth and development. In the past 25 years, nutritional investigators have concentrated on the needs of the ideal, healthy preterm infant to try to mimic intrauterine growth and body composition.

Although great progress has been made in characterizing the needs of healthy preterm and term infants, the needs of ill, physiologically unstable infants largely have been neglected. The primary reasons for this lack of investigation are the assumption that the needs of ill infants are similar to those of healthy infants and the difficulty of studying metabolic needs in ill infants. The persistent efforts of several groups of investigators and the development of new techniques to study metabolism now have begun to delineate the specific nutritional needs of this particular patient population.

Drawing on models generated in the adult surgical intensive care literature of the 1980s makes it possible to try to elucidate the effect of common illnesses and conditions (eg, acute pulmonary disease, bronchopulmonary dysplasia [BPD], congenital heart disease [CHD], sepsis, and surgery) on neonatal metabolism and, therefore, nutritional requirements. The assumption is that changes from the norm in metabolism require alterations in substrate delivery (ie, nutrition). As with adults, it is likely that each illness induces characteristic changes in metabolism. The task for the practitioner is to customize nutritional delivery to fit the specific infant’s needs.

We will review current knowledge about the metabolic changes induced by common neonatal illnesses by comparing the nutritional needs of ill infants with the well-established standards for healthy newborns. Nutritional needs induced by some diseases have been characterized better than others. For example, there is an extensive literature on the energy (but not the protein) needs of infants who have BPD. The protein and energy needs of infants undergoing surgery have received substantial attention recently. Other aspects of neonatal nutrition, particularly micronutrient requirements, have not been studied specifically in ill compared with healthy infants. Where possible, we have attempted to make specific recommendations for nutrient delivery when such values are available.

Normal Requirements
Understanding the nutritional requirements of healthy term and preterm infants forms a basis for assessing the effects of disease processes on nutrient needs. A complete list of normal neonatal nutritional requirements is beyond the scope of this article; rather, we focus primarily on nutrients that potentially are affected by disease states (Table).

Acute Pulmonary Disease
Acute pulmonary disease not only is the most common admission diagnosis in the neonatal intensive care unit (NICU), but it is the most common severe illness of the neonate. It encompasses respiratory distress syndrome (hyaline membrane disease), pneumonia, meconium aspiration syndrome, and other disease states, such as congenital diaphragmatic hernia and acute respiratory distress syndrome due to sepsis. Several studies in adults, children, and infants have demonstrated that acute pulmonary disease increases oxygen consumption, thus increasing energy requirements. Infants who have respiratory distress syndrome have a range of estimated resting energy expenditure of 40 to 60 kcal/kg per day, with caloric needs directly proportional to the severity of the illness.

ENERGY NEEDS
The nutritional goal with any ill infant is to attempt to achieve a positive energy balance. We generally use a two-tiered approach. The initial objective is to meet resting energy expenditure during acute illness without superimposing an increased metabolic demand by providing excess calories. Acutely ill neonates are likely to be insulin-resistant and have elevated levels of counterregulatory hormones (eg, cortisol, epinephrine, and norepinephrine) that promote tissue catabolism to provide amino acids for substrate for gluconeogenesis. Energy delivered in excess of the amount needed to fuel the basal metabolic rate is likely to be “wasted” at best and to increase total energy demand at worst. It is only after the infant has become more  

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ABBREVIATIONS
BPD: bronchopulmonary dysplasia
CHD: congenital heart disease
IM: intramuscular
NICU: neonatal intensive care unit
RQ: respiratory quotient
Energy expenditure increases thereby increasing the work of breathing or exposure to barotrauma in infants who are receiving mechanical ventilation. Lipids are an excellent source of energy because they are calorically dense. They have a lower RQ (0.7) and, therefore, create less carbon dioxide when metabolized. This may confer an advantage to a neonate who is receiving mechanical ventilation. However, lipid emulsions have been shown to have a direct effect on pulmonary function by impairing gas exchange. This has been attributed to the production of vasoactive metabolites, which uncouples hypoxic vasoconstriction and increases ventilation/perfusion mismatching. Infusing the lipid solution over at least 16 hours during a 24-hour period may decrease this effect. Despite being associated with problems such as hypoxia and pulmonary hypertension (which generally occur at substantially higher rates of infusion than currently recommended), early initiation of lipids seems prudent because significant growth failure is associated with severe lung disease. The initial objectives in beginning lipid infusions is to prevent essential fatty acid deficiency, resume growth, and facilitate the transition to enteral feedings. In general, lipid emulsion can be started at 1 g/kg per day and advanced in increments of 0.5 to 1 g/kg per day, depending on serum triglyceride clearance. The addition of carnitine to parenteral nutrition in the preterm infant has been shown to promote fatty acid oxidation and prevent the rare occurrence of carnitine deficiency. Although further investigation is needed, medium-chain triglycerides may be an alternative fat source because they are calorically more efficient and reduce fat storage rates.

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term infant on track with expected in utero accretion rates.

Preterm infants who have varying degrees of respiratory distress syndrome and are receiving 1 g/kg per day of amino acids are in negative nitrogen balance. Recent studies from Thureen et al (see Suggested Reading) demonstrate no evidence of protein intolerance in ventilated neonates during the first week of life who are receiving amino acid intakes of up to 2.9 g/kg per day. Thus, sufficient protein delivery to achieve positive nitrogen balance can be attained by providing at least 1.5 g/kg per day and increasing the intake by 0.5 to 1.0 g/kg per day to a total of 3.0 to 4.0 g/kg per day of amino acids parenterally. In addition, studies suggest that it may not be necessary to increase protein administration incrementally; infants can be started at or close to the maximal protein dose. There appears to be no need to increase protein delivery simply on the basis of degree of respiratory illness because the degree of nitrogen loss is not related to the severity of respiratory distress.

MINERALS

Disorders of calcium, phosphorus, and magnesium metabolism are common in acute pulmonary disease. Maintaining homeostasis and normal serum concentrations of these minerals is important because hypocalcemia, hypophosphatemia, and hypomagnesemia each can affect optimal respiratory and cardiac function. Transient neonatal hypocalcemia often is exacerbated by acute respiratory disease and, when severe, can cause tetany and cardiac arrhythmias. Typically, we add 600 mg of calcium gluconate per 100 mL of intravenous fluids on day 1 in infants who have acute pulmonary disease to provide prophylaxis against hypocalcemia. Similarly, hypophosphatemia and hypomagnesemia can cause muscle weakness, lethargy, and poor respiratory effort. Hypermagnesemia can lead to apnea, which is seen commonly among infants whose mothers have been treated with magnesium sulfate for preterm labor or pregnancy-induced hypertension. Monitoring calcium, phosphorus, magnesium, and alkaline phosphatase levels is important in assessing nutrient delivery, remembering that calcium levels always will be maintained at the expense of bone.

Although it may be important to maintain normal hemoglobin concentrations in infants who have acute pulmonary disease to optimize oxygen delivery, iron rarely is the limiting factor. Most infants are born with sufficient iron stores to maintain them through the period of acute disease, and rapid decreases in hemoglobin (due to blood drawing) are treated best by transfusion, not by infusion of parenteral iron.

VITAMINS

It is unclear whether acute pulmonary disease has any specific effects on vitamin metabolism. Recent studies suggest that infants who are at high risk for BPD and have low vitamin A levels may benefit from vitamin supplementation during the time of acute pulmonary disease. The current recommended dose is at least 2,000 U intramuscularly (IM) every other day. The goal is to achieve a serum retinol level of greater than 20 mcg/dL.

Bronchopulmonary Dysplasia

ENERGY NEEDS

Infants who have BPD have 25% higher resting energy expenditures, which results in a 10% to 15% increase in total caloric need compared with infants who do not have BPD. Much of this is related to their pulmonary status and increased work of breathing, with a correlation between degree of respiratory compromise and oxygen consumption. Energy requirements for growth generally are in the range of 130 to 150 kcal/kg per day. Options to meet this increased metabolic demand are aimed at decreasing the work of breathing, increasing the caloric intake, or both. Fat is a good nutritional adjuvant for infants who have compromised lung function, such as those who have BPD, because of both its high caloric density and its low RQ. Fat should not provide more than 60% of the total calories.

PROTEIN

There are few specific studies of protein status among infants who have established BPD except to note that they typically have lower somatic muscle stores. This finding, combined with their high fat mass, suggests that these infants are chronically receiving less-than-optimal amounts of protein for the amount of energy intake. Stable isotope studies of protein needs in infants who have BPD have been performed primarily within the context of studying the effect of glucocorticosteroids on protein status. Using stable isotopic techniques, van Goudoever et al (see Suggested Reading) demonstrated that high-dose dexamethasone (0.5 mg/kg per day) reduced linear growth and weight gain by markedly increasing protein breakdown, albeit without affecting rates of protein synthesis. Whether this effect can be tempered by administering higher amounts of protein during treatment with steroids currently is under investigation.

Because these infants already frequently are receiving high-solute, high-nitrogen diets, we do not routinely increase protein delivery during steroid treatment. Rather, we try to limit the duration and magnitude of exposure of young preterm infants to this drug. Overall, enterally fed infants who have BPD and are receiving more than 120 kcal/kg per day require protein intakes of at least 3.5 g/kg per day. Any increase in the caloric intake through supplementation of fat or carbohydrate should be accompanied by increased protein delivery.

MINERALS

Infants who have BPD often are receiving diuretic therapy. Unfortunately, the diuretics commonly used (eg, furosemide and bumetanide) cause increased urinary sodium, potassium, chloride, and calcium losses. Whereas the baseline sodium requirement for a healthy preterm infant is 3 to 4 mEq/kg per day, diuretic usage may increase this need to as high as 12 mEq/kg per day.
day. Similarly, the potassium requirement, which normally averages 2 to 4 mEq/kg per day in the healthy infant, will rise to 7 to 10 mEq/kg per day under diuretic pressure. Because the primary deficit is of chloride, sodium and potassium must be repleted as sodium chloride and potassium chloride. Infants who have persistent hyponatremia exhibit poor growth, and severe hypochloremia has been associated with sudden infant death in those who have BPD. The infant receiving diuretics and electrolyte supplements may demonstrate wide swings in serum potassium levels.

Urinary calcium loss with diuretics exacerbates an already tenuous balance and increases the risk of osteopenia of prematurity and nephrocalcinosis. Whereas the in utero rate of calcium accretion in the third trimester is 150 to 180 mg/kg per day, the calcium requirements of the preterm infant who has BPD and is receiving furosemide is nearly 200 to 225 mg/kg per day. The addition of glucocorticosteroids will increase bone remodeling and calcium needs further.

Infants who have BPD are faced with the classic dilemma of the risks and benefits of iron. Iron is necessary for normal organ function, but it is potentially toxic because it can create strong oxidant stress. The infant who has BPD may well benefit from a higher circulating hemoglobin concentration, which can be induced with consistent enteral iron therapy. However, iron delivered in excess of serum iron binding capacity may place the infant at greater oxidant risk. It appears that current recommendations for healthy preterm infants also are appropriate for those who have chronic lung disease.

VITAMINS
Vitamin A is a biologic antioxidant. Antioxidants are important in protecting cell membranes from oxygen free radical damage. Vitamin A influences epithelial growth, differentiation, and repair. Vitamin A deficiency and its possible association with the development of BPD has been the subject of several investigations. The overall consensus seems to be that persistent low serum retinol concentrations (<20 mcg/dL) are associated with a higher risk of BPD. Vitamin A deficiency also affects T-cell proliferation and phagocytic immunomodulatory activity of polymorphonuclear leukocytes. Prevention of vitamin A deficiency or treatment of infants at risk for BPD who have vitamin levels less than 20 mcg/dL, with at least 2,000 IU administered IM every other day appears to be an effective strategy for reducing BPD risk.

Vitamin E is a biologic antioxidant that protects the polyunsaturated fatty acids of cell membranes from peroxidation. Deficiency of this vitamin compromises cellular and humoral immunity and antimicrobial phagocytic action. It can cause a severe hemolytic anemia, which will be made worse with iron therapy. On the other hand, it has been difficult to link vitamin E status with other diseases due to oxidant stress, such as BPD, retinopathy of prematurity, and intraventricular hemorrhage. Results of studies examining the role of vitamin E supplementation in preventing or treating these conditions have not been convincing. As with most other nutrients, it appears prudent to maintain sufficient vitamin E status without running the risks of oversupplementation. We currently supplement preterm infants who have low vitamin E levels with 50 to 75 IU/d, and levels are monitored weekly.

Congenital Heart Disease

ENERGY NEEDS
Infants who have CHD, particularly with an element of congestive heart failure, have higher resting and total energy expenditures. Infants who have heart disease and are undernourished or malnourished tend to have a body composition that is higher in lean body mass and lower in fat content. Lean body mass is more metabolically active. The administration of optimal energy to these infants is a challenge because of the high metabolic demands of the myocardium, the muscles of respiration, and the hematopoietic system. High-energy feedings have been shown to improve both energy balance and growth.

The effects of cardiac surgery have been studied extensively in adults, less in children, and even less in neonates. In the immediate postoperative period, meeting the nutritional/energy needs of the neonate always is a challenge based on their delicate fluid balance, type of repair (curative versus palliative), respiratory compromise, and degree of renal failure. Additionally, catecholamine medications that increase oxygen consumption (eg, epinephrine, dopamine, and dobutamine) typically are required for cardiac support until the myocardium has recovered. As with the management of acute respiratory disease, the initial goal is to reduce catabolism by trying to meet the infant’s resting energy requirements (60 kcal/kg per day). As the infant recovers, the energy delivery is increased to promote adequate growth (130 to 150 kcal/kg per day).

Common problems seen in these infants include delayed gastric emptying, fatigability with feeds, vomiting, and malabsorption. Infants who have congenital heart disease, particularly when it is complicated by congestive heart failure, cyanosis, or both, generally require a diet that is not only high in calories but also calorically dense. They may need as much as 150 kcal/kg per day to achieve optimal growth, which can be difficult to achieve in infants who have poor oral intake. Studies have shown that continuous enteral feedings are more beneficial than intermittent bolus feedings.

PROTEIN
The effect of CHD on protein needs, either in the immediate postoperative period or chronically, has not been studied extensively. Because investigators have demonstrated substantial protein needs following noncardiac surgery, it seems reasonable to assume that infants are similarly catabolic immediately after cardiac surgery and have increased protein requirements. Based on these data, it seems prudent to provide at least 2.5 g/kg per day of protein in the immediate postoperative period with the intent to increase the delivery...
ultimately to 3.5 g/kg per day as tolerated.

The protein requirement of the infant who has chronic congestive heart failure frequently is underestimated. Because these infants have high energy needs, a common strategy is to supplement standard formulas with carbohydrates (glucose polymers) or lipids (oils, fats). Providing increased energy without concurrently increasing protein intake results in relative protein insufficiency and suboptimal growth. Because total protein should constitute 8% to 10% of the infant’s diet, it is important to supplement formulas with protein as well. However, delivery of too much protein adds to the renal solute load in infants who already receive limited free water, which could lead to decreased nitrogen utilization. Maintaining a nonprotein energy-to-nitrogen ratio of 150 to 200:1 appears to be optimal.

MINERALS

As in the infant who has BPD, the use of diuretics to treat CHD can compromise sodium, potassium, chloride, calcium, and phosphorus balances significantly. Potassium balance bears particular attention in the infant who has cardiac disease in whom hypokalemia, but more particularly hyperkalemia, can result in fatal arrhythmias. Close attention to calcium and phosphorus delivery and serum levels of these nutrients is warranted. Infants who undergo cardiac surgery also are at risk for transient but significant hypocalcemia in the immediate pre- and postoperative period because of the generous use of citrated blood products. Adequate phosphorous must be delivered to support generation of adenosine triphosphate for optimal myocardial function.

Infants who have cyanotic congenital heart disease have high iron requirements because of their expanded red cell mass. Persistent cyanosis increases production of endogenous erythropoietin, resulting in secondary polycythemia, to improve tissue oxygen delivery. The synthesis of each additional gram of hemoglobin requires an additional 3.4 mg of elemental iron. It is important to screen infants who have cyanotic CHD for iron deficiency using ferritin, red cell indices, and total iron-binding capacity saturation because the hemoglobin may be within the normal range for noncyanotic infants even though the infant is deficient in iron. It appears that a minimum dose of 2 mg/kg day of iron is prudent in these infants.

VITAMINS

Although no specific studies have addressed the effect of CHD on vitamin levels and requirements, it is likely that congestive heart failure decreases intestinal absorption of fats in general and fat-soluble vitamins in particular. In addition, if cardiac surgery is complicated by traumatic chylothorax, fat-soluble vitamin status can be reduced significantly. Water-soluble forms of vitamin A and vitamin E are available and can be used as alternative forms of supplementation when there is a question of fat malabsorption.

Sepsis

ENERGY NEEDS

The energy requirements during sepsis are well-characterized in adults. In this “hypermetabolic” state, there is a marked catabolic response, with profound changes in energy and protein metabolism. The state is driven by increased levels of cytokines (particularly tumor necrosis factor TNF alpha, interleukin 6 IL6, and IL1b) and increased activity of the sympathetic nervous system, with increased catecholamine levels, increased oxygen consumption, and negative nitrogen balance.

The metabolic response to and nutritional requirements of sepsis in the neonate are not well-defined. Several clinical studies in neonates who had sepsis and necrotizing enterocolitis have demonstrated increased levels of both TNF alpha and IL6, cytokines known to be involved in the septic response and multisystem organ failure syndrome seen in adults. Energy requirements in these neonates were elevated in proportion to the degree of septic illness. The septic neonates required higher energy delivery during the acute phase of their illness than similarly ill nonseptic infants. A goal of at least 60 kcal/kg per day seems prudent to meet the energy requirements during the acute phase of illness.

PROTEIN

Sepsis alters protein requirements more acutely by its effect on cytokine-mediated muscle catabolism. In adults this condition causes a dramatic increase in muscle catabolism, most likely to provide a ready source of amino acids to the liver for acute-phase reactant synthesis. Sepsis causes the most profound changes in negative nitrogen balance among all adult illnesses. A recent study suggests that the same catabolic effect occurs in septic neonates in which the degree of negative nitrogen balance is related directly to the severity of physiologic instability. There are concomitant increases in cytokine and acute-phase reactant protein concentrations. The mean nitrogen balance in these septic patients was -141±316 mg/kg per day, but it was as great as -800 mg/kg in certain patients. The same study demonstrated that some infants remained in negative nitrogen balance for as long as 10 days after the sepsis began. The concern is that during negative nitrogen balance would lead to long-term morbidity (predisposition to further episodes of sepsis) and growth delay. No study has assessed whether provision of extra protein will reduce this catabolic response, but at this point it seems prudent to provide at least 2.5 g/kg per day of protein to the septic infant.

MINERALS

Sepsis has no known specific effect on mineral homeostasis, but it is important to recognize that significant fluid shifts requiring the use of colloids for blood pressure and volume support can occur with sepsis syndrome, which will alter fluid and electrolyte balance. Therefore, close attention to serum electrolyte and mineral levels is necessary.

Infants who have sepsis do not need treatment with iron and, in
theory, such treatment may exacerbate the syndrome. Iron is an essential nutrient for bacterial proliferation, and the body appears to “hide” iron during infection by decreasing serum concentrations.

**VITAMINS**

The roles of fat-soluble vitamins such as A and E have not been well defined in neonatal sepsis. Vitamin E supplementation has not proven to be beneficial in decreasing infection or improving response to infection. Excess vitamin E may impair the bactericidal capacity of white blood cells and increase the infant’s risk of sepsis. Antibiotics used in the treatment of sepsis syndrome significantly reduce bacterial colonization of the gastrointestinal tract, which decreases the inherent production of vitamin K by gastrointestinal flora. We recommend administering vitamin K 1 mg at least two times per week to infants who are receiving antibiotic therapy.

**Surgery**

**ENERGY NEEDS**

Although surgery increases energy requirements in the adult, its effect on neonatal energy metabolism is less clear. Surgery increases endogenous catecholamine and cytokine levels in neonates, but this response is of a shorter duration than in adults. Although this probably has a significant effect on protein metabolism, infants undergoing an uncomplicated operation who are receiving adequate anesthesia postoperatively have no apparent increase in energy requirements. In contrast, infants undergoing surgery who are physiologically unstable due to an acute underlying illness have the expected rise in energy requirements seen with nonsurgical acute illnesses. Lipid peroxidation is increased in direct proportion to the degree of physiologic stress. Lipids are well-used and are an important source of energy in acutely stressed infants who are having surgery. Because excess carbohydrate delivery will shift the RQ cellular metabolism toward greater production of carbon dioxide, a balanced mixed-fuel (carbohydrate and lipid) approach should be used to provide nutritional support to these infants.

**PROTEIN**

Elective surgery in adults causes a small but significant reduction in nitrogen balance, but there is little evidence for induction of a full hypercatabolic response. Similarly, stable neonates undergoing elective, uncomplicated surgery do not have markedly increased protein requirements. Anderson et al (see Suggested Reading) have studied infants operated on within the first 24 hours of life for gastroschisis or congenital diaphragmatic hernia. The infants were started on parenteral nutrition with a fenotylin infusion (which appears to suppress the catabolic response to surgery in adults). Infants receiving 2.5 g/kg per day of amino acids remained in positive nitrogen balance immediately postoperatively, had higher amino acid values, and had no evidence of toxicity. Thus, it appears that infants can receive 2.5 g/kg per day of protein on postoperative day 1 with minimal risk and with positive effects on nitrogen balance.

**MINERALS**

Surgery has no known specific effect on electrolytes, trace elements, and vitamins. Nevertheless, surgery and therapies associated with surgery and postoperative management (eg, diuretics, citrated blood products) can affect fluid balance and mineral homeostasis. Therefore, it is important to monitor calcium and phosphorus levels closely in infants receiving colloid and/or blood products and electrolytes in infants receiving postsurgical diuretics. We typically add 600 to 1,200 mg of calcium gluconate per 100 mL of intravenous fluid. Similarly, sodium and potassium dosages may approach 10 and 8 mEq/kg per day, respectively.

**Summary**

It is important for the clinician to appreciate the specific nutrient requirements associated with various disease states and their therapies in the ill newborn. Neonatal illnesses significantly alter energy, protein, and mineral metabolism in disease-specific manners. Alterations in metabolism during illness translate directly into changes in nutrient requirements from the healthy state. Failure to provide appropriate nutritional support during illness may delay recovery from or even exacerbate common neonatal diseases.

**SUGGESTED READING**


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