

Symposium: Pediatric Pulmonary Insufficiency: Nutritional Strategies for Prevention and Treatment

Special Nutritional Needs of Infants for Prevention of and Recovery from Bronchopulmonary Dysplasia^{1,2}

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ABSTRACT Extremely low birth weight infants who develop severe respiratory disease may have special nutrient requirements imposed by a combination of enhanced utilization of nutrients or the need for epithelial cell repair resulting from the disease process, as well as to support catch-up growth. Inositol, free fatty acids, vitamin E and vitamin A are proposed as nutrients for which infants at risk of chronic pulmonary insufficiency may have special requirements. Of these nutrients, only for vitamin A does suggestive evidence exist that high doses when given intramuscularly may reduce the incidence of death or chronic lung disease. Exogenous steroid therapy (dexamethasone), which is often used to improve pulmonary compliance in ventilated premature infants, may compromise vitamin A status and induce restricted somatic and bone mineral growth. Supplemental nutrition by means of enriched infant formulas has provided benefits in growth and bone mass accretion to infants recovering from bronchopulmonary dysplasia up to 3-mo corrected age. This growth advantage was not sustained over the subsequent 9 mo, suggesting that prolonged nutritional support is required until catch-up growth is complete. Further studies are required to delineate the needs for specific nutrients such as antioxidant vitamins and minerals or vitamin A that may play a role in preventing severe chronic lung disease in premature infants. As well, the role of supplemental nutrition (beyond the requirements of term infants) to support catch-up growth and maintenance during the critical stages of early development requires further investigation before evidence-based nutrient recommendations can be developed for this special population of infants. *J. Nutr.* 131: 942S–946S, 2001.

KEY WORDS: • bronchopulmonary dysplasia • premature infants • dexamethasone • enriched formula • bone mineral content

Although it is recognized that extremely low birth weight infants (ELBW) are at risk of multiple nutritional deficiencies, and that concomitant development of bronchopulmonary dysplasia (BPD) compounds the potential for nutritional problems, evidence-based nutrition recommendations do not exist for this special infant population. Observations of detrimental effects at school age on linear growth, lean mass and whole body bone mineral mass, in former premature infants who had BPD compared to term born infants (Giaccoia et al. 1997, Furman et al. 1999), suggest that early nutrition may be

critical to recovery and promotion of optimal growth. The efficacy of selected nutrients for the prevention and/or treatment of BPD, as well as for nutritional rehabilitation and catch-up growth is beginning to be investigated. This review examines existing knowledge for special nutritional support in each of these clinical scenarios.

Special nutrient needs for the prevention and/or treatment of BPD

Nutrient-based interventions for the prevention and/or treatment of BPD have been investigated for inositol, intravenous fatty acids, vitamin E and vitamin A. Inositol is a phospholipid that is proposed to enhance the synthesis and secretion of pulmonary surfactant, which could influence pulmonary mechanics and reduce severity of lung disease. In a randomized double-blind study (Hallman et al. 1992), lower inspiratory oxygen and airway pressure requirements were associated with intravenous use of inositol. Clinically, the infants who received the inositol treatment had greater survival without BPD or neurodevelopmental handicap at 28 d of age, and a reduced incidence of retinopathy of prematurity and blindness. No further studies to confirm these findings have been reported.

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Both intravenous fatty acids and vitamin E have been used as adjunctive antioxidant therapy in ventilated infants. In theory these nutrients could serve as scavengers of excessive oxygen radicals produced during exposure to high oxygen delivery, thereby diminishing the risk of pulmonary oxygen toxicity that presents as BPD or retrolental fibroplasia. To date, clinical trials have not proven that either polyunsaturated fatty acids (PUFA) or vitamin E given prophylactically promotes lung maturation or attenuates the development of BPD or retrolental fibroplasia. PUFA delivered in intravenous lipid emulsions starting in the first day of life did not reduce oxygen or ventilatory needs, and in infants of 600 to 800 g birth weight, mortality was significantly greater in those infants who had received the fatty acids (Sosenko et al. 1993). For vitamin E, a meta analysis (Specker et al. 1992) did not provide support for a clinical benefit of vitamin E at intakes above that which maintains a normal serum alpha-tocopherol. A more detailed discussion of the role of dietary antioxidants in prevention of lung disorders in infants is provided in the accompanying report from this symposium by Welty (2001).

Vitamin A

Infants of ELBW are at risk of vitamin A deficiency because they have low plasma retinol concentrations at birth or shortly afterward (Greene et al. 1987, Koo et al. 1995), with mean values often in the range considered reflective of marginal vitamin A status [$<0.7 \mu\text{mol/L}$ ($200 \mu\text{g/L}$)] or even vitamin A deficiency [$<0.35 \mu\text{mol/L}$ ($100 \mu\text{g/L}$)]. The recent recommendation for vitamin A intake in premature infants by the American Academy of Pediatrics (1998) is 210–450 μg retinol $\cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, but whether this is an adequate intake for ELBW infants requires further study. Infants of < 1500 g birth weight who were given 102 μg retinol equivalents/100 kcal or about 122 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for 1 mo all developed hyporetinolemia (Koo et al. 1995). This is of particular concern in infants fed standard formulas, mother's milk (which provides only about 100 μg vitamin A $\cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) or intravenous nutrition for extended periods unless such feedings are supplemented with extra vitamin A. Delivery of vitamin A via parenteral nutrition is inefficient, such that when retinyl palmitate is added to dextrose and amino acid infusion, as little as 20% of administered vitamin may actually reach the infant as a result of adherence to plastic feeding devices and photoinactivation (Green et al. 1987, Gillis et al. 1983). Enhanced delivery is possible if retinyl palmitate is infused via the lipid emulsion, with close to 90% of administered vitamin being delivered to the infant (Greene et al. 1987).

Knowledge of the function of vitamin A in epithelial cell differentiation led to investigations into the role of high dose vitamin A in ELBW infants as a stimulant for the reepithelialization of lung tissue after acute injury induced by barotrauma or oxygen toxicity. The overall goal was to prevent dysplastic lung disease or BPD. The key published studies that evaluated the role of vitamin A in ELBW infants were evaluated in a recent Cochrane systematic review by Darlow and Graham (1999). The goal of this review was to determine the influence of vitamin A supplementation on the prevention of mortality and morbidity (defined as chronic lung disease, bronchopulmonary dysplasia, retinopathy of prematurity), and the response of circulating vitamin A concentrations in infants between 700 and 1500 g birth weight. Five (Bental et al. 1994, Papagaroufalis et al. 1988, Pearson et al. 1992, Shenai et al. 1987, Werkman et al. 1994) of the 10 published studies met the eligibility criteria for this Cochrane review, although not all studies reported the same outcomes. All studies included

were randomized or quasirandomized trials comparing high dose vitamin A (given intramuscularly or orally) to a placebo or no treatment. The key problems in conducting a meta analysis based on the results of these reports were inconsistencies in the dose of vitamin A given, the route of administration [intramuscular (IM) vs. intravenous (IV)] and the total amount of vitamin A provided to both the control and experimental groups.

The meta analysis was completed on reported measures in 149 infants treated with vitamin A and 141 nontreated infants in the five studies that met the review criteria. Four of the studies gave intramuscular injections of water-soluble retinyl palmitate [600–1200 μg (2000 to 4000 IU) vitamin A given alternate days or three times per week] for about 28 d (Bental et al. 1994, Pearson et al. 1992, Shenai et al. 1987, Papagaroufalis et al. 1988); and one study gave about 750 μg (2500 IU) daily by the intravenous route in the lipid emulsion (Werkman et al. 1994). It is important to note that at the time these studies were conducted there was minimal or no use of antenatal or postnatal steroids and no use of surfactant.

The overall results of the meta analysis (Darlow and Graham 1999) found that high doses of vitamin A did not influence rate of death by 1 mo of age but there was a trend to reduction of dependency on oxygen therapy. If death and oxygen dependency were combined as outcomes, then a significant effect of high dose vitamin A was found. There was a trend for retinopathy of prematurity to be reduced by treatment with high dose vitamin A. In a multicenter study ($n = 807$ infants of birth weight < 1 kg) published since the meta analysis (Tyson et al. 1999), infants randomized to 1500 μg (5000 IU) of vitamin A as retinyl palmitate given IM three times per week for 4 wk compared to nonplacebo-controlled infants exhibited a small but significant reduction (62% vs. 55% in unsupplemented controls) in incidence of death or chronic lung disease at 36 wk postmenstrual age. No difference in retinopathy of prematurity was observed (Tyson et al. 1999).

For the studies reviewed for the meta analysis (Darlow and Graham 1999) that measured plasma retinol, supplemental vitamin A did not always maintain circulating retinol at concentrations above that considered to reflect biochemical deficiency (0.7 mol/L). Based on the multicenter study by Tyson et al. (1999), it was suggested that a dose of 1500 μg (5000 IU) of vitamin A given IM three times per week is necessary to maintain normal biochemical status of vitamin A. This contrasts with the results of the study by Landman et al. (1991), in which oral supplements of 1500 μg daily normalized plasma retinol to the same degree as IM supplements of 600 μg vitamin A given on alternate days. However, functional outcomes of mortality or morbidity of lung disease were not assessed in the latter study.

In summary, the available evidence is only suggestive of a role for high dose vitamin A in the prevention of BPD. Such benefits must be weighed against the invasiveness of giving intramuscular injections, unless oral high dose vitamin A is proven effective and without side effects. Further study is required concerning the fate of high dose vitamin A when given concurrently with steroid therapy, as would often be the case in today's clinical practice. A steroid, particularly dexamethasone, which is used in ELBW infants, is associated with a transient rise in plasma retinol and retinol binding protein presumably as a result of stimulation of release of these compounds from the liver (Georgieff et al. 1989, Shenai et al. 2000). Thus, caution must be exercised by not administering large doses of vitamin A during therapy with dexamethasone, to avoid exposure of high circulating concentrations of retinol.

In addition, the effectiveness and safety of administering high dose vitamin A in ELBW infants < 700 g birth weight awaits evaluation.

Nutritional interventions to promote recovery from BPD

Growth restriction, delayed bone mass accretion (Brunton et al. 1998, Greer and McCormick 1986) and delayed catch-up growth (Furman et al. 1995, Giacoia et al. 1997) in infants who develop chronic lung disease is well documented. The etiology of this delayed growth performance is multifactorial including the following: limited nutrient intake because of restricted fluid intake; feeding intolerance and/or extended parenteral nutrition; extreme prematurity; and the interference with growth processes by exogenous steroids, when prescribed to enhance pulmonary compliance (Weiler et al. 1997a, Ward et al. 1999a).

The steroid dexamethasone is commonly used in ELBW infants as therapy to promote earlier weaning from the ventilator and possibly prevention of BPD (Ng 1993). Unfortunately, the negative effects of the potent steroid on growth and mineral and bone metabolism must be weighed against the short-term clinical benefits of dexamethasone. In studies from my laboratory we observed that dexamethasone was associated with abrupt growth restriction without recovery by term age. Although the infants were born appropriate for gestational age (birthweight: 782 ± 185 g, gestational 25 ± 1 wk), length fell to < 5% percentile during dexamethasone treatment with only 1/17 infants demonstrating significant catch-up (> 5% percentile) by term age (Ward et al. 1999a). Weight fell to < 5% percentile in 13/17 infants during dexamethasone and only 2/13 infants crossed above the 5% percentile by term age (Ward et al. 1999a).

Postnatal steroids induce abnormalities in bone metabolism by interfering with one or more aspects of the growth hormone–insulin-like growth factor (GH-IGF-1) axis (Ward et al. 1999a). Bone cell activity is suppressed during steroid therapy, as indicated by reduced circulating osteocalcin (a bone-formation marker) and N-telopeptide (a bone-resorption marker), although both markers rose by 10 d after the completion of dexamethasone therapy (Ward et al. 1999a). Even tapered dosing regimens of dexamethasone are associated with restriction in weight, length and head circumference growth and abnormalities in biochemical markers of bone turnover (Weiler et al. 1997a, Ward et al. 1999a). Using the early weaned piglet model, we reproduced the steroid-induced abnormalities observed in ELBW infants, thus proving that the

restrictions in growth and bone are a result of the steroid drug and not a result of the lung disease or extreme prematurity per se (Weiler et al. 1995, Ward et al. 1998, Guo et al. 2000).

In that ELBW infants, especially those with BPD, have a multitude of feeding problems as noted above, it is reasonable that the restricted growth could be the result of inadequate nutrient delivery rather than a direct effect of the steroid drug. Two prospective descriptive studies with follow-up completed in our institution demonstrated that nutrient intake of dexamethasone-treated infants was not different either during or after dexamethasone (Ward et al. 1999a) or when compared to nontreated infants matched for size and gestation (Weiler et al. 1997a). Thus, the catabolic effects of dexamethasone on protein metabolism (Weiler et al. 1997b, Ward et al. 1999b) and its interference with the GH-IGF-1 axis (Ward et al. 1998, 1999a) are the more likely explanations for the immediate influence of the drug on normal development. Administration of GH with or without IGF-1, only partially attenuated the steroid-induced abnormalities in growth and bone metabolism (Ward et al. 1998). The role of nutrition in attenuating the negative effects of steroid drugs on growth processes during drug administration or as rehabilitation after the completion of drug treatment needs to be investigated.

Nutrient-enriched formula to support catch-up growth in BPD infants

Because nutrient intake was not compromised in ELBW infants treated with dexamethasone, it seemed appropriate to provide supplemental nutrition after the completion of steroid therapy, to promote catch-up growth in this vulnerable population. Catch-up growth, or an accelerated growth, is known to be delayed in infants with BPD, often well into childhood, and most report lack of achievement of catch-up within the first year (Furman et al. 1995, Giacoia et al. 1997). With the current emphasis on the importance of fetal and early nutrition to later metabolic programming for normal development and onset of chronic disease (Lucas 1998), we proposed that early nutritional intervention to promote growth recovery in infants with BPD had the promise of clinical benefit.

In a randomized double-blind nutrition intervention study with follow-up to 1-y corrected age, we studied the response in growth and body composition in infants recovering from BPD to a diet high in energy [3760 kJ/L (910 kcal/L)] and providing either protein and minerals similar to standard-term infant formula or a formula enriched with protein and minerals (Brunton et al. 1998). The infants ($n = 30$ per treatment

TABLE 1

Nutrient intakes of premature infants with bronchopulmonary dysplasia fed a nutrient enriched or control high energy formula to 3-mo corrected age

	Standard formula	Enriched formula	CPS-P-RNI ¹
N	30	30	
At 1-m corrected age			
Energy ($\text{kJ} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$)	536 ± 133^2	491 ± 95	417–501
Protein ($\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$)	2.1 ± 0.6	$2.8 \pm 0.6^*$	2.2
Calcium ($\text{mmol} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$)	1.7 ± 0.5	$3.8 \pm 0.9^*$	6
At 3-mo corrected age			
Energy ($\text{kJ} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$)	496 ± 116	438 ± 92	417–501
Protein ($\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$)	2.0 ± 0.5	$2.5 \pm 0.5^*$	2.2
Calcium ($\text{mmol} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$)	1.7 ± 0.5	$3.2 \pm 1.1^*$	6

¹ CPS-PRNI—Recommended Nutrient Intakes for Premature Infants (Canadian Pediatric Society 1995).

² Values are means \pm sd. Means with asterisk (*) are significantly different between groups fed standard or enriched formula, $P < 0.001$.

TABLE 2

Z-scores for weight- and length-for-age in premature infants with bronchopulmonary dysplasia who were fed a nutrient-enriched or standard high energy formula to 3-mo corrected age

	Standard formula	Enriched formula
1-mo corrected age		
Weight-for-age	-1.49 ± 0.8 ¹	-1.14 ± 0.8
Length-for-age	-2.60 ± 1.1	-2.36 ± 1.1
3-mo corrected age		
Weight-for-age	-1.42 ± 0.9	-1.05 ± 1.1
Length-for-age	-2.36 ± 0.9	-1.80 ± 1.2*

¹ Values are means ± SD. Means with asterisk (*) are significantly different between groups fed standard or enriched formula, $P < 0.05$.

group, mean birth weight = 870 g, mean gestational age = 26 wk) were fed on the intervention diets for approximately 4 mo to an average of 3-mo corrected age. The nutrient-enriched formula demonstrated positive effects on length and lean mass after nearly 4 mo of feeding. Bone mineral content of the whole body was also higher in the infants receiving the enriched formula but only in the male infants (Brunton et al. 1998). The nutrient intakes consumed to achieve these positive benefits to growth are shown in Table 1 for 1 and 3 mo of age. As noted, the intakes for protein and energy were in excess of the current estimates of nutrient needs of premature infants after hospital discharge (Canadian Pediatric Society 1995). Weight and length, however, both remained well below reference standards, as indicated by the Z-scores in Table 2. Of interest, linear growth was disproportionately restricted relative to weight (Table 2).

By design the energy intakes were similar between treatment groups, in that both study formulas had an energy content of 3760 kJ/L (910 kcal/L). At the protein:energy ratio of the control formula (1.6 g protein/1000 kJ or 2.5 g/100 kcal) the infants developed a greater percentage body fat than those fed the nutrient-enriched formula (4 g protein/1000 kJ or 6 g/100 kcal) (Brunton et al. 1998).

The greatest disappointment of this study in BPD infants was the lack of a sustained benefit at 1-y corrected age in length, lean mass and bone mass that was observed at 3 mo when the intervention was completed (Brunton et al. 1997). Clearly, continuation of nutrient-enriched feeding at least to 1-y corrected age in such a vulnerable infant population may be appropriate. Nutrient-enriched formulas fed for extended periods to premature infants without BPD have been associated with longer-term benefits to growth (Lucas et al. 1992, Cooke et al. 1998, Atkinson et al. 1999).

Extremely low birth weight infants who have pulmonary insufficiency in early life may benefit from special nutritional management both for the prevention of and recovery from BPD. Unfortunately, clear evidence-based guidelines for optimal nutrition to ELBW infants with BPD are not yet available. Ensuring adequate intakes of vitamin A by either the oral or IM route in early life so as to maintain a normal circulating retinol is a reasonable objective (Shenai 1999, Darlow and Graham 1999). Nutritional support after hospital discharge should be assessed with the goal to promote catch-up growth but specific nutrient requirements to achieve this goal need to be defined.

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