

NUTRIENT NEEDS AND FEEDING OF PREMATURE INFANTS

Nutrition Committee, Canadian Paediatric Society

Abstract • Résumé

Objective: To recommend appropriate intake of nutrients, food sources and feeding practices for premature infants.

Options: Unfortified milk from the premature infant's own mother, fortified milk from the premature infant's own mother, formula designed for preterm infants and parenteral nutrition.

Outcomes: From birth to 7 days, the minimum achievable goal is the provision of sufficient nutrients to prevent deficiencies and catabolism of nutrient substrate in premature infants; from 7 days to discharge from the neonatal intensive care unit, growth and nutrient retention at a rate similar to that which would have been achieved had the infant remained in utero; and for 1 year following discharge, nutrient intake to achieve catch-up growth.

Evidence: Few randomized clinical trials of feeding infants specific nutrients or of feeding choices have been conducted. On the basis of a MEDLINE search of the literature, committee members prepared reviews of the available information on each nutrient and feeding choice. The reviews were critically appraised by the committee. Recommendations were based on the consensus of the committee.

Values: Whenever possible, the evidence was weighed in favour of randomized controlled trials. If such trials were unavailable, cohort studies were considered. If trials of either kind were unavailable, published data were reviewed and recommendations were based on consensus opinion.

Benefits, harms and costs: The advantages of feeding premature infants unfortified milk from their own mothers are psychologic benefits for the mother as well as anti-infective benefits and possibly improved intellectual development for the infant. However, unfortified milk from the infant's own mother is inadequate as a sole source of nutrients. The use of fortified milk from the mother results in faster growth as well as having the other benefits of mother's milk. When formulas designed for premature infants are given in adequate volumes, they provide an intake of nutrients that allows the infant to duplicate intrauterine growth without undue metabolic stress.

Recommendations: The preferred food for premature infants is fortified milk from the infant's own mother or, alternatively, formula designed for premature infants. This recommendation applies to infants with birth weights of a minimum of 500 g to a maximum of 1800 to 2000 g, or with a gestational age at birth of a minimum of 24 weeks to a maximum of 34 to 38 weeks (until the infant is able to nurse effectively).

Validation: These guidelines are in line with, but not identical to, recent guidelines by the Committee on Nutrition of the American Academy of Pediatrics and the Committee on Nutrition of the Preterm Infant of the European Society of Paediatric Gastroenterology and Nutrition.

Sponsor: The preparation of these guidelines was sponsored and funded by the Canadian Paediatric Society.

Objectif : Recommander un apport approprié de nutriments, des sources d'aliments et des pratiques d'alimentation pour les nouveau-nés prématurés.

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Options : Lait non fortifié de la mère du nouveau-né prématuré, lait maternel fortifié de la mère du nouveau-né prématuré, lait maternisé pour nouveau-nés prématurés et alimentation parentérale.

Résultats : De la naissance à 7 jours, l'objectif minimum à atteindre est un apport suffisant en nutriments pour prévenir des carences et le catabolisme du substrat de nutriments chez les nouveau-nés prématurés; de 7 jours à la libération de l'unité des soins intensifs néonataux, croissance et rétention des nutriments à un taux comparable au taux qui aurait été atteint si le nourrisson était demeuré dans le sein de sa mère; pendant 1 an après la libération, apport de nutriments pour réaliser un rattrapage de croissance.

Preuve : Les essais cliniques randomisés sur les nutriments spécifiques absorbés par les nouveau-nés ou sur les choix d'alimentation sont peu nombreux. S'appuyant sur une recension des écrits dans MEDLINE, les membres du comité ont préparé des examens des renseignements disponibles sur chaque nutriment et chaque choix d'alimentation. Le comité a procédé à une évaluation critique des revues. Ses recommandations sont fondées sur un consensus.

Valeurs : Lorsque ce fut possible, on a pondéré les preuves en faveur des essais contrôlés randomisés. Lorsque de tels essais n'étaient pas disponibles, on a envisagé des études de cohortes. S'il n'existait pas d'essais de l'un ou l'autre des deux types, on a examiné les données publiées et fondé les recommandations sur le consensus.

Avantages, préjudices et coûts : Les avantages que présente pour les enfants prématurés une alimentation fondée sur le lait maternel non fortifié sont d'ordre psychologique pour la mère et présentent aussi un moyen de lutte contre l'infection et, peut-être, de développement intellectuel amélioré pour le nouveau-né. Le lait non fortifié de la mère du nouveau-né ne suffit toutefois pas comme seule source de nutriments. Le lait maternel fortifié accélère la croissance et offre aussi les autres avantages du lait maternel. Lorsqu'on donne aux nouveau-nés suffisamment de lait maternisé pour prématurés, le lait fournit un apport de nutriments qui reproduit chez les nouveau-nés la croissance intra-utérine sans causer d'effort métabolique inutile.

Recommandations : L'alimentation privilégiée chez les nouveau-nés prématurés est le lait fortifié de la mère du nouveau-né ou, comme solution de rechange, le lait maternisé pour prématurés. Cette recommandation vaut pour les nouveau-nés dont le poids à la naissance varie d'au moins 500 g jusqu'à 1 800 à 2 000 g, ou dont l'âge de la grossesse à la naissance varie d'au moins 24 semaines à au plus 34 à 38 semaines (jusqu'à ce que le nouveau-né puisse téter efficacement).

Validation : Ces lignes directrices sont conformes mais non identiques aux lignes directrices établies récemment par le Committee on Nutrition de l'American Academy of Pediatrics et par le Committee on Nutrition of the Preterm Infant de la European Society of Paediatric Gastroenterology and Nutrition.

Commanditaire : La préparation de ces lignes directrices a été commanditée et financée par la Société canadienne de pédiatrie.

Since the Canadian Paediatric Society (CPS) published recommendations concerning the feeding of premature infants in 1981,¹ there have been enormous advances in the type and quality of clinical care offered to infants born prematurely. It is therefore appropriate to revise the recommendations concerning nutrition for preterm infants. A subcommittee of the Nutrition Committee of the CPS was formed to review the recent literature on nutrient metabolism and feeding of premature infants and to make new nutrition recommendations. The subcommittee included neonatologists, clinical nutritionists and dietitians.

METHODS

For most nutrients it was impossible to derive recommendations through the use of established research methods for defining nutrient requirements (i.e., factorial analyses, information on nutrient balances, controlled studies and epidemiologic data) because the data simply do not exist. For term infants, mother's milk is the "gold standard" for nutrient requirements. However, it is not

the reference standard for nutrients for premature infants because of the risk of inadequate growth and nutrient deficiencies when mother's milk is used without fortification. The committee therefore had to find a different method to establish nutrition recommendations. Specific outcome goals were predetermined on the basis of the infant's birth weight and age after birth. Two birth-weight categories (below 1000 g and 1000 g or more) and three age categories (birth to 7 days, or the "transition" period; stabilization to discharge from the neonatal intensive care unit (NICU), or the "stable-growing" period; and 1 year following discharge from the NICU, or the "postdischarge" period) were defined. The birth-weight categories reflect the difference in accretion of nutrients before birth, and the postnatal periods reflect the changing growth and nutrient metabolism that accompany postnatal maturation.

During the transition period, infants (particularly those with a birth weight below 1000 g) are likely to be clinically and metabolically unstable and to lose weight, primarily as a result of shifts in water balance and relative starvation. The minimum achievable goal during

this period is the provision of sufficient nutrients, parenterally or enterally (by tube through the gastrointestinal tract), to prevent nutrient deficiencies and substrate catabolism. If the infant is stable, higher intakes can be provided during the later part of the transition period. The stable-growing period begins when the infant is metabolically and clinically stable and ends when the infant is discharged from the NICU. During this period the primary nutritional goal is growth and nutrient-retention rates similar to those that would have been achieved in utero. According to Lubchenco and associates,² between 24 and 36 weeks of gestation, a fetus who grows at a rate at the 50th percentile gains 14.5 g/kg per day. This means that a 1 kg infant needs to gain 14.5 g per day to grow as if in utero. An infant growing at a rate at the 90th percentile grows 12.2 g/kg per day; for an infant at the 10th percentile, the rate of weight gain is 15.6 g/kg per day. During the postdischarge period the goal is a nutrient intake that is adequate to achieve catch-up growth. Establishing recommendations for this period was hampered by a marked lack of research.

The nutrient intake needed to achieve these outcome goals is called the "preterm recommended nutrient intake" (P-RNI). If there was inadequate information available to establish a P-RNI, a "best estimate for safety and efficacy" was made. These estimates were based on the estimated nutrient intake from preterm-mother's milk (milk produced by the mother of a preterm infant for her own infant, as distinguished from banked human milk) fed to the infant at recommended volumes and on available clinical studies of efficacy. On the basis of the P-RNI for each nutrient, the adequacy of preterm-mother's milk and of formula designed for premature infants was determined.

Few studies have examined the long-term outcomes among infants fed with different nutrient sources or fed via different routes. Therefore, estimates of need were based mainly on short-term outcomes. The evidence included much more information on low-birth-weight (greater than 1000 g) infants than on those with extremely low birth weights (less than 750 g). Thus, for many nutrients, estimates of the intake required by infants with extremely low birth weights were extrapolated from data involving larger premature infants. Therefore, recommendations for these infants are more tentative than those for larger infants. As more data on infants with extremely low birth weights are collected, the strength of future recommendations for nutrient intake will likely improve.

The first section of this article provides a brief discussion of the importance of each nutrient, followed by specific recommendations for achieving an adequate intake from preterm-mother's milk, formula and parenteral nutrition. The second section provides the options for feeding preterm infants.

These guidelines are intended to assist health care

professionals in making informed decisions about infant foods and feeding, to provide background information for regulation of infant foods, and to stimulate the infant-food industry to continue to manufacture products that meet the needs of premature infants. Whenever possible, the evidence supporting recommendations was weighed in favour of randomized controlled trials. If such trials were unavailable, cohort studies were considered. If both types of study were unavailable, published data were reviewed and recommendations were based on consensus opinion. The recommendations are in line with, but not identical to, recent guidelines from the Committee on Nutrition of the American Academy of Pediatrics and the Committee on Nutrition of the Preterm Infant of the European Society of Paediatric Gastroenterology and Nutrition.^{3,4}

RECOMMENDATIONS CONCERNING NUTRIENTS

P-RNIs established by the committee are given in Table 1.

WATER

Water intake must maintain normal fluid and electrolyte balances, through renal excretion of metabolic wastes and replacement of water lost through the skin and the respiratory and digestive tracts, and meet the need for growth. Achieving these goals is complicated by the immaturity of homeostatic mechanisms in preterm infants, by any coexisting illnesses and by non-physiologic environmental conditions.^{5,6}

During the transition period, preterm infants are clinically unstable, and devices or interventions that affect water balance (e.g., warming the infant with a radiant heater) are frequently used. Therefore, water requirements must be determined for each infant, and a standard recommendation cannot be made. In the results of two randomized clinical trials, high-volume water intake was associated with an increased risk of patent ductus arteriosus.^{7,8} However, intake must be sufficient to prevent dehydration. Careful monitoring of water intake and output as well as at least one daily weight measurement and electrolyte assessment are needed. During the stable-growing period, we recommend intake within a range (see Table 1) because of the wide variation in water needs for infants of different gestational and postnatal ages and of varying clinical circumstances. The range is based on the assumptions that the infant is stable, not exposed to a radiant heater, heat shield or cellophane wrap and is not given phototherapy. Infants who are small for their gestational age lose less water through the skin than infants who are an appropriate size for their

gestational age. Therefore, the former group may have lower water needs. Although feeding an infant in this period 120 mL/kg per day of preterm-mother's milk or formula may meet fluid needs, it is too low a volume to meet P-RNIs for some nutrients (Table 2). During the postdischarge period, water needs are assumed to be equivalent to those for term infants (Table 1).

ENERGY

Growth is very rapid during the third trimester of gestation, and total energy needs are very high. Infants in utero gain 12 to 16 g/kg per day.² Energy expenditure during this period varies widely, depending on conditions and diseases affecting the infant.¹⁸ Energy expenditure by

Table 1: Recommended nutrient intakes for premature infants (P-RNIs)

Nutrient	Period after birth; P-RNI per day			Volume of preterm-mother's milk needed to meet P-RNI during stable-growing period, mL/kg per day
	Transition (birth to 7 days)	Stable-growing (stabilization to discharge from NICU*)	Postdischarge (1 year following discharge from NICU)	
Water, mL/kg	Variable	120–200	120–160	120–200
Macronutrients				
Energy,† kJ/kg (kcal/kg)	292–334 (70–80)	438–563 (105–135)	417–501 (100–120)	145–185
Protein,‡ g/kg	1.0–3.0	3.5–4.0 (birth weight < 1000 g) 3.0–3.6 (birth weight ≥ 1000 g)	2.2	180–210
Fat, g/kg	0.5–3.6	4.5–6.8	4.4–7.3	
Fat,† % of energy	10–50	40–55	40–55	
Linoleic acid, % of energy	4–5	4–5	4–5	
Linolenic acid, % of energy	1	1	1	
Carbohydrate, g/kg	5.0–20.0 (3.5–16.5 mg/kg per min)	7.5–15.5	7.5–15.5	120–200
Minerals				
Calcium, mmol/kg	1.5–2.0	4.0–6.0	6.3 mmol/d (breast fed) 9.4 mmol/d (formula fed)	NA‡
Phosphorus, mmol/kg	1.0–1.5	2.5–3.8	3.4 mmol/d (breast fed) 8.8 mmol/d (formula fed)	NA
Magnesium, mmol/kg	0.20–0.25	0.20–0.40§	0.20–0.60	165–335
Sodium, mmol/kg	1.0–3.0	2.5–4.0	2.0–3.0	NA
Chloride, mmol/kg	1.0–3.0	2.5–4.0	2.0–3.0	145–235
Potassium, mmol/kg	2.5–3.5	2.5–3.5	2.5–3.5	155–220
Iron, mg/kg	0	(starting 6 to 8 wk after birth) 3.0–4.0 (birth weight < 1000 g) 2.0–3.0 (birth weight ≥ 1000 g)	3.0–4.0 (birth weight < 1000 g) 2.0–3.0 (birth weight ≥ 1000 g)	NA

*NICU = neonatal intensive care unit.

†Amount required if the infant is fed parenterally differs; see discussion in text.

‡NA = not achievable at recommended fluid intake of 120 to 200 mL/kg per day.

§Amount required is higher if milk from the premature infant's mother is fortified with other minerals that may diminish the bioavailability and absorption of magnesium.

||In specific clinical situations, sodium and chlorine may need to be omitted for short periods.

infants can be divided into four categories: the resting metabolic rate (196 to 217 kJ/kg [47 to 52 kcal/kg] per day); the rate during activity (13 to 17 kJ/kg [3 to 4 kcal/kg] per day); the loss of energy through excretion (46 to 74 kJ/kg [11 to 18 kcal/kg] per day); and the energy cost of weight gain (13 to 17 kJ [3 to 4 kcal] per gram of weight gained).¹⁹ Therefore, required energy intake varies

widely depending on the goal for weight gain; it is between 209 and 250 kJ/kg (50 to 60 kcal/kg) per day for an infant fed parenterally who is not growing and is in a thermoneutral environment; however, it is 542 to 584 kJ/kg (130 to 140 kcal/kg) per day for an infant growing at a "catch-up" rate (faster than an intrauterine growth rate). Infants fed parenterally have lower total energy needs

Table 1 continued

Nutrient	Period after birth; P-RNI per day			Volume of preterm-mother's milk needed to meet P-RNI during stable-growing period, mL/kg per day
	Transition (birth to 7 days)	Stable-growing (stabilization to discharge from NICU*)	Postdischarge (1 year following discharge from NICU)	
Zinc, $\mu\text{mol/kg}$	6.5	7.7–12.3	15.0 (estimate)	120–190
Copper,†¶ $\mu\text{mol/kg}$	1.1–1.9	1.1–1.9**	1.1–1.9**	115–200
Selenium,†¶ $\mu\text{mol/kg}$	0.04–0.06	0.04–0.06	0.04–0.06	120–200
Chromium,†¶ nmol/kg	1.0–1.9	1.0–1.9	1.0–1.9	120–200
Manganese,†¶ nmol/kg	10–20	10–20	10–20	120–200
Molybdenum,†¶ nmol/kg	2.0–4.0	2.0–4.0	2.0–4.0	120–200
Iodine,†¶ $\mu\text{mol/kg}$	0.20	0.25–0.50	0.25–0.50	190–375
Vitamins				
Vitamin D, IU	40–120 (birth weight < 1000 g) 40–260 (birth weight ≥ 1000 g)	400 (800 for certain infants; see text)	400	NA
Vitamin A, $\mu\text{g/kg}$	450	450 (birth weight < 1000 g) 200–450 (birth weight ≥ 1000 g; lower intake for larger infants)	400 μg	NA
Vitamin E,† mg/kg	0.5–0.9	0.5–0.9	0.5**	120–200
Vitamin C, mg/kg	6–10	6–10	20 mg	120–200
Vitamin B ₁ , mg/kg	0.04–0.05	0.04–0.05	0.05	120–200
Vitamin B ₂ , mg/kg	0.36–0.46	0.36–0.46	0.05	NA
Vitamin B ₆ , mg/g of protein	0.015	0.015	0.015	120–200
Vitamin B ₁₂ , μg	0.15	0.15	0.15	120–200
Niacin, NE††/5000 kJ	8.6	8.6	8.6	120–200
Folate, μg	50	50	25	NA
Biotin, $\mu\text{g/kg}$	1.5	1.5	1.5	120–200
Pantothenic acid, mg/kg	0.8–1.3	0.8–1.3	0.8–1.3	120–200

¶May be omitted from parenteral nutrition during the transition period.

**For infants fed formula, this amount may differ; see discussion in text.

††NE = niacin equivalents.

Table 2: Intake from preterm-mother's milk (120–200 mL/kg per day) alone, and in combination with commercial fortifiers

Nutrient*	P-RNI for stable-growing period, per kg per day unless otherwise indicated	Concentration of nutrient in preterm-mother's milk, per L unless otherwise indicated	Intake from preterm-mother's milk, per kg per day	Fortifier; total intake from preterm-mother's milk in combination with fortifier, per kg per day	
				Enfamil HumanMilk Fortifier† (4 packs to 100 mL human milk)	Similac Natural Care† (added to an equal volume of human milk)
Energy, kJ (kcal)	438–563 (105–135)	3046 ⁹ (730)	367–605 (88–145)	434–726 (104–174)	388–642 (93–154)
Protein, g	3.5–4.0 (birth weight < 1000 g) 3.0–3.6 (birth weight ≥ 1000 g)	17 ⁹	2.0–3.4	2.9–4.8	2.3–3.9
Calcium, mmol	4.0–6.0	7.5 ¹⁰	0.9–1.5	3.6–6.0	3.0–5.0
Phosphorus, mmol	2.5–3.8	4.5 ¹⁰	0.5–0.9	2.3–3.8	1.9–3.2
Magnesium, mmol	0.2–0.4‡§	1.2 ¹¹	0.14–0.24	0.20–0.32	0.3–0.5
Sodium, mmol	2.5–4.0	11 ¹¹	1.3–2.2	1.7–2.8	1.6–2.6
Chloride, mmol	2.5–4.0	13 ¹¹	1.6–2.6	2.2–3.6	1.9–3.2
Iron, mg	(starting 6 to 8 wk after birth) 3.0–4.0 (birth weight < 1000 g) 2.0–3.0 (birth weight ≥ 1000 g)	0.3	0.04–0.06	0.04–0.06	0.2–0.3
Zinc, µmol	7.7–12.3‡	63 mmol/L ¹²	7.7–12.3	20.6–34.3	15.0–25.0
Copper, µmol	1.1–1.9‡¶	9.4 ¹²	1.1–1.9	2.3–3.8	2.5–4.1
Iodine, µmol	0.25–0.50	1.25 ¹³	0.15–0.25	0.15–0.25	0.1–0.16
Vitamin D, IU/d	400 (800 for certain infants; see text)	40 ¹⁴	4.8–8.0	257–428	75–126
Vitamin A, µg	450 (birth weight < 1000 g) 200–450 (birth weight ≥ 1000 g)	830 mg/L ¹⁵	100–165	442–736	149–249
Vitamin B ₁ , mg	0.04–0.05**		0.04–0.05	0.22–0.36	0.14–0.23
Vitamin B ₂ , mg	0.36–0.46	0.055 mg/418 kJ ¹⁶	0.04–0.07	0.3–0.5	0.33–0.54
Vitamin B ₆ , mg/g of protein	0.015		0.015	0.16††	0.05
Niacin, NE/5000 kJ	8.6 NE/5000 kJ**		8.6	42	30
Folate, µg/d	50 µg/d	33 mg/L ¹⁷	4.0–6.6	34–57	20–33

*The recommendations for supplementation of energy, protein, calcium, phosphorus, sodium, iron, vitamins A, B₂ and D are definite; those for supplementation of magnesium, chloride, zinc, copper, iodine, vitamins B₁ and B₆, folate and niacin are provisional.

†Enfamil, Mead Johnson, Ottawa; Similac, Abbott Laboratories, Montreal.

‡The P-RNI is based on the assumption that the bioavailability of this mineral is affected by other minerals in the supplement.

§The estimated need for magnesium is increased to 0.6 mmol/kg per day.

||The estimated need for zinc is increased to 17 µmol/kg per day.

¶The estimated need for copper is increased to 1.6–3.2 µmol/kg per day.

**The need for a supplement is based on the assumption that the supplement contains carbohydrate as the energy source.

††Amount provided by Enfamil Human Milk Fortifier only.

than those fed enterally because of lower energy losses in stools and, possibly, more efficient use of energy.²⁰

During the transition period, weight gain is unlikely. Infants lose up to 15% of body weight during this period. The "maintenance" energy intake is 209 to 250 kJ/kg (50 to 60 kcal/kg) per day if the infant is totally parenterally fed and higher if the infant is fed enterally (Table 1). If the infant is metabolically stable, an energy intake higher than the P-RNI may be achieved. During the stable-growing period, weight gain at the intrauterine rate of 12 to 16 g/kg per day can be reasonably expected with the recommended energy intake.² Since the mean gross (metabolizable) energy content of preterm-mother's milk is about 3046 kJ/L (750 kcal/L) after the second week of life,^{9,21} an intake of 145 to 185 mL/kg per day is needed. If the infant is fed parenterally, energy needs are 334 to 459 kJ/kg (80 to 110 kcal/kg) per day.²⁰

During the postdischarge period, growth rates equivalent to those of term infants or greater can be achieved with the recommended energy intakes, unless the infant has unusually high continuing energy needs as a result of an illness such as chronic lung disease of infancy.²²

PROTEIN

Preterm infants grow at similar rates despite varying protein intake, as long as energy intake does not limit growth.^{20,23} However, premature infants are metabolically immature; therefore, protein turnover is high²⁴ and the endogenous synthesis of certain amino acids is delayed during the first months of life.²⁵⁻²⁷ This metabolic immaturity affects the quantity of protein as well as the balance of amino acids required by infants. A goal in providing protein is optimal nitrogen retention, often defined as equivalent to the intrauterine protein gain of a normal fetus without metabolic stress, such as uremia or distorted blood amino-acid patterns.^{1,3,28} Recently, however, it has been suggested that optimal neurodevelopmental outcome may be an equally important goal.²⁹

During the transition period, protein (amino-acid) intake should be sufficient to prevent breakdown of endogenous tissue; that is, approximately 1.5 g/kg per day.²⁴ If the infant is stable during the latter part of the transition period, higher amounts of protein (amino acids) may be given with safety. During the stable-growing period, the goal is to provide the protein intake needed to achieve intrauterine accretion. In infants with a birth weight lower than 1000 g, this goal can be achieved with the P-RNI, as long as the energy intake is adequate. In infants fed parenterally, a range of 2.7 to 3.5 g/kg per day is recommended. Preterm-mother's milk has a mean protein concentration of 16 to 18 g/L;^{9,21} hence, the average intake volumes of milk may not meet the goals for protein intake.^{26,30} A protein supplement to augment preterm-

mother's milk is therefore recommended (Table 2).

The recommended postdischarge protein intake is based on the Canadian RNI for term newborns. For premature infants who are growing rapidly during this period, higher intakes are acceptable to achieve catch-up growth.³¹

Clinical trials have not proved that taurine is an essential component of nutrition for newborns; however, taurine is found in high concentrations in human milk. All formulas based on cow's milk are currently supplemented with taurine. Such supplementation should not exceed the taurine content of human milk (0.25 to 0.75 mmol/L).

The use of formulas containing nucleotide supplements has not been shown to improve resistance against infections in premature infants;³² therefore, addition of nucleotides to formulas for premature infants is not recommended.

FAT

Fat is the major source of dietary energy for premature infants, and it constitutes 40% to 60% of the energy in human milk and infant formulas. Oxidation of fat provides energy to support basal metabolic functions and to meet the energy costs of tissue synthesis. The amount of fat required by premature infants is determined by the energy requirement, the limits to the amounts of protein and carbohydrates that can be fed to the infant, and the volume of food the infant can eat.³³ Essential fatty acids w6 and w3 are needed for cell-membrane function, eicosanoid metabolism and central-nervous-system development.³⁴ Hence, the recommended fat requirements are based on the amount needed to ensure adequate energy intake for appropriate growth and the amount of w3 and w6 essential fatty acids needed for optimal tissue fatty-acid composition and function.

During the transition period, providing a source of fat that includes the essential fatty acids is critical. Biochemical indices of essential-fatty-acid deficiency are common in premature infants 2 to 3 days old with birth weights of less than 1250 g.³³⁻³⁵ During the stable-growing period, the recommended total fat intake is based on the fat content of human milk.³⁶ Intake of linoleic and linolenic acids should be the same as during the transition period. For infants fed parenterally, fat intake may comprise 20% to 45% of the total energy intake. Little is known about the fat needs of preterm infants during the postdischarge period. Therefore, the recommendation is identical to that during the stable-growing period.

Lipid composition

Long-chain fatty acids

There is no definitive information that arachidonic acid

(20:4w6) and docosahexaenoic acid (22:6w3) are essential dietary nutrients at any period of development. However, an exogenous source of these fatty acids, constituting 0.25% of total energy intake, is likely needed. Although several sources of these fatty acids (such as fish oils) may be available, their long-term safety and efficacy in infant nutrition has not been determined.³⁷⁻³⁹ Because suitable sources of oils have not been adequately tested and inappropriate supplementation appears to present real risks of deleterious effects, we cannot make any specific recommendations for inclusion of these fatty acids in formulas.

Medium-chain triglycerides (MCTs)

MCTs usually constitute only 1% to 2% of fatty acids in human milk.³⁶ Results of recent studies show that growth is not improved with the use of MCTs and do not support its routine use in formula.⁴⁰ Therefore, the amount in formula should approximate that found in human milk without compromising total fat absorption or necessitating the use of large amounts of linoleic acid.

Nutrients involved in fat metabolism

Inositol

The need to include this nutrient in parenteral or enteral formulations cannot be confirmed. Inositol can be synthesized endogenously, and inositol deficiency in premature infants has not been found.⁴¹

Choline

Choline can be synthesized endogenously from protein and is found in mammalian milk. There is no documentation of choline deficiency in premature infants; therefore, the addition of choline to formulas based on cow's milk or to human milk is unwarranted.⁴² Likewise, there is no documentation of the efficacy of adding choline to formulations used for parenteral nutrition.

CARBOHYDRATE

Lactose makes up 40% to 50% of the nonprotein energy in human milk. Most premature infants, even those fed 200 mL/kg per day (13.0 to 15.5 g of lactose/kg per day), can tolerate the high intake of lactose from human milk.⁴³ A total carbohydrate intake higher than 15.5 g/kg per day may be acceptable for infants whose weight gain is poor. Many formulas for preterm infants now include glucose polymers as their primary source of carbohydrate. The activity of α -glucosidases in the fetus reaches at least 70% of the activity in adults at a gestational age of about 26 to 34 weeks, whereas lactase activity at that

gestational age is only 30% of adult activity.^{44,45} Salivary and mammary amylases, along with small-intestinal glucoamylase, partly compensate for the relative deficiency of pancreatic amylase, thereby allowing premature infants to digest α -glucosides better than lactose.^{44,45} Although, theoretically, lactose digestion should be limited, there is no evidence of clinical intolerance among these infants.^{46,47} However, there are other reasons for adding glucose polymers to formulas: they may result in faster gastric emptying, and they may increase caloric density without a corresponding rise in osmolality.

Hence, despite these theoretic considerations, there is no proof that lactose should be replaced by glucose polymers in formulas for preterm infants to improve carbohydrate absorption. Nevertheless, to ensure that the osmolality of formula is close to that of human milk, some lactose may need to be replaced by glucose polymers in formulas with high energy and mineral content.

During the transition period, the serum glucose concentration in infants should be carefully monitored. Infants who are small for their gestational age or who weigh less than 1000 g are particularly vulnerable to hypoglycemia and hyperglycemia during the first days of life. In parenteral nutrition, carbohydrate (as glucose) should be supplied at a rate that allows the infant to remain euglycemic (Table 1).^{48,49} The use of lactose-containing milks should not be restricted during this period. During the stable-growing period, carbohydrate intake should be 35% to 50% of total energy intake. The recommended carbohydrate intake is based on the lactose content of human milk. Carbohydrate may be given in the form of lactose, glucose polymers or both. For infants fed parenterally, glucose should comprise 50% to 60% of total energy intake. The recommendation for carbohydrate intake during the postdischarge period is identical to that during the stable-growing period.

RECOMMENDATIONS CONCERNING MINERALS

Calcium and phosphorus

Neither preterm-mother's milk alone nor standard formulas provide sufficient calcium and phosphorus to meet the predicted needs of growing premature infants.^{50,51} The use of prolonged total parenteral nutrition, preterm-mother's milk or standard formula has been associated with low serum and urine levels of phosphorus, hypercalciuria,^{11,52} elevated levels of alkaline phosphatase⁵³ and 1,25-dihydroxyvitamin D₃,⁵⁴ low content of radial-bone minerals (compared with intrauterine standards)^{55,56} and fractures and rickets in some infants.⁵⁷ A consensus of available studies of the calcium and phosphorus needs of premature infants is that feedings containing about 20 to 30 mmol/L of calcium and 16 to 20 mmol/L of phospho-

rus are appropriate in early neonatal life.⁵¹ Caution must be taken if infants are fed large amounts of calcium and phosphorus in combination with loop diuretics or glucocorticoids, both of which cause increased calciuria and increase the risk of renal calcification.⁵⁸

Some studies,^{59,60} but not all,^{56,61} have shown that calcium and phosphorus supplementation achieves postnatal bone-mineral content consistent with intrauterine accretion. Small increments in bone-mineral content in early life may be important to long-term skeletal development.⁶² As well, some premature infants with a very low birth weight who have had long periods of fluid restriction and therapy with calciuric drugs may benefit from receiving supplements for 2 to 3 months to attain catch-up bone growth. The amount and duration of mineral supplementation and the complications of prolonged infant feeding with mineral-fortified milk require further study.

During the transition period, calcium and phosphorus intake should be adequate to achieve normal serum concentrations of these minerals and to prevent hypercalciuria (Table 1). If the infant is fed exclusively through total parenteral nutrition, the upper limits of solubility with available salts (calcium gluconate and mixed monobasic and dibasic sodium or potassium phosphate) are 15 mmol/L for both calcium and phosphorus.⁶³ This concentration is only attainable when the amino-acid content of the parenteral formulation is 25 g/L or less; otherwise, there is a risk of calcium or phosphorus precipitation. During the stable-growing period, the goal is to achieve intrauterine calcium and phosphorus accretion and bone mineralization. Unfortunately, we cannot yet accurately predict intakes that will achieve normal long-term bone mineralization. For premature infants, regardless of birth weight, intrauterine bone growth may be approximated by providing the recommended calcium and phosphorus intakes.⁵⁹ The recommended molar ratio of calcium to phosphorus is 1.6 to 2.0. For infants fed preterm-mother's milk, this intake can be achieved only through adding calcium and phosphorus as individual salts or as a human-milk fortifier⁶⁴ (Table 2). Some formulas designed for preterm infants contain the amounts of calcium and phosphorus needed to achieve intrauterine accretion of bone minerals; however, due to variations in absorption, adequate retention is not guaranteed in all infants. The recommended postdischarge intake of calcium and phosphorus is based on the current Canadian RNI for term infants during the first 6 months.⁶⁵ Long-term studies suggest that the use of fortified formulas or preterm-mother's milk is associated with improved bone-mineral content,^{66,67} but further studies are required.

Magnesium

The magnesium requirement for premature infants is

estimated to be similar to that for term infants fed human milk. Infants fed preterm-mother's milk, which contains 1.2 mmol/L of magnesium, fortified preterm-mother's milk, standard formula or formula for preterm infants retain magnesium at or just below the predicted intrauterine-retention rate (0.15 mmol/kg per day).^{11,68,69} High concentrations of calcium in formulas for preterm infants and fortified preterm-mother's milk may depress magnesium absorption;⁷⁰ therefore, intakes from these sources should contain higher amounts of magnesium than that found in unfortified preterm-mother's milk.

During the transition period, the infant's magnesium intake should be adequate to maintain the normal serum concentration of magnesium. If the infant is stable during the later part of the transition period, higher intakes may be given with safety. During the stable-growing period, the intake needed to meet intrauterine accretion, regardless of birth weight, can be achieved with the use of preterm-mother's milk or formula.¹¹ For premature-infant formulas that have a high calcium content the ratio of calcium to magnesium should be less than 11 mmol of calcium to 1 mmol of magnesium in order to maximize absorption of magnesium.⁷⁰ The Canadian RNI for term infants⁶⁵ is based on the content of magnesium in human milk; this RNI is likely to be adequate for premature infants during the postdischarge period.

Sodium, chloride and potassium

Premature infants generally require a higher sodium intake than term infants and a higher intake than that supplied in human milk of mothers delivered at term (5 to 7 mmol/L) or in formulas designed for term infants (8 to 9 mmol/L).^{69,71,72} The supply of chloride and potassium from human milk, however, is generally adequate for preterm infants.¹¹

During the transition period, sodium and chloride needs are difficult to predict because of developmental and clinical factors affecting homeostasis of these minerals. The needs of each infant should be assessed to determine if they are higher or lower than basal requirements, which can be met through feeding with preterm-mother's milk.^{11,72} During the stable-growing period, human milk may meet the recommended intake of sodium and chloride if the infant is fed large volumes (185 to 200 mL/kg per day).⁷¹ However, concentrations of these nutrients in human milk decline after this period, so a supplement may be required. Serum levels of sodium should be monitored to determine the need for supplementation. Estimated potassium requirements can be met through feeding with preterm-mother's milk, which contains 12.5 to 16 mmol/L of potassium. The concentrations of sodium, chloride and potassium in formulas designed for premature infants may exceed the P-RNI;

however, there are no reports of toxic effects associated with these levels. During the postdischarge period, sodium, chloride and potassium needs are likely similar to those of term infants.

Iron

The major reserve of iron for premature infants at birth is the hemoglobin mass; there is little iron stored in the liver or the spleen. Despite the low stores, iron deficiency is unlikely to play a role in the anemia of prematurity during the first 2 months of life unless blood was lost during birth or as the result of phlebotomies to collect specimens for laboratory tests, and the lost blood was not replaced through an erythrocyte transfusion.^{73,74} In addition, erythrocyte synthesis is limited by very low erythropoietic activity until 5 to 7 weeks after birth. Prophylactic use of iron supplements or iron-fortified formula during the first 2 months of life have no effect on the fall in hemoglobin concentration during this period.^{75,76} Once active erythropoiesis begins, however, all premature infants require iron to maintain optimal hemoglobin production.^{77,78}

During the transition period, there is no need for iron. At the start of the stable-growing period, iron supplements are not recommended. However, starting 6 to 8 weeks after birth, infants with birth weights of 1000 g or more should have their diet supplemented with iron (2 to 3 mg/kg per day) or be given formula containing iron (12 mg/L) to prevent iron-deficiency anemia.⁷⁷ The iron needs of infants with birth weights below 1000 g are likely greater. Therefore, for these infants, a total intake of 3 to 4 mg/kg per day starting 6 to 8 weeks after birth is recommended.⁷⁷ An oral iron supplement is needed to achieve this intake. Iron supplementation should be continued until the infant is 12 months corrected age (the infant's age had he or she been born at term).⁷⁸ At that time infant's hemoglobin and ferritin levels should be monitored to ensure adequate hematologic status.

RECOMMENDATIONS CONCERNING TRACE MINERALS

Nutritionally essential trace minerals include zinc, copper, selenium, chromium, manganese, molybdenum and iodine. Published reports of mineral deficiencies among premature infants have involved only six of these elements. However, infants born prematurely are at increased risk of trace-mineral deficiencies because of low stores at birth, very rapid postnatal growth and variable intake.^{79,80} The trace-mineral content of human milk is the gold standard for requirements for term infants, provided that they ingest an adequate volume of milk.⁶⁵ However, for preterm infants there is no gold standard.

Instead, there are three acceptable objectives in setting intake amounts: prevention of trace-mineral deficiencies, replenishment of stores that would normally have been deposited in the developing fetus during the last trimester, and the avoidance of excessive intakes, which could have toxic effects.

During the transition period, when the infant is likely to be clinically unstable, intakes of trace minerals may not be necessary, since deficiencies are unlikely to develop during such a short period. If trace minerals are included in the feeding regimen of infants during this period, the intake should be adequate to prevent deficiency yet not enough to cause toxic effects. If parenteral nutrition is given during the transition period, trace minerals, with the exception of zinc, need not be included. The recommended intakes for infants fed parenterally are in keeping with the recent recommendations by the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition.⁶³ During the stable-growing period, when rapid growth resumes, trace minerals should be included in infants' diet at concentrations that prevent deficiencies or at the higher concentrations that also replace body stores. Higher intakes should continue during the postdischarge period when growth is rapid and the risk of trace-mineral deficiencies is high.

Zinc

The zinc content of human milk cannot be used as a gold standard to establish dietary zinc requirements for preterm infants. In fact, frank zinc deficiency developed in many breast-fed preterm infants.^{81,82} Although such frank deficiency is rare, many breast-fed premature infants may suffer from a zinc depletion without showing any signs of deficiency. Longitudinal studies of the zinc status of premature infants during the first year of life have found that these infants have a hair zinc level significantly lower than that of term infants.^{83,84} This evidence supports the suggestion that a zinc deficiency limits growth during the first year.

No cases of acute zinc deficiency during the first weeks after birth have been described. Therefore, during the transition period, the amount of zinc in human milk is likely adequate. For parenteral nutrition, a zinc intake of 6.5 μ mol/kg per day is recommended.⁸⁵ During the stable-growing period, infants fed preterm-mother's milk have not had a zinc deficiency. Our recommendation is based on the zinc content of preterm-mother's milk, fed to infants in adequate amounts. Because of a postulated depression of zinc absorption caused by other minerals in human-milk fortifiers,⁵⁹ fortified preterm-mother's milk and high-calcium formulas should contain additional zinc. During the postdischarge period, zinc intake

from human milk may be inadequate to meet the needs of a rapidly growing infant.^{81,82} An intake of 15 $\mu\text{mol/kg}$ per day should meet these needs and can be achieved through the use of formulas designed for term or preterm infants. Breast-fed infants would need a zinc-gluconate or zinc-sulfate supplement of 7.5 $\mu\text{mol/kg}$ per day to achieve this intake. However, the effect of zinc supplementation on breast-fed preterm infants has not been studied; thus, a definitive recommendation for zinc supplementation cannot be made.

Copper

Copper deficiency has been reported in preterm and term infants fed primarily cow's milk, iron-fortified formula, pasteurized human milk or a total-parenteral-nutrition formulation that does not include copper.⁸⁶⁻⁸⁹ Deficiency has not occurred in infants fed current formulas or preterm-mother's milk. Although acute toxic effects of copper are rare, long-term excessive intake or reduced hepatic excretion can result in liver cirrhosis.⁹⁰

During the transition period, copper intake should be equivalent to that provided by human milk. If short-term total parenteral nutrition is used, supplementation may not be necessary.⁶³ During the stable-growing and postdischarge periods, the intake of copper from human milk prevents deficiency. However, because copper absorption may be depressed by the large amounts of zinc⁹¹ found in some preterm formulas and human-milk fortifiers, a copper intake of 1.6 to 3.2 $\mu\text{mol/kg}$ per day is recommended for infants, regardless of birth weight, fed fortified human milk or formula designed for preterm infants. For those fed parenterally, recommended intakes are 0.3 $\mu\text{mol/kg}$ per day.^{85,63} Infants with cholestasis should not receive copper parenterally, since biliary excretion is the main excretory route.

Selenium

Although selenium deficiency in infants is rare, the mineral is recognized as nutritionally essential.⁹² Infants fed preterm-mother's milk (which contains 0.3 $\mu\text{mol/L}$ of selenium), standard formula for premature infants (which contains 0.1 $\mu\text{mol/L}$) or formula for premature infants supplemented with 0.4 $\mu\text{mol/L}$ of selenium have been shown to have similar erythrocyte selenium and glutathione-peroxidase concentrations. There is no evidence of selenium deficiency among older preterm infants.

During the transition period, selenium intake should be equivalent to that provided in human milk. Selenium may be omitted from solutions used in total parenteral nutrition. During the stable-growing and postdischarge periods, however, total parenteral nutrition should provide 0.02 to 0.025 $\mu\text{mol/kg}$ per day of selenium. Because

selenium is primarily excreted by the kidneys, the amount should be lowered if the renal output of the infant is decreased.⁶³

Chromium

Chromium deficiency has been reported in three adult patients receiving long-term total parenteral nutrition that did not contain chromium; however, such deficiency has not been reported in children.^{93,94} Trivalent chromium has a very low order of toxic effects.⁹⁵ Term infants fed their preterm-mother's milk receive about 1.0 to 1.9 nmol/kg per day of chromium.⁹⁵ There is no information on the chromium content of the human milk of mothers who have delivered preterm; however, since preterm infants fed their preterm-mother's milk have not developed chromium deficiency, this intake is likely adequate. Similarly, since infants fed formula with higher concentrations of chromium than those found in human milk have not suffered overt toxic effects, there is likely a wide range of safe intake.⁹⁵

During the transition period, an intake equivalent to that provided in human milk is recommended,⁹⁶ but chromium may be omitted from solutions for total parenteral nutrition. The same amount is recommended during the stable-growing and postdischarge periods; however, total parenteral nutrition should provide 3.8 nmol/kg per day. Because chromium is excreted by the kidneys, the amount should be lower if infant's renal output is decreased.⁶³

Manganese

Manganese deficiency in humans has not been conclusively shown; however, the toxic effects of excessive manganese in adults have been well described. Human milk contains about 0.1 $\mu\text{mol/L}$ of manganese, and formulas contain higher concentrations. There is no evidence that the low intake of manganese in infants receiving preterm-mother's milk is associated with deficiency or that higher intakes in infants fed formulas are associated with toxic effects.⁹⁷

During the transition period, the manganese intake should be equivalent to that provided in human milk; manganese may be omitted from solutions for total parenteral nutrition. This intake is also considered adequate during the stable-growing and postdischarge periods. Total parenteral nutrition should provide 0.02 $\mu\text{mol/kg}$ per day of manganese. Manganese should be omitted from total parenteral nutrition given to infants with hepatic cholestasis.^{63,98}

Molybdenum

Only one case of molybdenum deficiency in an adult

and none in infants has been reported.⁹⁹ The molybdenum concentration in the breast milk of mothers delivered at term is about 2.0 nmol/L,¹⁰⁰ but that of mothers delivered preterm is unknown. During the transition period, an infant fed human milk receives 2.0 to 4.0 nmol/kg per day, which is also considered adequate during the stable-growing and postdischarge periods. Molybdenum supplementation of 2.6 nmol/kg per day is recommended only for infants needing long-term total parenteral nutrition.⁶³

Iodine

In premature infants, the mechanisms that regulate iodine levels are immature. Hence, if the infant's diet is deficient, the infant cannot compensate by retaining more iodine and requires a higher iodine intake to maintain a euthyroid state. Premature infants may experience transient hypothyroidism when receiving iodine intakes of 0.08 to 0.24 $\mu\text{mol/kg}$ per day.¹⁰¹ If premature infants of a gestational age of less than 34 weeks are exposed to high amounts of iodine (0.8 μmol per day or more) by cutaneous administration of iodine solutions, a decreased level of T4 (tetraiodothyronine) and an increased serum level of thyroid stimulating hormone may result.¹⁰² The content of iodine in human milk varies, depending on the dietary intake of the mother, between 1.1 to 1.4 $\mu\text{mol/L}$.¹³ Formulas for preterm infants contain similar amounts.¹⁰³ Thus, an average intake is about 0.2 $\mu\text{mol/kg}$ per day. Since breast-fed infants receiving less than 0.24 $\mu\text{mol/kg}$ per day have a negative iodine balance¹⁰⁴ (assuming they do not absorb iodine from iodine-containing skin cleansers), supplementation is recommended.

During the transition period, an intake equivalent to the amount in human milk is recommended. Iodine may be omitted from solutions for total parenteral nutrition. During the stable-growing and postdischarge periods, if a preterm infant is breast fed exclusively, an iodine supplement is needed to achieve the recommended intake. Neither breast-milk fortifiers nor commercially available mineral-and-vitamin supplements contain iodine. Most infants receiving total parenteral nutrition are cleaned with iodine-containing disinfectants or detergents, and one may assume that a significant amount of iodine is absorbed through the skin. On the basis of this assumption, the recommended parenteral intake of iodine is 8 nmol/kg per day.

RECOMMENDATIONS CONCERNING VITAMINS

Fat-soluble vitamins

Vitamin D

The main factor affecting the need for vitamin D in

early life is the infant's vitamin-D status at birth, which is related to maternal intake of vitamin D during pregnancy. Human milk contains only small concentrations of vitamin D (10 to 80 IU/L), whereas the vitamin-D requirement of premature infants has been estimated at between 400 and 5000 IU per day.¹⁰⁵⁻¹⁰⁷ Estimates vary so widely because, in the populations studied, the vitamin-D status of mothers, and thus of infants at birth, differed greatly. Premature infants of a gestational age of greater than 28 weeks appear to be able to hydroxylate vitamin-D metabolites adequately and to elicit a normal physiologic response to hypocalcemia and hypophosphatemia¹⁰⁸ as well as to absorb an adequate amount of fat-soluble vitamins. Little is known about the capacity of premature infants with a very low birth weight and a gestational age of less than 28 weeks to absorb or hydroxylate vitamin D.

During the transition period, the need to include vitamin D in formulations for total parenteral nutrition is unknown. Recommended total intake of the vitamin from parenteral and enteral feeding is 40 to 120 IU per day for infants with a birth weight of less than 1000 g and 40 to 260 IU per day for infants with a birth weight of 1000 g or more.⁶³ If the infant is stable during the latter part of the transition period, higher intakes of vitamin D may be used with safety. During the stable-growing period, regardless of the infant's birth weight, a vitamin-D intake of 400 IU per day is needed to achieve a normal serum concentration of 25-OH vitamin D without increasing the risk of toxic effects.¹⁰⁶ If the infant is black or of Asian descent or has a low plasma concentration of 25-OH vitamin D (10 to 20 ng/mL), the recommended vitamin-D intake is 800 IU per day. Formulas or human-milk fortifiers should contain 300 IU/417 kJ (300 IU/100 kcal) of vitamin D to ensure that most infants receive adequate amounts. For small infants, vitamin D supplements are required to achieve these amounts. During the postdischarge period, the vitamin-D intake recommended is 400 IU per day.⁶⁵

Vitamin A

The retinol concentration of early milk of mothers delivered preterm (from the 6th to the 37th day of lactation) varies but is usually higher than that of mothers delivered at term. Both retinol ester and total carotene concentrations in human milk decrease during the course of lactation.^{15,109} In addition, photodegradation of vitamin A may occur in formula or human milk fed to infants through plastic nasogastric tubes. Preterm infants have been shown to have low hepatic stores of retinol at birth and lower concentrations of plasma retinol and retinol-binding protein (RBP) than term newborns. Many infants have a plasma concentration of retinol of below

0.35 $\mu\text{mol/L}$, which indicates a deficiency. Serum retinol and RBP concentrations are higher in infants receiving formulas designed for preterm infants than in those receiving human milk; however, only infants fed formula supplemented with 450 to 840 μg per day of retinol maintain serum concentrations of retinol at prefeeding levels.^{110,111} The lack of clinical and biochemical toxic effects among infants given a vitamin-A supplement suggests that this supplement range (450 to 840 μg per day) is safe for preterm infants. Although several randomized controlled studies have been conducted to determine the effect of retinol supplementation on the incidence of and outcomes from bronchopulmonary dysplasia (BPD), the results have been inconclusive.^{51,112} Therefore, we cannot recommend giving a vitamin-A supplement to all infants at risk of BPD.

During the transition period, infants generally receive nutrition both parenterally and enterally. The recommended amount of vitamin A to be included in parenteral nutrition is 500 $\mu\text{g/kg}$ per day.⁶³ No additional vitamin-A supplements are recommended. Once parenteral nutrition is discontinued, and during the stable-growing period, the intake from human milk is below the estimated intake needed to maintain normal serum concentrations. A total intake of 450 $\mu\text{g/kg}$ per day is recommended for infants with a birth weight of less than 1000 g birth weight and of 200 to 450 $\mu\text{g/kg}$ per day for those with a birth weight between 1000 and 2000 g (higher amounts per kilogram should be supplied to lower-birth-weight infants and lower amounts to heavier infants). For infants fed formula for preterm infants, the need for additional vitamin A depends on the concentration of vitamin A in the formula and the volume of formula ingested. During the postdischarge period, it is recommended that infants fed preterm-mother's milk receive a vitamin-A supplement until they have achieved a weight of 3.5 kg, when the supplement may be discontinued. Infants fed formula for term infants at an adequate volume (150 mL/kg per day or more) achieve the RNI.⁶⁵

Vitamin E

Dietary vitamin-E requirements depend on the dietary content and interaction of vitamin E, polyunsaturated fatty acids and iron. Vitamin E is found in low concentrations in the plasma and liver of infants born prematurely.¹¹³ At least 10 trials of vitamin E supplementation have examined its effects on the retinopathy of prematurity (ROP). A meta-analysis of the trials does not support supplementation for the treatment or prevention of ROP.⁵¹ Although there is no clear clinical benefit of vitamin-E supplementation in premature infants, it seems prudent to maintain plasma vitamin-E concentrations in a range of 10 to 30 mg/L, and a ratio of serum α -tocopherol of 1 mg or more

to 1 g total lipids. Milk from mothers delivered preterm contains greater concentrations of vitamin E (4.5 mg/L) than that from mothers delivered at term.¹⁵ Hence, preterm infants fed their own mother's milk maintain adequate levels of vitamin E.¹⁵

During the transition period, infants receive parenteral nutrition, which contains multivitamins including vitamin E; therefore, no additional vitamin E is recommended. A parenteral intake of 2.8 mg/kg per day appears to be adequate.⁶³ Once parenteral nutrition is discontinued, and during the stable-growing period, the vitamin-E content of adequate volumes of human milk should meet the needs of most preterm infants with normal absorptive capacity. For infants fed formula designed for preterm infants, the need for additional vitamin E depends on the concentrations of polyunsaturated fatty acids and iron in the formula. A vitamin-E intake from formula of 4 mg per day or more, with a ratio of 1.0 mg or more of vitamin E to 1 g of linoleic and linolenic acids, results in normal plasma concentrations of vitamin E.

During the postdischarge period, no supplements are recommended for breast-fed infants. Among those fed formula, the need for additional vitamin E depends on the concentration of polyunsaturated fatty acids and iron in the formula.

Vitamin K

In 1988 the Fetus and Newborn Committee of the Canadian Paediatric Society¹¹⁴ recommended that all preterm and ill infants receive a 1.0-mg intramuscular injection of vitamin K₁ within 6 hours after birth to prevent hemorrhagic disease of the newborn. There is conflicting evidence concerning the efficacy of single or multiple oral doses of vitamin K in comparison with intramuscular injection among term infants;^{115,116} the effect of vitamin-K supplementation given orally among preterm infants has not been studied. In infants fed human milk exclusively, serum concentrations of phyloquinone and intake of vitamin K are very low;¹¹⁷ however, there is insufficient data to recommend supplementation in addition to the recommended prophylactic dose. Infants breast fed exclusively after discharge who are given antibiotics for a prolonged period or who have fat malabsorption may need vitamin-K supplements.

We continue to recommend that all premature infants receive a 1.0-mg intramuscular dose of vitamin K within 6 hours of birth. For infants receiving parenteral nutrition, 2 to 100 $\mu\text{g/kg}$ per day of vitamin K should be provided until oral feeding is started.⁶³

Water-soluble vitamins

There is little information available from well-

designed clinical trials to support specific recommendations for intakes of most water-soluble vitamins. Therefore, most of the current recommendations are based on observed biochemical responses to variations in enteral or parenteral intake.¹¹⁸⁻¹³⁸ To the best of current knowledge, these estimates are safe. Further research is needed to determine the optimal vitamin intakes.

For infants fed parenterally during the transition and stable-growing periods, we agree with the 1988 guidelines of the Subcommittee on Pediatric Parenteral Nutrient Requirements of the American Society for Clinical Nutrition for the use of vitamins in total parenteral nutrition given to infants, including premature infants.⁶³ For infants fed enterally, the P-RNIs for water-soluble vitamins, the volumes of preterm-mother's milk and formula required to meet these P-RNI during the stable-growing period and the recommended supplemental intakes are provided in Tables 1 to 3.

FEEDING THE INFANT BORN PREMATURELY

The CPS Nutrition Committee recommends fortified preterm-mother's milk or, alternatively, formula designed for preterm infants as the feeding of choice for premature infants with a birth weight of less than 1800 g and possibly up to 2000 g or a gestational age of less than 34 weeks and possibly up to 38 weeks (at this age the infant is often able to nurse effectively). The benefits of fortified preterm-mother's milk and the need for a formula for preterm infants become less apparent as the infant approaches the weight and gestational age of a term infant, although an exact weight or gestational-age cut-off cannot be clearly defined. An exception should be made to the recommendation for larger premature infants whose fluid intake is restricted or who grow poorly when fed unfortified preterm-mother's milk. For infants with a birth weight less than 1800 g, preterm-mother's milk, if available, may be used without fortification until full feeding has been established during the stable-growing period, at which point preterm-mother's milk should be fortified with an additional source of nutrients. If preterm-mother's milk is unavailable, formula for preterm infants is recommended from the beginning of enteral feeding.

PRETERM-MOTHER'S MILK

The use of human milk as a sole source of nutrients for preterm infants has been the subject of controversy and debate during recent years.¹³⁹ Early preterm-mother's milk (from the first production of colostrum to 4 weeks after birth) is more dense in nutrients than milk from mothers delivered at term and thus comes closer to providing the nutrient requirements of preterm infants. This observation supports the position that such milk should

be considered optimal primary nutrition for preterm infants. In addition to the nutritional properties of human milk, breast-feeding has psychologic benefits for the mother and anti-infective benefits for the infant. Infants fed their own mother's milk have a lower risk of necrotizing enterocolitis,¹⁴⁰ and even short-term use of preterm-mother's milk may be associated with long-term advantages for intellectual development.^{29,141}

However, preterm-mother's milk is not completely adequate as a sole source of nutrients, particularly protein, minerals and some vitamins, or to duplicate intrauterine growth (Table 2).¹⁴² The use of human-milk "fortifiers" containing protein, minerals and vitamins ensures that infants fed their preterm-mother's milk receive a nutrient intake that meets estimated needs. Powdered or liquid fortifiers may be added to preterm-mother's milk that is expressed and fed to the infant by tube or bottle. Since liquid human-milk fortifiers, used in a 50:50 ratio with human milk, contribute a significant proportion of the infant's fluid intake, they are designed to contain adequate quantities of all essential nutrients. However, mixing preterm-mother's milk with an equal volume of liquid fortifier dilutes the constituents of the human milk, including the nutrients, growth factors and anti-infective properties.¹⁴³ Powdered fortifiers allow the feeding of undiluted preterm-mother's milk. Like any powdered-milk product, powdered fortifiers are not guaranteed microbiologically sterile,¹⁴⁴⁻¹⁴⁶ although their use is not associated with increased rates of neonatal infection. Because powdered fortifier is added to undiluted milk, some nutrients (particularly protein and calcium) may be oversupplied, depending on the content of these nutrients in the milk. In addition, because available powdered fortifiers may be insoluble in human milk, unless the fortifier-milk mixture is well shaken, the nutrients may not be available for absorption.

There is limited evidence to support nutrient fortification of preterm-mother's milk.^{53,69,147} However, for some nutrients the evidence shows that a deficiency may develop if premature infants are fed preterm-mother's milk alone and that their status improves if they are fed fortified milk. Therefore, fortification with these nutrients — total energy, protein, calcium, phosphorus, sodium, vitamins (riboflavin, vitamins A and D) and iron (during the postdischarge period) — is definitely indicated (Table 2). For zinc, folate, iodine and magnesium, theoretic calculations support the need for fortification; however, there is no evidence of nutrient deficiencies or responses to fortification. Therefore, fortification with these nutrients is only provisionally recommended (Table 2). Supplementation may also be indicated if elements contained in a human-milk fortifier reduce the bioavailability of another nutrient (e.g., zinc, magnesium and manganese) or increase the requirement for a metabolic cofactor (e.g., for vitamin B₆ in a protein supplement).

Table 3: Intake volumes of formulas designed for preterm infants needed to meet P-RNIs during the stable-growing period (see Table 1)

Nutrient	Formula; intake volume needed to meet P-RNI, mL/kg per day except where indicated		
	Similac Special Care*†	EPF-Plus*‡	SMA Preemie*§
Water	120–200	120–200	120–200
Macronutrients			
Energy	130–167	130–167	130–167
Protein	160–182	145–167	175–200
Carbohydrate	110–180	109–178	110–180
Minerals			
Calcium	122–182	122–182	214–320
Phosphorus	108–164	117–178	194–295
Magnesium	50–100¶	81–162¶	70–140¶
Sodium	164–263	180–287	180–287
Chloride	137–218	129–206	167–268
Potassium	98–137¶	122–170	130–182
Iron	7500	7500	7500
Zinc	42–67¶	63–100¶	63–100¶
Copper	34–60¶	73–125¶	100–170¶
Selenium	207–414	NA**	NA
Chromium	NA	NA	NA
Manganese	4–38¶	8–75¶	4–38¶
Molybdenum	NA	NA	NA
Iodine	205–410	500–1000	360–720
Vitamins			
Vitamin D, mL/d	800	725	833
Vitamin A	480	427	625
Vitamin E, mL/d	83–117¶	68–95¶	167–233¶
Vitamin C, mL/d	25¶	25¶	107¶
Vitamin B ₁	20–25¶	20–25¶	50–63¶
Vitamin B ₂	72–92¶	72–92¶	277–354
Vitamin B ₆	25–30¶	25–30¶	100–120¶
Vitamin B ₁₂ , mL/d	33¶	33¶	75¶
Niacin	19–24¶	19–24¶	120–154
Folate	167	167	500
Biotin	5¶	50¶	83¶
Pantothenic acid	160–207	160–207	665–860

*Energy concentration of all formulas is assumed to be 3380 kJ/L.

†Abbott Laboratories, Montreal.

‡Mead Johnson, Ottawa.

§Wyeth-Ayerst, North York, Ont.

||This volume is above the recommended fluid intake (120 to 200 mL/kg per day).

¶This volume is below the recommended fluid intake (120 to 200 mL/kg per day).

**Not available.

Although the long-term effects of fortification of human milk have yet to be evaluated, randomized trials have shown that infants given fortification have faster rates of growth than those receiving unfortified preterm-mother's milk.^{61,69,147,148} This increased growth rate may lead to shorter hospital stays, with economic and psychologic benefits for the hospital and the parents.

During the transition period, when growth is variable and infants are metabolically unstable, all infants, regardless of birth weight, should receive a combination of parenteral and enteral nutrition. Expressed preterm-mother's milk, without fortification, is the first choice for enteral feeding during this period. During the stable-growing period, for all preterm infants regardless of birth weight, feeding exclusively with preterm-mother's milk does not meet the P-RNIs. Supplements of energy, protein, calcium, phosphorus, sodium, vitamins A and D and riboflavin are needed to achieve these recommended intakes (Table 2). Supplementation with vitamin B₆, folate, zinc, magnesium and iodine are provisionally indicated. In addition, an iron supplement is recommended after 2 months. When an infant is able to nurse effectively (at a postnatal age of 34 to 38 weeks and a weight of 1800 to 2000 g), fortification may be stopped.

There are few data on the growth and development of premature infants breast-fed milk exclusively during the postdischarge period. Infants with illnesses and conditions requiring complicated and medical care are likely to require more nutrients.³¹ This group may benefit from prolonged feeding with human milk, accompanied by specific nutrient supplements. Until further data are available, however, exclusive breast-feeding is recommended until the infant reaches 4 to 6 months corrected age, when solid food should be introduced. Iron supplements should be given beginning at 2 months and should be continued throughout the first year of life (Table 1). Growth and development must be monitored closely. Although the effectiveness and timing of biochemical and hematologic monitoring has not been established, blood tests should be carried out at 4 to 5 months corrected age to ensure that the infant does not have a zinc deficiency, iron-deficiency anemia or early rickets.

FORMULA

There are many circumstances in which feeding an infant preterm-mother's milk is impossible, and cow's-milk-based formulas for preterm infants should be used. When fed to infants in adequate volumes, these formulas provide an intake of nutrients that promotes the duplication of intrauterine growth without undue metabolic stress.^{71,149,150} However, although growth rates may be

similar to estimates of intrauterine growth, the composition of the new tissue may not be identical to intrauterine tissue composition. Formulas do not contain any of the biologically active immune substances, nor some of the enzymes, hormones or growth factors, found in human milk. The long-term significance of the lack of these components has not been determined; however, recent studies suggest that mental and motor development are affected by the type of early feeding provided.^{38,141}

Premature formulas available in Canada have energy concentrations of 2796 or 3380 kJ/L, and the nutrient composition of each formula is slightly different, reflecting the uncertainty about premature infants' needs for nutrients, specifically protein-energy ratio, fat blend and amounts of calcium and phosphorus. In general, the formulas provide inadequate amounts of sodium, chloride, iodine and vitamins A and D, and excessive concentrations of trace minerals and water-soluble vitamins (Table 3). Other types of specialized infant formulas, including soy-based, protein-hydrolysate, lactose-free, low-solute and hypercaloric formulas,¹⁵¹ were designed for term infants and should be used only for limited periods, if at all, to feed premature infants.

During the transition period, if preterm-mother's milk is not available, formula for preterm infants should be used; it may be used without supplementation. Many clinicians advocate a gradual increase in the concentration of energy in the formula to facilitate gastrointestinal tolerance; however, the benefit of this practice is unproven.^{152,153} During the stable-growing period, if preterm-mother's milk is unavailable, formula for preterm infants is recommended. To meet the P-RNIs, the concentration of energy in the formula should be 3380 kJ/L, and supplements of sodium and chloride, vitamins A and D and iodine may be needed. Formula for preterm infants is usually given until infants have attained a weight of 1800 to 2000 g, which corresponds to the usual time of discharge from the NICU.¹⁵⁴⁻¹⁵⁶ Preliminary evidence shows that premature infants, especially those with a birth weight of less than 1000 g, who have illnesses or conditions necessitating complicated and medical care may benefit from prolonged feeding with formulas with a higher nutrient concentration during the postdischarge period.^{31,66,67} This applies as well to infants who remain below the 3rd percentile for growth or who have illnesses such as bronchopulmonary dysplasia. There have been few studies of the adequacy of standard formula designed for term infants in meeting vitamin, mineral and trace-element needs of premature infants, and more research in this area is required. However, until more evidence is available, we recommend the use of iron-fortified formulas designed for term infants beginning at discharge until 12 months corrected age.

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