Introduction

The concept of evidence-based medicine has become essential for health care providers, as well as in the nutritional field. In 1992, David Sackett defined evidence-based medicine as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.” As the best is needed for feeding preterm and term infants, it is of paramount importance to perform well-designed studies.

In the present chapter, we focused on 15 articles related to nutrition in preterm and term infants. We have selected 3 randomized clinical trials (RCTs) on vitamin D, iodine, and protein intake in premature babies during the first months of life. They add more information to the critical choice of the most adequate dietary intake in this population, to avoid not only deficiencies but also excessive intake that may contribute to a higher risk of metabolic disorders later in life. Two other papers on preterm infants assess controversial issues, that is, the role of post-discharge formula and the impact of the feeding schedule on time to achieve full enteral feeding.

Gross compositional similarity with the human milk of healthy women is not an adequate indicator of the safety and suitability of infant formula. Infant formulae (IF) should only contain components in certain amounts that serve a nutritional purpose or other benefit. Since dietary composition in infants has a major impact on short- and long-term child health and development, the scientific evidence to support modifications of IF beyond the established standards should be assessed by well-designed studies before evaluation by independent scientific bodies prior to the acceptance of
introduction of such products on the market. We have selected 2 RCTs assessing, respectively, the safety and suitability of human milk oligosaccharides (HMOs) added to an infant formula, and the effect of a young child formula on the iron and vitamin D status of healthy young European children. The addition of long chain polyunsaturated fatty acid to infant formula is also a controversial issue in term infants. We selected a Cochrane Review on this topic that summarizes available data and asks for more research.

Despite a growing interest of the scientific community, there is limited scientific evidence on complementary feeding (CF), especially the time of introduction and the type of foods given. We selected 3 papers on CF: (1) an RCT on the appropriate time for introduction of complementary foods in infants born at less than 34 weeks of gestation; (2) a meta-analysis and systematic review on the timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease; and (3) a position paper on CF by the ESPGHAN Committee on Nutrition (CoN).

Last but not least our review also includes an Australian study of food protein-induced enterocolitis syndrome (FPIES), guidelines on the diagnosis and management of FPIES and a position paper by ESPGHAN CoN on the prevention of vitamin K deficiency bleeding (VKDB) in newborn infants.

It has been a very fruitful year in terms of research in infant nutrition. New important and exciting data are available that will help all of us for the nutritional management of infants and young children.

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### Key articles reviewed for this chapter

#### Term Infants

**Prevention of vitamin K deficiency bleeding in newborn infants: a position paper by the ESPGHAN Committee on Nutrition**


*J Pediatr Gastroenterol Nutr* 2016;63:123–139

**Long chain polyunsaturated fatty acid supplementation in infants born at term**

Jasani B, Simmer K, Patole SK, Rao SC

*Cochrane Database Syst Rev* 2017;3:CD000376

**Effects of infant formula with human milk oligosaccharides on growth and morbidity: a randomized multicenter trial**


*J Pediatr Gastroenterol Nutr* 2017;64:624–631
First infant formula type and risk of islet autoimmunity in The Environmental Determinants of Diabetes in the Young (TEDDY) Study
Diabetes Care 2017;40:398–404

Mehr S, Frith K, Barnes EH, Campbell DE, on behalf of the FPIES Study Group
J Allergy Clin Immunol 2017;140:1323–1330

International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive Summary – Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma and Immunology
J Allergy Clin Immunol 2017;139:1111–1126

Complementary feeding: a position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition
Fewtrell M, Bronsky J, Campoy C, Domellöf M, Embleton N, Mis NF, Hojsak I, Hulst JM, Indrio F, Lapillonne A, Molgaard C

Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: A systematic review and meta-analysis
JAMA 2016;316:1181–1192

Complementary feeding at 4 versus 6 months of age for preterm infants born at less than 34 weeks of gestation: a randomised, open-label, multicentre trial
Lancet Glob Health 2017;5:e501–e511

A micronutrient-fortified young-child formula improves the iron and vitamin D status of healthy young European children: a randomized, double-blind controlled trial
Akkermans MD, Eussen SR, van der Horst-Graat JM, van Elburg RM, van Goudoever JB, Brus F
**Preterm Infants**

**Randomized trial of two doses of vitamin D3 in preterm infants <32 weeks: Dose impact on achieving desired serum 25(OH)D3 in a NICU population**  
Anderson-Berry A, Thoene M, Wagner J, Lyden E, Jones G, Kaufmann M, Van Ormer M, Hanson C  

**Follow-up of a randomized trial on postdischarge nutrition in preterm-born children at age 8 years**  
Ruys CA, van de Lagemaat M, Finken MJ, Lafeber HN  
*Am J Clin Nutr* 2017;106:549–558

**Supplemental iodide for preterm infants and developmental outcomes at 2 years: an RCT**  
*Pediatrics* 2017;139:e20163703

**Effect of increased enteral protein intake on growth in human milk-fed preterm infants: a randomized clinical trial**  
*JAMA Pediatr* 2017;171:16–22

**Two-hourly versus 3-hourly feeding for very low birthweight infants: a randomised controlled trial**  
Ibrahim NR, Kheng TH, Nasir A, Ramli N, Foo JLK, Syed Alwi SH, Van Rostenberghe H  
*Arch Dis Child Fetal Neonatal Ed* 2017;102:F225–F229
Prevention of vitamin K deficiency bleeding in newborn infants: a position paper by the ESPGHAN Committee on Nutrition

Mihatsch WA1, Braegger C2, Bronsky J3, Campoy C4, Domellöf M5, Fewtrell M6, Mis NF7, Hojsak I8, Hulst J9, Indrio F10, Lapillonne A11, Molgaard C12, Embleton N13, van Goudoever J14, ESPGHAN Committee on Nutrition

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*J Pediatr Gastroenterol Nutr* 2016;63:123–139

**Background:** Healthy newborns and infants are at risk of vitamin K deficiency bleeding (VKDB) owing to physiologically low levels of vitamin K after birth. Bleeding can be prevented by vitamin K supplementation. This position paper was published to provide a definition of the condition, to report the prevalence, review current prophylaxis practices and outcomes, and to provide recommendations.

**Results:** It is recommended that all newborn infants receive vitamin K prophylaxis. Possible regimens include: (1) 1 mg of vitamin K1 by intramuscular injection at birth; or (2) 3 x 2 mg vitamin K1 orally at birth, at 4–6 days and at 4–6 weeks; or (3) 2 mg vitamin K1 orally at birth, and a weekly dose of 1 mg orally for 3 months. Parental refusal to treatment should be documented. The optimal route is the intramuscular application, because it is efficient and assures full dose administration. Oral administration is not suitable for preterm infants, for newborns who have cholestasis or impaired intestinal absorption, or for newborns who are unwell and unable to take oral medications. Neither should it be given to infants whose mothers have taken medications that interfere with vitamin K metabolism. Parental education about the importance of vitamin K supplementation may improve compliance.

**Comments** Vitamin K is required for the γ-carboxylation of coagulation factors II (prothrombin), VII, IX, X, protein C, and protein S [1]. It acts as an essential cofactor for the conversion of specific peptide-bound glutamate residues to γ-carboxyglutamate residues. The abbreviation for these under-carboxylated molecules is PIVKA (proteins induced by vitamin K absence). Vitamin K does not easily cross the placenta. The fetal plasma vi-
tamin K concentration is very low and consequently at birth, concentrations of clotting factors are low. Increased PIVKA II concentrations (>10 ng/mL), which is a biomarker of low vitamin K level, have been found in the umbilical cord blood in 10–50% of healthy term and preterm infants. Prenatal maternal vitamin K supplementation does not prevent VKDB. VKDB has been classified by age of onset into early (<24 h), classic (days 1–7), and late (>1 week <6 months). Although plasma vitamin K concentration is very low immediately after birth, adult levels have been recorded on days 3–4 following supplementation. Human milk vitamin K concentration (median: 2.5 μg/L [0.85–9.2 μg/L]) is significantly lower than the currently available formula milk (4–25 μg/100 kcal corresponding to 24–175 μg/L). On average, daily vitamin K intake of breastfed infants is <1 μg within the first 6 months of life, whereas the intake of formula-fed infants is on average up to 100 times higher. With regard to global coagulation tests such as prothrombin time, there is no significant difference between breast- and formula-fed infants. However, PIVKAs are more commonly reported in breastfed infants. Formula vitamin K exceeds the recommended vitamin K intake of at least 5 μg/day. Because breastfeeding fails to provide this intake, and VKDB is much more common in unsupplemented breastfed infants, it is recommended that all infants receive some form of supplementation.

ESPGHAN CoN emphasizes in this paper that if the infant vomits or regurgitates the formulation within 1 h of administration, repeating the oral dose may be appropriate. ESPGHAN CoN also emphasizes that data from some countries suggest intramuscular application may be more effective than 3 × 2 mg oral prophylaxis for prevention of late VKDB. However, the more recent epidemiological data obtained from >4.5 million children show no significant difference between these 2 options with regard to the efficacy in the prevention of late VKDB. This position paper of ESPGHAN CoN will help health care providers to prevent efficiently the risk for VKDB in healthy term infants.

Long chain polyunsaturated fatty acid supplementation in infants born at term

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Cochrane Database Syst Rev 2017;3:CD000376

This manuscript is also discussed in Chapter 4, pages 66–83.

Background: The long chain polyunsaturated fatty acids (LCPUFA) are considered vital for the maturation of the developing brain, retina, and other organs in newborn infants. Some manufacturers have added LCPUFA to IF, claiming these confer a benefit to the child’s development compared with standard formula. The aim of this review was to evaluate whether adding LCPUFA to IF results in improved visual function, neurodevelopment, and physical growth.

Methods: Two review authors searched the Cochrane Central Register of Controlled Trials, Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature and abstracts of the Pediatric Academic Societies. They reviewed all RCTs that dealt with the effects of LCPUFA supple-
ments on visual function, neurodevelopment, and physical growth, conducting a meta-analysis when appropriate.

**Results:** A total of 31 RCTs were identified, 15 of which were included in the review (n = 1,889). Nine studies evaluated visual acuity, 6 by visual evoked potentials, 2 by Teller cards and one study using both. An advantage for LCPUFA was reported in 4 of these studies, but not in the remaining 5. Meta-analysis of 3 RCTs revealed significant advantage for sweep visual evoked potential acuity at 12 months (mean difference [MD] –0.15, 95% CI –0.17 to –0.13; I² = 0; 3 trials; n = 244), however, meta-analysis of 3 additional RCTs demonstrated no difference for visual acuity assessed with Teller cards at 12 months (MD –0.01, 95% CI –0.12 to 0.11; I² = 0; 3 trials; n = 256). GRADE analysis for the outcome of visual acuity implied that the overall quality of evidence was low. Eleven studies evaluated neurodevelopmental outcomes at 2 years or under. Of them, 9 studies employed Bayley Scales of Infant Development, version II (BSID-II). Benefits were demonstrated only in 2 of these studies. Meta-analysis found no significant distinction between LCPUFA and placebo groups in BSID Mental Developmental Index scores at 18 months (MD 0.06, 95% CI –2.01 to 2.14; I² = 75%; 4 trials; n = 661), or in BSID Psychomotor Development Index scores at 18 months (MD 0.69, 95% CI –0.78 to 2.16; I² = 61%; 4 trials; n = 661). Neither were significant differences between the 2 groups found in BSID-II scores at 12 and 24 months of age. One study described better novelty preference at 9 months. A different study reported improved problem solving at 10 months. One study used the Brunet and Lezine test for the evaluation of the developmental quotient and discovered no beneficial effects. Children who were followed until the age of 3, 6, and 9 years, in different studies, had gained no benefit by supplementation. GRADE analysis of these results revealed that the overall quality of evidence was low. Thirteen studies evaluated anthropometry; none of them exhibited a favorable or negative effect of supplementation. Meta-analysis of 5 RCTs demonstrated that the LCPUFA group had lower weight (z scores) at 12 months (MD –0.23, 95% CI –0.40 to –0.06; I² = 83%; n = 521) and that the 2 groups had similar results in length and head circumference. Meta-analysis at 18 months and at 24 months found no significant differences between the 2 groups in weight, length, and head circumference. GRADE analysis of these outcomes showed that the overall quality of evidence was low.

**Conclusion:** The majority of RCTs demonstrated no significant influence of LCPUFA supplementation on neurodevelopmental outcomes, and only an inconsistent beneficial impact on visual acuity. For this reason, it is currently not recommended to supplement milk formula with LCPUFA.

**Comments**

Docosahexaenoic acid (DHA) is needed for the normal development of the nervous system and the retina and accumulates in fetal brain and retina during pregnancy and in early childhood. Dietary linoleic acid (LA) and alpha-linolenic acid (ALA) can be converted by elongation of the carbon chain and the introduction of double bonds into LCPUFAs; however, the rate of conversion of ALA to DHA in humans is low (less than 1%). The content of arachidonic acid (AA) in human milk varies throughout the world (0.31–1.00 weight% of total fatty acids). The average AA content of human milk has been reported to be 0.47 ± 0.13 weight% of total fatty acids. DHA is the most important n-3 LC-PUFA in human milk. Depending on the region of the world and habitual dietary habits, DHA contents varying from 0.15 to 1.4 weight% of total fatty acids have been observed. Breast-fed infants accumulate more DHA in brain than infants fed formula containing ALA only and no DHA. The levels of AA and DHA in breast milk are mainly derived from maternal stores. They are, moreover, influenced by the maternal diet, in particular by its fatty acid composition and its content of trans fatty acids, and by smoking (negative for DHA). Taking into account the above-mentioned data, the European Food Safety Authority (EFSA) proposed for young infants (0–6 months) an adequate intake of 100 mg/day for DHA and 140 mg/day for AA [2]. In its Scientific Opinion on the essential composition of infant (IF) and follow-on formulae (FOF), EFSA considered, in accordance with the conclusions of the above-men-
tioned Cochrane review, that there is currently no conclusive evidence for any effects beyond infancy of addition of DHA to IF or FOF on the following health outcomes: neurodevelopment, visual acuity, blood pressure, and asthma [3]. However, in contrast to the Cochrane review, EFSA considered that DHA should be added to infant and FOF IF and FOF for the following reasons: (i) DHA is an essential structural component of the nervous tissue and the retina, and is involved in normal brain and visual development; (ii) the developing brain has to accumulate large amounts of DHA in the first 2 years of life; (iii) although DHA can be synthesized in the body from ALA, the intake of pre-formed DHA generally results in an erythrocyte DHA status more closely resembling that of a breast-fed infant than is achieved with ALA alone; and (iii) although, to date, there is no convincing evidence that the addition of DHA to IF and FOF has benefits beyond infancy on any functional outcomes, there is also a lack of long-term follow-up data on specific aspects of cognitive and behavioral function from adequately powered RCTs of DHA addition to IF and FOF. Considering all of these factors, it seems prudent to provide pre-formed DHA to formula-fed infants in similar amounts as breast-fed infants.

EFSA pointed out that even though studies have shown that feeding an IF-containing DHA alone (without addition of AA) leads to lower concentrations of AA in erythrocytes compared with the consumption of control formula without DHA, no direct functional consequences have been observed in relation to growth and neurodevelopment and this lower concentration of AA in erythrocytes seems not to be associated with a decrease in concentrations of AA in the brain. The adverse effects on growth which had been reported in one RCT in pre-term infants have not been replicated in other recent trials. Therefore, EFSA considers that there is no necessity to add AA to IF even in the presence of DHA [3].

The Commission regulated regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for IF and FOF will apply from 22 February 2020 [4]. In this regulation, it is stated that supplementation of DHA in both IF and FOF is mandatory, with a minimum content of 20 mg/100 kcal and a maximum content of 50 mg/100 kcal. Supplementation of IF and FOF with AA is not mandatory. If added, AA should not represent more than 1% of the total fat content.

Effects of infant formula with human milk oligosaccharides on growth and morbidity: a randomized multicenter trial

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Background: The main goal of this study was to assess the impact of the addition of 2 human milk oligosaccharides (HMOs) to infant formula on infant growth, tolerance, and morbidity.
Methods: This was a randomized trial of 2 parallel groups: the intervention group was fed with cow’s milk-based infant formula with a supplement of 1.0 g/L 2’fucosyllactose (2’FL) and 0.5 g/L lacto-N-neotetraose (LNnT; test, n = 88) and the control group (control, n = 87) was fed with the same formula without supplements. Both formulae were given to healthy children from the age of 0–14 days for 6 months. All infants received standard follow-up formula without HMOs from 6 to 12 months. Primary endpoint was weight gain at age 4 months. Secondary endpoints were weight, length, body mass index, head circumference, and corresponding z scores, gastrointestinal tolerance, behavioral patterns, and morbidity during the first year of life.

Results: There was no significant difference in weight gain between the groups. Most digestive symptoms and behavioral patterns were comparable between the groups; softer stool (p = 0.021) and fewer nighttime wake-ups (p = 0.036) were found in the test group at 2 months. Infants receiving HMOs had significantly fewer events of bronchitis (p = 0.004–0.047) by 4 (2.3 vs. 12.6%), 6 (6.8 vs. 21.8%), and 12 months (10.2 vs. 27.6%) compared to controls (as reported by the parents); lower respiratory tract infections by 12 months (19.3 vs. 34.5%); antipyretics use at 4 months (15.9 vs. 29.9%); and antibiotics use at 6 (34.1 vs. 49.4%) and 12 months (42.0 vs. 60.9%).

Conclusion: This study demonstrated that infant formula with supplements of 2’FL and LNnT is safe and well-tolerated and does not impair growth. The association between consumption of HMO-supplemented formula and a reduction in parent-reported morbidity and medication use requires confirmation in future studies.

Comments: HMOs represent approximately 20% of the total carbohydrate content of human milk and are the third largest solid component after lactose and lipids, present at concentrations of up to 20 g/L or more in colostrum [5]. Currently, approximately 150 oligosaccharide structures in human milk have been elucidated, and many more are present, at least in small quantities. The prebiotic effect of HMOs was the first function discovered. There is increasing evidence that HMOs have other functions as well, as indicated by the direct interaction of HMOs with bacterial or protozoan lectins as well as with epithelial or immune cell receptor [6]. HMOs enhance the development of the intestinal microbiota and support immune protection in breastfed infants. Although the types and concentrations of HMOs vary considerably among lactating women and over time, 2 that are commonly found in abundance in human milk are 2’FL and LNnT. This study is the first randomized, controlled trial of infant formula supplemented with both 2’FL and LNnT, that represent 37% of total HMOs in breast milk. Compared with infants fed the control formula, those fed the test formula with HMOs experienced similar age-appropriate growth, had some indication of improved GI comfort in the first few months of life, and had lower rates of parent-reported morbidities related to lower respiratory tract infections as well as antipyretic and antibiotic use. Formula intake and tolerance were not different in both groups. This study has several limitations. Gastrointestinal tolerance data were based on parent report, which are very likely to be susceptible to under- or overreporting. The use of morbidity assessments based on parent-reported symptoms/illnesses and medication use, rather than a physician-based diagnosis, is also an important limitation. Moreover, there is no information that statistical analysis took into account multiple testing. More studies on growth, prevalence of infections, and adverse events are urgently needed to confirm whether the supplementation of IF with HMOs is of interest.
First infant formula type and risk of islet autoimmunity in The Environmental Determinants of Diabetes in the Young (TEDDY) Study

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Background: Several studies have examined the association between infant formulas and their impact on the risk of islet autoimmunity and type 1 diabetes (T1D), with inconsistent findings. The aim of this study was to investigate whether the introduction of infant formula based on hydrolyzed cow’s milk as the first formula is related to a reduced risk of islet autoimmunity in a large prospective cohort.

Methods: The Environmental Determinants of Diabetes in the Young study follows 8,676 children at increased genetic risk for T1D. Autoantibodies to insulin, GAD65, and IA2 were routinely monitored as markers of islet autoimmunity. Information regarding infant formula feeding was elicited from questionnaires at 3 months of age.

Results: After adjustment for family history of T1D, HLA genotype, gender, country, delivery mode, breast-feeding ≥ 3 months, and seasonality of birth, no significant association with islet autoimmunity was observed in infants who received extensively hydrolyzed versus non-hydrolyzed cow’s milk-based formula as the first formula during the first 3 months of life (adjusted hazard ratio 1.38 [95% CI 0.95–2.01]). A significantly higher risk was found when extensively hydrolyzed formula was introduced during the first 7 days of life (adjusted hazard ratio 1.57 [1.04–2.38]). Infants fed with a partially hydrolyzed or other formula as the first formula, or no formula, did not have an increased islet autoimmunity risk.

Conclusion: This study supports previous evidence implying that islet autoimmunity risk is not reduced, and may be elevated, in children at increased genetic risk for T1D who received extensively hydrolyzed rather than non-hydrolyzed cow’s milk-based infant formula as the first formula.

Comments: Numerous studies have examined the association between age at first exposure to cow’s milk and T1D, resulting in inconsistent findings. Moreover, most prospective cohort studies showed no association between cow’s milk introduction and islet autoimmunity and/or T1D risk. Most of these studies focused on whether the formulas contained cow’s milk protein or not, and did not account for the use of protein hydro-
lysates and the degree of hydrolysis. The use of hydrolyzed cow’s milk proteins has also been hypothesized to protect infants at increased T1D risk from developing islet autoimmunity [7]. However, in the Trial to Reduce IDDM in the Genetically at Risk (TRIGR), which studied 2,159 newborn infants from 15 countries, the use of an extensively hydrolyzed formula did not reduce the islet autoimmunity risk compared with conventional formula [8]. Consistent with findings from the TRIGR trial, the results of this study provide evidence that introducing an extensively hydrolyzed formula as the first infant formula does not protect children with an HLA-conferred increased risk for T1D from the development of islet autoimmunity.


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Background: Food protein induced enterocolitis syndrome (FPIES) is a non-IgE-mediated allergic disorder that occurs mainly in infants and children. The aim of the study was to determine the incidence and clinical characteristics of FPIES in Australian infants.

Methods: Each month between 2012 and 2014, 1,400 participating pediatricians in Australia reported to the Australian Paediatric Surveillance Unit of new cases of acute FPIES in infants less than 24 months old.

Results: Two hundred and thirty infants were diagnosed with FPIES with an incidence of 15.4/100,000/year. The median age of the first episode and diagnosis were 5, and 7 months, respectively. Seven percent of the children had siblings with a history of FPIES, and 5% developed FPIES while feeding exclusively on breastmilk. Sixty-eight per cent of infants had a single food trigger, while 20% had 2, and 12% had ≥3 food triggers. The most frequently reported triggers were rice (45%), cow’s milk (33%), and egg (12%). Fifty-one percent of the children reacted on their first known exposure. Infants with FPIES to multiple versus single food groups were younger at the first event (mean age: 4.6 vs. 5.8 months, p = 0.001) and more commonly had FPIES to fruits, vegetables, or both (66 vs. 21%, p < 0.0001). Sixty-four percent of infants with FPIES to multiple foods, which included cow’s milk, also had FPIES to solid foods. Forty-two percent of infants with FPIES to fish developed a reaction to additional food groups.

Conclusion: FPIES is not uncommon and most commonly occurs as a response to a single food group. The authors suggest that infants at high risk of FPIES to multiple foods are those who present early with FPIES to fruits, vegetables, or both.

Comments: The true population incidence of FPIES is unknown [9]. The only other current study on the epidemiology of FPIES, the Israeli single-center large birth cohort study by Katz et al. [10], reported a 2-year cumulative incidence of 0.34% of FPIES to cow’s milk. The proportion of FPIES compared to other allergic disorders presenting at tertiary allergy clinics is estimated at about 1%. The authors of this manuscript report that rice is the most common cause of FPIES, which is in contrast to data from the US and Europe,
where FPIES to cow’s milk predominates and FPIES to rice represents 4–23% of all triggers. The reported US rates of FPIES to rice (19–23%) are approximately half the Australian rate. The reasons for these differences are not known, and the introduction of rice or cow’s milk as the first complementary food was not an associated risk factor for the development of FPIES to either of these food triggers. Approximately two-thirds of infants in this Australian cohort had a single food trigger and 73% reacted to a single food group, which is in keeping with reports from the US and the UK. Although a causal relationship cannot be proven, this study highlights that FPIES through breast milk exposure can occur, and food proteins in breast milk appear more likely to trigger non-IgE-mediated food reactions than IgE-mediated food reactions. This study also shows that FPIES is not rare, has no sex predilection, and most commonly occurs as a response to a single food and single food group.

International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive Summary – Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma and Immunology


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Background: Although food protein-induced enterocolitis syndrome (FPIES) may manifest as a severe food allergy, the awareness to it is low, and there is a lack of high-quality data on the pathophysiology, diagnosis, and management of this disease. This consensus document was written by an international workgroup assembled through the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma and Immunology and the International FPIES Association advocacy group.

Methods: A comprehensive literature review was performed by searching PubMed/Medline, Web of Science, and Embase. Excluding abstracts, a total of 879 citations were found through February 2014; of these, 110 were included. Work was divided to individual subgroup teams whose findings received feedback from all authors until a consensus was obtained. Evidence was graded according to the previously established grading system for clinical practice guidelines used by the Joint Task Force on Allergy Practice Parameters.

Results: This consensus document on FPIES comprises of the following sections: I (Definition and clinical manifestations); II (Epidemiology); III (Diagnosis of FPIES); IV (Pathophysiology of FPIES); V (Gastrointestinal manifestations of FPIES); VI (Management of acute FPIES); and VII (Nutritional management for FPIES). A list of 30 summary statements is also provided.
The following areas have been identified as having high priority for advancing the care of patients with FPIES: (1) characterize chronic FPIES; (2) establish FPIES prevalence; (3) identify FPIES risk factors; (4) validate the proposed diagnostic criteria; (5) standardize the OFC protocol and criteria for challenge positivity; (6) determine the pathophysiology of acute and chronic FPIES; (7) understand the relationship between atopy and FPIES; (8) develop noninvasive biomarkers for diagnosis and for monitoring for resolution; (9) develop therapeutic approaches to accelerate FPIES resolution; (10) determine the role of ondansetron in managing FPIES reactions; (11) determine whether extensively heated (baked) cow’s milk and egg white proteins can be tolerated by children with FPIES to these foods; (12) perform systematic evaluation of the prevalence of nutrient deficiencies, poor growth, and feeding difficulties in patients with FPIES and provide guidance for preventative intervention; (13) perform longitudinal cohort studies to improve our understanding of the outcomes and the natural history of FPIES in children and adults.

**Conclusion:** These are the first international evidence-based guidelines to improve the diagnosis and management of patients with FPIES. These guidelines will be updated as more evidence accumulates.

**Comments**

This consensus document is the first international evidence-based guidelines to improve the diagnosis and management of patients with FPIES [11]. It also identifies unmet needs and future directions for research. These guidelines will be helpful for health professionals involved in FPIES diagnosis and management. Research on prevalence, pathophysiology, diagnostic markers, and future treatments is necessary to improve the care of patients with FPIES. The full report is available online as open access in this article’s Online Repository at www.jacionline.org.

**Complementary feeding: a position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition**

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**Background:** This position paper discusses various aspects of complementary feeding (CF) focusing on healthy infants born at term in Europe.

**Methods:** The authors conducted a systematic literature search and reviewed current knowledge and practices. Based on their findings, they formulated their recommendations.
**Results: Timing:** Exclusive or full breastfeeding should be strongly encouraged for a minimum of 4 months (17 weeks), and exclusive or predominant breastfeeding for approximately 6 months (26 weeks) should be aimed for. Complementary foods (solids and liquids other than breast milk or infant formula) should not be introduced before 4 months but should not be withheld beyond 6 months of age. **Content:** Different foods of various flavors and textures including bitter-tasting green vegetables should be offered as complementary foods. Breastfeeding alongside CF is recommended. Whole cows’ milk should not be provided as the main drink before the age of one year. Allergenic foods may be introduced when CF is commenced any time after 4 months. Infants who are at high risk of peanut allergy (those with severe eczema, egg allergy, or both) should have peanut introduced between 4 and 11 months, after being evaluated by a suitably trained specialist. Gluten may be introduced between 4 and 12 months, but consumption of large quantities should be avoided during the first weeks after gluten introduction and later during infancy. It is recommended that all infants receive iron-rich CF including meat products and/or iron-fortified foods. No sugar or salt should be added to CF and fruit juices or sugar-sweetened beverages should be discouraged. Vegan diets should only be applied under suitable medical or dietetic supervision, while making sure that the parents understand the importance of complying with the advice on supplementation of the diet.

**Methods:** Complementary food should be provided as a response to the infant’s hunger and satiety queues, not as a means of comfort or as a reward.

**Comments**

Complementary foods are important in the transition from milk feeding to family foods. The CF period is one of rapid growth and development when infants are susceptible to nutrient deficiencies and excesses, and during which there are marked changes in the diet with exposures to new foods, tastes, and feeding experiences. Little attention has been paid to the CF period, especially to the type of foods given, or whether this period of significant dietary change influences later health, development, or behavior. The relatively limited scientific evidence base is reflected in considerable variation in CF recommendations and practices between and within countries.

ESPGHAN CoN recommendations are intended for infants living in Europe, typically in relatively affluent populations with access to clean water and good healthcare. It is, however, important to ensure that advice reaches high-risk groups such as socioeconomically disadvantaged families and immigrant families, and to adapt advice for individual infants taking into account their circumstances and environment. The purpose of this position paper is to update the position paper published by ESPGHAN CoN in 2008 [12]. New evidence has been included, particularly data from randomized controlled trials on the introduction of gluten and allergenic foods.
Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease. A systematic review and meta-analysis

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Background: It is unclear whether the timing of introduction of allergenic foods to the infant diet can affect the risk of allergic or autoimmune disease. The objective of this paper was to systematically review and meta-analyze evidence regarding the association between timing of allergenic food introduction during infancy and the risk of allergic or autoimmune disease.

Methods: The authors conducted a search of Medline, Embase, Web of Science, Central, and Lilacs databases between January 1946 and March 2016. The review included both observational studies and interventional trials that evaluated timing of allergenic food introduction and reported allergic or autoimmune disease during the first year of life. Data were extracted in duplicate and synthesized for meta-analysis using generic inverse variance or Mantel-Haenszel methods with a random-effects model. GRADE was used to evaluate the quality of evidence. Main outcomes and measures were wheeze, eczema, allergic rhinitis, food allergy, allergic sensitization, T1D mellitus, celiac disease, inflammatory bowel disease, autoimmune thyroid disease, and juvenile rheumatoid arthritis.

Results: The authors screened 16,289 original titles, eventually extracting data from 204 titles reporting 146 studies. There was moderate-certainty evidence from 5 trials (1,915 participants) that early egg introduction at 4–6 months was associated with a reduction in incidence of egg allergy (risk ratio 0.56; 95% CI 0.36–0.87; I² = 36%; p = 0.009). The absolute risk reduction for a population of whom 5.4% had an egg allergy was 24/1,000 (95% CI 7–35 cases). There was moderate-certainty evidence from 2 studies (1,550 participants) that early peanut introduction at age 4–11 months corresponded with reduced peanut allergy (risk ratio 0.29; 95% CI 0.11–0.74; I² = 66%; p = 0.009). Absolute risk reduction for a population with 2.5% risk of peanut allergy was 18/1,000 cases (95% CI 6–22 cases). Certainty of evidence was downgraded because of imprecision of effect estimates and indirectness of the populations and interventions studied. Timing of egg or peanut introduction was not associated with the risk of allergy to other foods. There was low- to very low-certainty evidence that early introduction of fish correlated with reduced allergic sensitization and rhinitis. There was high-certainty evidence that timing of gluten introduction was not associated with the risk of celiac disease, and that timing of initiation of other allergenic foods was not associated with other outcomes.

Conclusion: It was found that early egg or peanut introduction to infants’ diets carries a lower risk of developing egg or peanut allergy.

Comments: Food allergy is a difficult disorder without a cure or treatment and with negative health and economic outcomes [13]. Prevention of disease occurrence and related negative consequences through an inexpensive intervention is of high interest. Infant feeding guidelines have moved away from advising parents to delay the introduction of allergenic food, but most guidelines do not yet advise early feeding of such foods. The evidence base for a relationship between early allergenic food introduction and
food allergy to the same food was limited to a relatively small number of studies and events and was only statistically significant for egg and peanut. The findings of this review are consistent with a large body of experimental data in various animal models in which early enteral antigen exposure is established as effective for preventing allergic sensitization to the same antigen. Oral tolerance in humans appears to be antigen specific, with no data showing early introduction of one allergenic food influences the development of allergy to a different allergenic food. In contrast to egg and peanut allergies, this review found that oral tolerance was not relevant to celiac disease, suggesting that the findings may not be generalizable beyond food allergy mediated by IgE antibodies. These data suggest that current guidelines that do not advise early introduction of allergenic foods may need to be revised.

Early introduction of foods may not be a panacea to address the food allergy epidemic. In addition, it is not clear that it is the specific early introduction of an allergenic food that renders immunological protection, rather than the accompanying increased diversity in the diet that occurs concomitantly.

Complementary feeding at 4 versus 6 months of age for preterm infants born at less than 34 weeks of gestation: a randomised, open-label, multicentre trial

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**Background:** Evidence on the preferable time to of complementary feeding (CF) in preterm infants is lacking. The influence of initiation of CF at 4 months versus 6 months (corrected age) on weight for age at the age of one year corrected age in preterm infants born at less than 34 weeks of gestation was therefore examined.

**Methods:** This was an open-label, randomized trial, in which infants born at less than 34 weeks of gestation with no major malformation were enrolled from 3 centers in India. Eligible infants were followed from birth and were randomly assigned at 4 months corrected age to begin CF at 4 months corrected age (4 month group), or to continue with milk feeding and initiate CF at 6 months corrected age (6 month group). Groups were stratified according to gestation (30 weeks or under, and 31–33 weeks). All participants received standard iron supplementation. Primary outcome was weight for age z-score at 12 months corrected age (WAZ12) based on WHO Multicentre Growth Reference Study growth standards. Analyses were by intention to treat.

**Results:** A total of 403 infants were randomly assigned: 206 to initiate CF at 4 months and 197 to initiate CF at 6 months. Twenty-two infants in the 4-month group (4 deaths, 2 withdrawals, 16 lost to follow-up) and 8 infants in the 6-month group (2 deaths, 6 lost to follow-up) were excluded from analysis of primary outcome. No difference in WAZ12 was found among the 2 groups: –1.6 (SD 1.2) in the 4-month group versus –1.6 (SD 1.3) in the 6 month group. A higher rate of hospital admissions was reported in the 4-month group compared with the 6-month group: 2.5 episodes/100 infant-months versus 1.4 episodes/100 infant-months, respectively (incidence rate ratio 1.8, 95% CI 1.0–3.1, p = 0.03).

**Conclusion:** Early versus late introduction of CF in preterm infants did not affect WAZ12. However, a higher rate of hospital admission in the 4-month group supports the introduction of CF.
at 6 months rather than at 4 months of corrected age, in infants born before 34 weeks of gestation.

Comments

Very few data are available with respect to the optimal time of initiation of CF in preterm infants who are at a much higher risk of postnatal growth restriction than full-term infants [14]. Extrapolating or not the recommendation for full-term infants to initiate CF at 6 months of age to preterm infants depends on 2 major questions: what does 6 months refer to in a preterm infant – chronological (postnatal) age or corrected age? Healthcare providers generally use corrected age for monitoring the physical growth and development of preterm infants. In addition, if it is assumed that 6 months refers to the corrected age, should these infants not start CF earlier than full-term infants? Preterm infants have higher energy requirements compared with full-term infants, and it is not known how long in infancy milk feeds alone (breast milk or formula) are sufficient to meet their requirements. Most complementary foods provide higher caloric density compared with milk feeds. Therefore, an early introduction of CF in preterm infants than is recommended for full-term infants might improve their growth. This study shows that early initiation of CF at 4 month compared with 6 months of corrected age does not improve the growth of preterm infants at corrected age of 12 months. It also does not result in a difference in developmental outcomes, body composition, bone mineralization, and any marker for metabolic syndrome like insulin resistance, lipid profile, and blood pressure in infancy. Rather, early initiation of CF at 4 months corrected age increases the risk of hospital admission due to concurrent morbidities, predominantly diarrhoea and lower tract respiratory infections. In both groups, dietary patterns remained poor and body iron stores remained depleted despite iron supplementation until 12 months of corrected age. This may be related to the vegetarian diet received by most infants, with co-consumption of phytates and oxalates, and low vitamin C intake, and/or to infrequent practice of delayed umbilical cord clamping.

This well-designed randomized study is of high relevance for preterm infants from low-income populations. However, conclusions cannot be generalized to high-income countries mainly because of high mortality rate, different conditions of hygiene and environment, and vegetarian dietary practices. High-quality studies on the timing of CF in preterm infants are urgently needed in high-income populations.

A micronutrient-fortified young-child formula improves the iron and vitamin D status of healthy young European children: a randomized, double-blind controlled trial

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**Background:** Many young European children develop iron deficiency (ID) and vitamin D deficiency (VDD) due to insufficient dietary intakes and poor compliance to vitamin D supplementa-
The aim of this study was to evaluate the effect of a micronutrient-fortified young-child formula (YCF) on the iron and vitamin D status of young European children.

**Methods:** This randomized, double-blind controlled trial, was conducted in Western Europe (Germany, the Netherlands, and England) from October 2012 to September 2014. Healthy children aged 1–3 years received either YCF (1.2 mg Fe/100 mL; 1.7 μg vitamin D/100 mL) or non-fortified cow’s milk (CM; 0.02 mg Fe/100 mL; no vitamin D) for 20 weeks. The primary and secondary outcomes were change from baseline in serum ferritin (SF) and 25-hydroxyvitamin D (25(OH)D), respectively. ID was defined as SF <12 μg/L in the absence of infection (high-sensitivity C-reactive protein <10 mg/L) and VDD as 25(OH)D <50 nmol/L. Statistical adjustments were made in intention-to-treat analyses for sex, country, age, baseline micronutrient status, and micronutrient intake from food and supplements (and sun exposure for vitamin D outcomes).

**Results:** Three hundred and eighteen children, mainly Caucasian, participated in this study. The difference between the groups in the SF and 25(OH)D status from baseline was 6.6 μg/L (95% CI 1.4–11.7 μg/L; p = 0.013) and 16.4 nmol/L (95% CI 9.5–21.4 nmol/L; p < 0.001), respectively. The risk of developing ID (OR 0.42; 95% CI 0.18–0.95; p = 0.036) and VDD (OR 0.22; 95% CI 0.01–0.51; p < 0.001) after the intervention was lower in the YCF group than in the CM group.

**Conclusion:** Consumption of micronutrient-fortified YCF daily for 20 weeks preserved the iron status, lowered the risk of ID, and improved vitamin D status in healthy young children in Western Europe.

**Comments** Despite national nutritional recommendations, ID and VDD are among the most common micronutrient deficiencies in young children living in industrialized countries. Compliance to the use of iron and/or vitamin D supplements seems to be low. Therefore, fortification of commonly used products has been suggested. Milk is a popular source for delivering fortification in non-breastfed infants because of its wide availability and acceptance (infant formula from 0 to 6 months; follow-on formula from 6 to 12 months; YCF in young children from 1 to 3 years).

In the study, the estimated mean ± SEM change in SF concentration from baseline was −4.9 ± 2.2 μg/L for the CM group and +1.7 ± 2.4 μg/L for the YCF group. The estimated mean ± SEM change in 25(OH)D concentration from baseline was −7.2 ± 2.5 nmol/L for the CM group and +9.2 ± 2.8 nmol/L for the YCF group. At baseline, 8.2% of the YCF group and 5.6% of the CM group were iron- and vitamin D-deficient. These prevalence rates increased in the CM group to 15.3% and decreased for YCF users to 4.0% after 20 weeks of study product intake. There were no statistical differences in anthropometric data, stool pattern, and occurrence of overall adverse events between the YCF and the CM groups. This well-designed study is the first randomized, double-blind controlled trial assessing the impact of YCF on both the iron and vitamin D status. The daily consumption of YCF for 20 weeks was shown to preserve the iron status and improve vitamin D status. The authors conclude that the use of YCF may be an effective and practical strategy for preventing both ID and VDD in young European children.

In its Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union [2], EFSA pointed out that dietary intakes of ALA, DHA, iron, vitamin D, and iodine (in some European countries) are low in infants and young children living in Europe. Particular attention should be paid to ensuring an appropriate supply of ALA, DHA, iron, vitamin D, and iodine in infants and young children with inadequate or at-risk of inadequate status of these nutrients.

There is as yet no European legislation covering the composition and main characteristics of young-child formulae. In comparison with CM, YCF currently marketed in the
European Union contain more ALA, DHA (if added), iron, and vitamin D but similar amounts of iodine. The median content of these nutrients in YCF is within the range of permitted concentrations in FOF and, except for iron, also in IF. Fortified formulae, including YCF, are one of the several means to increase n-3 PUFA, iron, vitamin D, and iodine intakes in infants and young children living in Europe with inadequate or at-risk of inadequate status of these nutrients. However, other means, such as fortified cow’s milk, fortified cereals and cereal-based foods, supplements or the early introduction of meat and fish into CF and their continued regular consumption, are alternatives to increase intakes of these nutrients. The selection of the appropriate form and vehicle through which these nutrients are provided in the diet will depend on national dietary habits, health authorities, the regulatory context, and caregivers’ preference. At the present time, no unique role of YCF with respect to the provision of critical nutrients in the diet of infants and young children living in Europe can be identified, so that they cannot be considered as a necessity to satisfy the nutritional requirements of young children.

To conclude, this very interesting study shows the usefulness of YCF to prevent ID and VDD in young children. It was not designed to demonstrate that it is the only means to do it. There is a controversy as to whether a specific regulation on YCF marketed in the EU is needed. An easy alternative to such a regulation is the use of FOF between 1 and 3 years of age as one of the means to compensate for lower intake of iron, vitamin D, DHA, ALA, and iodine in this at-risk population.

**Preterm Infants**

**Randomized trial of two doses of vitamin D3 in preterm infants <32 weeks: dose impact on achieving desired serum 25(OH)D3 in a NICU population**

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**Background:** Various different recommendations for vitamin D supplementation for preterm neonates exist. However, evidence regarding the effect of the different doses on outcomes of these infants is insufficient.

**Objective:** The aim of this double-blind randomized controlled study was to evaluate 2 different doses of serum 25(OH)D₃ concentration on a preterm population and assess the impact on Neonatal Intensive Care Unit (NICU) outcomes.

**Design:** Out of 369 infants assessed for eligibility, 32 infants born at 24–32 weeks gestation were prospectively randomized into 2 groups: one received 400 IU/day and the other 800 IU/day of vi-
Vitamin D₃ supplementation. Serum 25(OH)D₃ levels were measured once in 4 weeks. The Wilcoxon signed rank test was used to compare serum levels of 25(OH)D₃ at 4 weeks and at each subsequent time point. A p value of <0.05 was considered statistically significant.

**Results:** Serum 25(OH)D₃ levels at birth were 41.9 and 42.9 nmol/L for infants in the 400 IU group and 800 IU group, respectively (p = 0.86). A significant correlation was found between cord 25(OH)D₃ concentrations and gestational age (r = 0.40, p = 0.04). The study demonstrated a significant improvement in 25(OH)D₃ status in the higher dose (p = 0.048). Infants in the 400 IU group were more prone to have dual energy X-ray absorptiometry bone density measurements below the 10th percentile. This difference was found to be significant (56 vs. 16%, p = 0.04). There was a trend towards improved linear growth in the 800 IU group.

**Conclusions:** The results suggest that there is a need for a daily supplementation of 800 IU of vitamin D for infants <32 weeks cared for in the NICU.

**Comments**

For years, controversy exists regarding the optimal dose of vitamin D administered to preterm infants. Daily dose recommendations vary from 200 to 1,000 IU/day. The wide variation is due to a lack of solid evidence what is best for preterm infants. Similarly, the target plasma concentrations are not defined consistently either. ESPGHAN recommends 25(OH)D₃ serum levels above 80 nmol/L, whereas other societies recommend serum levels >50 nmol/L while all aim at an outcome that involves bone health [15–17]. Altogether, this leads to uncertainty as to how much should be given to preterm infants, especially very preterm infants. The present study tries to provide an answer to both questions. The limited number of infants studied prevents any firm conclusions, but does show that 800 IU/day results in higher 25(OH)D₃ serum levels as expected. More importantly, a lower number of infants face levels below 50 nmol/L while the higher intakes were associated with a lower number of infants with a reduced bone mineral density. Safety is of course an issue, but no infants were observed with any sign of toxicity. Therefore, this study adds to the growing evidence that additional vitamin D intakes of 800 IU/day are needed for preterm infants.

**Follow-up of a randomized trial on post-discharge nutrition in preterm-born children at age 8 years**

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**Background:** Preterm-born infants are subject to adverse outcomes. Therefore, research in this population is focused not only on their survival but also on the improvement of their long-term outcomes. There is still a debate regarding the optimal post-discharge nutrition of preterm infants. This research follows a previous randomized controlled study that showed that preterm-born infants, fed an isocaloric protein- and mineral-enriched post-discharge formula (PDF) from term to 6-months corrected age (CA), gained more lean mass than did those fed with standard term formula (TF).

**Objective:** The goal of this follow-up study was to compare alterations in body size, body composition, and metabolic health at 8 years of age, in preterm-born children who were fed with either PDF or TF from term age until 6-month CA.
**Design:** Seventy-nine of 152 children (52%) who completed the original trial were included in this follow-up study at the age of 8-years. Anthropometry was measured by standard methods. Body composition, including fat mass, lean mass, bone mineral content, and bone mineral density, was ascertained by dual-energy X-ray absorptiometry. Blood pressure was measured in the supine position by using an automatic device. Blood samples for various metabolic variables were drawn after an overnight fast. Nutritional habits were recorded by the parents using a 3-day nutritional diary.

**Results:** The authors did not find any differences in body size, body composition, bone variables, and metabolic status at age of 8-years between those who fed PDF and those fed TF.

**Conclusions:** In this long-term follow-up study, the authors showed that the positive impact of PDF at 6-month CA was no longer evident at the age of 8 years, but this could also be attributed to attrition. They recommend that future studies focusing on nutritional interventions in the pre- and post-discharge period regard these interventions as a continuum rather than as separate entities.

**Comments**

The objective of nutritional management of neonatologist should be to mimic intrauterine growth and obtain a functional outcome comparable to those infants born at term [15]. That preterm infants have higher nutrient requirements than their term equivalents is obvious but until what period following birth one should provide these preterm born infants and children with additional nutrients is unclear. This study adds to the conclusion of the recent (2016) Cochrane review that the role of post-discharge formula is questionable [18]. Only when term formula was compared to preterm formula, an effect on anthropometric values was noticed. Important is that most studies are of questionable quality. Also, this publication suffers from a high loss to follow-up number, which is not surprising as the follow-up lasted up to 8 years. Recent studies show that direct and adequate nutrition management in the first week of life reduces the longitudinal standard deviation-loss in weight, height, and head circumference [19]. This policy reduces the need for catch-up growth, which is associated with long-term consequences with regard to blood pressure, cardiovascular biomarkers, and insulin sensitivity. Altogether, this emphasizes the importance of an adequate early nutritional supply to accomplish adequate postnatal growth and healthy neurocognitive and metabolic development [20].

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**Supplemental iodide for preterm infants and developmental outcomes at 2 years: an RCT**

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**Background:** Thyroid hormone is essential for normal brain development in utero and for the first 2 years of life. Preterm infants are particularly vulnerable to iodide insufficiency and thyroid dysfunction. The European guidelines for preterm enteral iodide intake is 11–55 μg/kg/day. However,
it has been suggested that the enteral intake for healthy preterm infants should be at least 30–40 and
1 μg/kg/day for parenteral intake. The aim of this study was to determine whether, compared with
placebo, iodide supplementation of preterm infants improves neurodevelopmental outcomes at 2
years.

Methods: In this randomized controlled trial, iodide supplementation or placebo was given to in-
fants born before 31 weeks’ gestation. Trial solutions of sodium iodide or sodium chloride were
given at 30 μg/kg/day beginning within 42 h of birth until 34 weeks’ gestational age. Thyroxine,
thyrotropin, and thyroid-binding globulin levels were measured in whole blood drawn on postna-
tal days 7, 14, 28, and at 34 weeks’ gestational age. The primary outcome was neurodevelopmental
status at 2 years of age, evaluated using the BSID–III. The primary analyses were by intention-to-
treat, and data were presented also for survivors.

Results: Out of 1,273 infants who were enrolled from 21 UK neonatal units, 997 infants survived
(498 intervention and 499 placebo) and underwent neurodevelopmental evaluation. No significa-
tive differences were found between the intervention and placebo groups in the primary outcome:
MD cognitive score, –0.34, 95% CI –2.57 to 1.89; motor composite score, 0.21, 95% CI –2.23 to
2.65; and language composite score, –0.05, 95% CI –2.48 to 2.39. There was a weak correlation
between iodide supplementation and hypothyroxinemia in the language composite score and 1
subtest score.

Conclusions: Results from this study revealed no overall benefit of iodide supplementation on neu-
rodevelopment of preterm infants at 2 years of age.

Comments

Iodide requirements for preterm infants are difficult to assess. Iodide is pivotal for thy-
roid hormone synthesis, and preterm infants are frequently facing transient hypothy-
roxinemia [21] because of iodide deficiency [22, 23]. Both iodide and T4 supplementa-
tion has been studied. Only 1 study of thyroxine supplementation in preterm infants
included long-term neurodevelopmental outcome and the results were equivocal
[24]. In that study, infants receiving T4 supplementation (compared with placebo)
scored 18 points higher than those aged 2 years on the Bayley-II cognitive compo-
nent, but only if they were <27 weeks’ gestation; supplemented infants born ≥27
weeks scored 10 points lower than non-supplemented infants. Subsequent follow-up
at 5.7 and 10 years confirmed these findings [25, 26]. Clinical treatment with thyroxine
has increased 2.6-fold in neonates born <27 weeks’ gestation [27], so the above men-
tioned study was very necessary. Huge numbers of infants were studied in this prag-
matic trial, with a clear primary outcome. The study group concluded that iodide sup-
plementation does not provide a benefit. For now, that is an appropriate conclusion
and no preterm infant that has no sign of hypothyroidism should be supplemented
until longer term data are available and more discriminating test can be used than the
BSID-III score.
Effect of increased enteral protein intake on growth in human milk-fed preterm infants: A randomized clinical trial

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Background: The optimal dose of enteral protein intake for very preterm infants has not yet been determined. It has been suggested that the amount of protein supplied in currently available commercial fortifiers is not sufficient. Furthermore, both intra- and inter-individual variabilities of human milk protein and energy content may be partially responsible for inadequate early postnatal growth.

Objective: To evaluate the influence of different amounts of enteral protein supplementation on growth in preterm infants fed with human milk.

Methods: This randomized, and partially blinded study, was conducted in a neonatal tertiary referral center in Germany between October 2012 and October 2014. Infants born at gestational age of under 32 weeks and of birth weight below 1,500 g were recruited. All analyses were conducted in an intention-to-treat population. At a postnatal age of 6–8 days, participants were randomly assigned either a lower-protein supplementation (1 g of bovine protein in 100 mL of breast milk; n = 30) or a higher-protein supplementation (study fortifier of 1.8 g of bovine protein/100 mL of breast milk [n = 15], or individualized high-protein supplementation based on protein and fat content of administered breast milk [n = 15]). Supplementations were given for 30–57 days and until definite discharge planning. Primary outcome was weight gain (g/kg/day) from birth to the end of intervention.

Results: Sixty participants were enrolled in the study (35% of 173 eligible infants). Both groups were similar in demographic characteristics and hospital courses. The median gestational age at birth was 29.9 weeks. The higher protein group consumed 0.6 g/kg/day (0.4–0.7 g/kg/day) more protein than the lower protein group (p < 0.001), while the proportion of total enteral feeding volume provided as breast milk was similar between the groups. Nevertheless, there was no difference in the primary outcome between the groups: weight gain was 16.3 g/kg/day (15.4–17.1 g/kg/day) in the lower protein group, and 16.0 g/kg/day (15.1–16.9 g/kg/day) in the higher protein group (p = 0.70). Head circumference and lower leg longitudinal growth were also comparable.

Conclusions: An increase of 0.6 g protein/kg/day to a mean intake of 4.3 g/kg/day did not improve the growth rate of very preterm infants with a median birth weight of 1,200 g. This may point to the optimal amount of protein required for enhancing growth in this population.

Comments: Have we reached the upper limit with regard to protein supplementation at around 3.5–4.0 g/kg/day for preterm infants? Yet another trial that shows no benefit of supplementation of additional protein as 2 were published recently as well [28, 29]. Although studies to date are very few in number, they point towards the same direction, although Miller et al. found a small effect on the head circumference growth. Could it be due to the quality of the supplement used? Not likely as weight gain is restricted by the first limiting essential amino acid if enough energy is provided. As both trials...
provided enough energy, the supplement is derived from bovine milk protein, the likelihood that all essential amino acids meet the requirement for optimal growth is very high. Thus, we can conclude that either other factors than essential amino acids are responsible for the ceiling effect or that the growth rates obtained in these studies are reaching intrauterine rates which is the maximum. Of course, it is possible to reach higher weight gain rates by providing more energy, but that is at the expense of additional fat accumulation. The early and adequate use of parenteral nutrition reduces the need for catch-up growth, so probably the intake of enteral protein should not exceed 4.0 g/kg/day under normal conditions.

Two-hourly versus 3-hourly feeding for very low birthweight infants: a randomised controlled trial

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Background and aim: The practice as to the time intervals at which enteral feeding is administered varies in different intensive care units. The aim of the study was to establish whether feeding with 2- versus 3-hourly intervals in very low birthweight infants has an effect on the time at which full enteral feeding is achieved, and on the regaining of birth weight.

Methods: A total of 144 preterm infants, from 2 regional tertiary neonatal intensive care units in Malaysia, with gestational age less than 35 weeks and birth weight between 1 and 1.5 kg participated in the study and were assigned to 2 groups of 72 subjects each: 2- or 3-hourly interval feeding after randomization.

The primary outcome was time to achieve full enteral feeding (≥100 mL/kg/day) and secondary outcomes were the time to regain birth weight, episodes of feeding intolerance, peak serum bilirubin levels, duration of phototherapy, episodes of necrotizing enterocolitis, nosocomial sepsis, and gastro-esophageal reflux.

Results: The mean time to full enteral feeding was 11.3 days in the 3-hourly group and 10.2 days in the 2-hourly group (MD 1.1 days; 95% CI –0.4 to 2.5; p = 0.14). Infants in the 3-hourly group regained birth weight earlier than those in the 2-hourly group (12.9 vs. 14.8 days, p = 0.04). Additional significant results were not found in subgroup analyses. There was no difference in adverse events between the groups.

Conclusions: Time to full enteral feeding was similar in infants fed every 2 h, and those fed every 3 h. The authors suggest that if these findings are confirmed by additional studies, a 3-hourly interval could be a preferable interval, in terms of reducing the work load of the NICU staff.

Comments

A pragmatic trial, as a follow-up to another recently published trial compared semi-continuous feeding versus a 3-hourly feeding. Although definitions were slightly different (here, full enteral feeding was defined as 100 mL/kg/day; in the RCT performed by Rövekamp-Abels et al. [30], the definition of full enteral feeding was set at 120 mL/kg/day), both studies did not find a statistically significant difference in time to reach full enteral nutrition. Noteworthy is that the time needed to reach this primary endpoint was approximately half in the Rövekamp-Abels study, while the definition was more strict, that is, a higher volume was needed to meet the criterion “full enteral nu-
This shows the difference in feeding schedules for many units between Asia and Europe and was a topic in a recent Cochrane review [31]. From the results of 9 trials, with approximately 1,000 preterm infants participating, the reviewers concluded that advancing enteral feed volumes at daily increments of 30–40 mL/kg (compared to 15–24 mL/kg) does not increase the risk of NEC or death in VLBW infants. Advancing the volume of enteral feeds at slow rates results in several days of delay in establishing full enteral feeds and increases the risk of invasive infection.

Of interest is a sub analysis of the Ibrahim manuscript. As Rövekamp-Abels concluded, larger infants seem to benefit more from bolus feeding than smaller infants. The applicability of these findings to extremely preterm, extremely low birth weight, or growth-restricted infants is limited. Further randomized controlled trials in these populations may be warranted to resolve this uncertainty.

References

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