Progress of Enteral Feeding Practice over Time: Moving from Energy Supply to Patient- and Disease-Adapted Formulations

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Abstract

Enteral nutrition comprises the delivery of a liquid formula beyond the esophagus via a feeding tube in a patient with insufficient oral intake, as well as the provision of specialized nutritional formula irrespective of the route of delivery. Pediatric formulae have been designed for different age groups, and for children with certain diseases; examples are special formulations for regurgitating infants, metabolic diseases, cow’s milk or multiple food allergies, intestinal, pancreatic, renal, and hepatic insufficiency. Exclusive enteral nutrition is a therapeutic concept to induce remission in children and adolescents with active Crohn’s disease. A new area of nutritional research in pediatrics is potential immunonutrition in critically ill children. Formulae are enriched with single components or a combination of key substrates that might play a crucial role during intermediary metabolism in sepsis, inflammation, tissue healing, and growth. For pharmaconutrition, single components are investigated in a scientific stepwise procedure in order to identify effective disease-dedicated nutrition therapy. Any new formula needs to be evaluated, if possible in comparison to a normal diet or the reference formulation to demonstrate its safety and efficacy (equal or superior to standard formula).

Introduction

Enteral nutrition (EN) has traditionally been defined as delivery of a liquid formula beyond the esophagus via a feeding tube, either to the stomach or directly to the duodenum or jejunum in a patient with insufficient or inadequate oral intake. More recently, the term EN has been expanded [1] to the
provision of specialized oral nutritional formulation and includes the use of ‘dietary foods for special medical purposes’ as defined in the European legal regulation of the Commission Directive [2], irrespective of the route of delivery. This new definition already implies that formulations can be tailored not only to the age-dependent nutritional needs, but also to the individual patient depending on the underlying disease, residual digestive function and certain situations (i.e. pre- and postoperatively feeding).

Although it has been recognized for long that the nutritional needs of children differ from those of adults, it was only during the last 2–3 decades that liquid formulations for children have been developed. Tube-fed children beyond infancy had received either an infant formula or a liquid diet designed for adults. In pediatric hospitals, decisions on nutrition were often left to nurses, and tube-fed patients, e.g. with cerebral palsy, were fed with infant formula as the only source of nutrition until late adolescence. Similarly, elemental or whole-protein liquid diets designed for adults were fed to toddlers and young children. This resulted in inappropriately high nitrogen supplies in young children, who were exclusively fed with these formulations, since the protein/energy ratio reflecting physiologic needs drops from 3.5 g/100 kcal in young infants to 1.3 in toddlers and increases again to over 2 in adolescence and adulthood. The composition of formulae for preterm infants reflects their even higher protein requirements, and human milk fortifiers were designed to top up pumped breast milk to match the nutritional needs of very premature infants.

The first formulations for disease-specific use were developed for infants with intractable diarrhea which was often due to cow’s milk protein allergy-induced enteropathy. Some of these infants were fed with home-made liquid diets based e.g. on chicken protein as nitrogen source, but failure to thrive was very common. The first formulae with hydrolyzed protein contained medium-chain triglycerides (MCTs) for infants with impaired digestive and absorptive capacity.

This chapter will focus on the development of specific pediatric formulations which have been designed for children with cow’s milk or multiple food allergies and specific formulations which may benefit children with other diseases such as short bowel syndrome, pancreatic, renal and hepatic insufficiency. A new area of research in pediatrics is potential pharmaconutrition in critically ill children. Formulae are enriched with single components or a combination of key substrates that might play a crucial role during intermediary metabolism in sepsis, inflammation, tissue healing, and growth. Pharmaconutrition is an extended concept where single components are investigated in a stepwise scientific procedure in order to identify effective disease-dedicated nutrition therapy. Finally, nutrigenomics refers to the findings that nutrients directly or indirectly alter gene expression in enterocytes, cytokine release and modulate immune function within and outside the gut.
Formulae for Treatment of Infants and Children with Intolerance to One or More Nutritional Components

Treating food allergy and other food intolerances is based on dietary elimination of causative food ingredients [3]. Therefore, formulations which exclude certain ingredients not only serve a nutritive purpose, but also serve as dietary treatment for a specific disease or condition. In older children, the exclusion of certain components may be possible by giving alternative foodstuffs which do not contain the non-tolerated nutrient. However, in infants or tube-fed older children, who fully or to a major part depend on a liquid formula, balanced formulations must be used in order to avoid under- and malnutrition. Intolerance may occur to one or more components in the food, such as carbohydrates, proteins, fats, or to selected amino acids or micronutrients due to allergic diseases, digestive disorders or inborn errors of metabolism.

Carbohydrate intolerance in young infants is rare. Lactose, the main carbohydrate in human milk and infant formula must be strictly avoided in infants with inherited galactosemia, and be largely removed in cases with the infantile form of lactase deficiency or with glucose-galactose malabsorption. These infants require a formulation largely (lactase deficiency) or completely (galactosemia) free of lactose or in the case of glucose-galactose malabsorption a glucose-free formula with fructose or inulin as the only carbohydrate. The genetic late-onset form of hypolactasia which becomes clinically relevant after 5–6 years hardly plays a role in EN since formulations designed for children beyond infancy are lactose free, with glucose polymers (maltodextrin) or occasionally starch as carbohydrates.

Glucose polymers have a low osmotic load and are well tolerated by most patients, except in the rare cases of inherited isomaltase or maltase deficiency. If carbohydrates reach the colon, they are metabolized by the colonic flora to short-chain fatty acids, which serve as energy fuel to the colonozytes or may be absorbed and contribute to the energy pool. However, if this rescue mechanism is overwhelmed, carbohydrate malabsorption results in osmotic diarrhea with acidic watery stools and bloating. In children with intestinal insufficiency, in particular severe enteropathy or short gut syndrome, the amount of carbohydrates is often the limiting factor to increase enteral feeding. This had been already recognized during the early balance studies with hydrolyzed infant formulations [4]. In these situations, special module feeding with a carbohydrate concentration of 2–3 g per 100 ml or per 70 kcal is recommended.

Protein intolerance is much more common and requires specific formulae. Normal infant formulae and formulations for enteral feeding in older children are based on cow’s milk protein, with casein and/or whey. Formula-fed infants with an immunologically mediated intolerance to certain proteins or peptides of cow’s milk (cow’s milk protein allergy) need either an extensively hydrolyzed protein or an amino acid-based formula. For infants, human milk
or infant formula is the only source of nutrition during the first 4 months of life and continues to be a major source throughout the 1st year. Therapeutic formulae that can replace a regular formula in these disease situations are required for adequate nutrition. Infant formula based on soy protein or other animal’s protein or formulae designed for adults are not recommended in infants who receive formula as the major nutritional intake [5, 6].

Formulae based on extensively hydrolyzed casein or whey have been used for more than 30 years. Due to amino acid imbalances, metabolic problems occurred with the old formulation [7]. The hydrolyzed formulae have been constantly adapted and improved, and fulfill a high safety profile with respect to growth pattern and plasma amino acid concentrations [8]. New formulae have been designed with highly purified lactose substituting part of the glucose polymer [9]. Lactose is beneficial for the infant’s gut flora and improves calcium absorption compared to a lactose-free formulation of otherwise the same composition [10].

In infants with rare amino acid disorders such as phenylketonuria or glutaraciduria, specific formulations depleted of specific amino acids (phenylalanine or lysine, respectively) have been developed.

### Formulae for Infants and Children with Chronic Diseases and Special Nutritional Needs

Formulations for specific chronic diseases or situations have been commercialized for pediatric patients with specific needs (table 1). For most of these specialized formulations, randomized controlled trials in children are not available due to the low number of patients or for ethical reasons in severely ill infants. Therefore, the superiority to standard formulae has not been proven for most formulations, although safety data are available.

For infants with faltering growth, it has been widespread practice to add energy supplements (fat and carbohydrates) to standard infant formula. Whilst increasing the energy density, the protein-to-energy ratio is changed. Consequently, nutrient-dense infant formulae have been developed to overcome these problems. In infants with bronchopulmonary dysplasia, a nutrient-dense formula resulted in significantly greater length (p < 0.05), radial bone mineral content (p < 0.01) and lean mass (p < 0.01) at 3 months corrected age compared to a supplemented standard formula [11]. Male infants in the nutrient-enriched group had significantly greater whole body bone mineral content (p = 0.02). In another open, parallel, randomized study, 49 infants with faltering growth were randomized to receive a nutrient-dense formula or an energy supplemented normal infant formula for 6 weeks. Both formulae provided 1 kcal/ml [12]. No significant differences in tolerance, feed volumes or energy intakes were recorded but the nutrient-dense formula group received 42% more protein and 15–40% more vitamins and minerals. Blood
urea concentration in the control group fell by 50% over the trial period, suggesting a suboptimal protein-to-energy ratio in the energy-supplemented feed.

For infants with frequent regurgitation, formulae with added thickening agents such as carob bean gum, starch or fibers have been developed. A recent meta-analysis including 14 RCTs concluded that thickening of the

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**Table 1.** Examples for special formulae for infants and children with certain diseases and situations

<table>
<thead>
<tr>
<th>Disease or condition</th>
<th>Energy density</th>
<th>Modification of macronutrients</th>
<th>Modification of electrolytes, trace elements and vitamins per 100 kcal energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk protein allergy</td>
<td>⇔</td>
<td>Protein: extensively hydrolyzed or amino acids only</td>
<td>⇔</td>
</tr>
<tr>
<td>Phenyketonuria</td>
<td>⇔</td>
<td>Phe free</td>
<td>⇔</td>
</tr>
<tr>
<td>Glutaraciduria</td>
<td>⇔</td>
<td>Lysin free</td>
<td>⇔</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>⇔</td>
<td>Lactose free</td>
<td>⇔</td>
</tr>
<tr>
<td>Infant with frequent regurgitation</td>
<td></td>
<td>Addition of starch or carob bean gum</td>
<td>⇔</td>
</tr>
<tr>
<td>Infants with failure to thrive, poor intake, heart disease</td>
<td>↑</td>
<td>Normal relation of P: L:CH, but higher concentration, polyglucose to reduce osmolality</td>
<td>⇔</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>↑</td>
<td>Lipids, but MCT ↑</td>
<td>Fat-soluble vitamins ↑</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>↑</td>
<td>Protein: hydrolyzed lipids ⇔ but MCT ↑</td>
<td>Na ↑, Se ↑, Fat-soluble vitamins ↑</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>⇔</td>
<td>Protein: ↓</td>
<td>K ↓, P ↓</td>
</tr>
<tr>
<td>Short bowel syndrome</td>
<td>⇔</td>
<td>Protein: extensively hydrolyzed</td>
<td>⇔</td>
</tr>
<tr>
<td>Oxidation of long-chain fatty acids, lymphatic loss</td>
<td>⇔</td>
<td>Lipids ⇔ but MCT ↑</td>
<td>⇔</td>
</tr>
<tr>
<td>Intractable epilepsy, GLUT1 transporter defect, PDH deficiency</td>
<td>⇔</td>
<td>Lipids ↑↑↑</td>
<td>⇔</td>
</tr>
</tbody>
</table>

PDH = Pyruvate-dehydrogenase; ⇔ = Unchanged, ↑ = increased, ↓ = decreased compared to standard formula for age.
feeding decreased episodes of regurgitation compared to controls, but not acid exposure to the esophageal mucosa [13]. In spite of the beneficial effect on the frequency of regurgitation, a switch to a so-called 'reflux formula' is not indicated in healthy and thriving infants who are not bothered by the symptom [14].

Fiber supplementation of enteral feeds for children and adults has been proposed to reduce gastrointestinal side effects of enteral feeding such as diarrhea or constipation [15, 16]. A recent meta-analysis of controlled studies in adults or children compared fiber-supplemented vs. fiber-free formulae given as the sole source of nutrition [17]. The analysis included 51 studies (43 randomized controlled trials) with a total of 1,762 subjects, but only few pediatric patients. In 13 randomized controlled trials, the incidence of diarrhea was reduced with fiber administration (OR 0.68, 95% CI: 0.48–0.96). In both patients and healthy subjects, fiber significantly reduced bowel frequency when baseline frequency was high and increased it when it was low, revealing a significant clinical benefit on bowel functioning.

**Exclusive Enteral Nutrition as Therapy for Active Crohn’s Disease**

Crohn’s disease (CD) and ulcerative colitis, the two major forms of inflammatory bowel disease, are characterized by a chronic relapsing course of destructing inflammation of the affected bowel. Recent studies have demonstrated rising incidences of pediatric CD [18]. It is generally accepted that environmental factors together with bacterial antigens cause a dysregulation of the immune system in genetically predisposed persons. Epidemiological studies identified several environmental risk factors for childhood onset inflammatory bowel disease. Dietary factors showed a shift towards high intake of the n-6 fatty acid linoleic acid and a high n-6/n-3 fatty acid ratio [19]. Following the concept of the hygiene hypothesis, a cleaner environment, lack of infections and exposure to certain microbes and an urban place of living, all predispose to inflammatory bowel disease [20].

At time of diagnosis, malnutrition and/or growth failure, a decreased muscle mass and bone mineral density are commonly present and may persist in spite of intensive therapy [21]. A therapy that leads to resolution of gut inflammation, whilst improving nutrition and growth could therefore be seen as an ideal therapy for the management of CD in children. Exclusive EN (EEN) provides optimal supply of energy, macro- and micronutrients and corrects malnutrition and its complications. EEN is as effective as systemic corticosteroids in decreasing inflammation, symptoms and inducing remission [22, 23], and even superior in achieving mucosal healing [24].

EEN is defined as exclusive intake of an elemental or polymeric formula given orally or via nasogastric tube feeding for at least 6–8 weeks instead of a
normal diet. The discovery that EEN is effective in decreasing bowel inflammation and inducing remission was found by chance in the late 60ies in adult CD patients who were fed with elemental diets to improve their nutritional status before surgery. After the first successful studies, it was already speculated that the diet may be effective because it provides nutritional support, is hypoallergenic, acts as a medical bypass around the affected area, or alters bowel flora [25]. The exact mechanism of how EEN leads to downregulation of the inflammatory process and mucosal healing in CD is still unclear.

Studies on EEN have focused on single components in the formulations such as nitrogen source and lipid composition. An updated Cochrane review of comparative studies confirmed that whole-protein formulae are as effective in inducing remission as amino acid-based formulae [26]. Several RCTs tried to identify the optimal lipid concentration (low versus high) and fat composition (MCTs versus long-chain triglycerides, n-6 polyunsaturated versus monounsaturated fatty acids, and n-3 polyunsaturated fatty acid) [27]. However, results are conflicting, with a nonsignificant trend for a better performance of a very low fat and/or very low long-chain triglyceride content in the formulations [26].

Only EEN, but not partially EN decreases inflammation in children with CD in spite of similar weight gain [28]. Close monitoring of CD patients demonstrated a rapid fall of c-reactive protein, the erythrocyte sedimentation rate, and immune markers such as IL-6 within 3 days of starting EEN, before any nutritional changes could be noticed [29]. Therefore, it is not a change in nutritional body status that induces remission in CD, but most likely a mechanism within the intestine itself. EEN leads to a rapid alteration of the luminal content and the gut flora [30], which in itself is modulating the cytokine response [31]. Leach et al. [32] investigated the changes to key intestinal bacterial groups of eubacteria, Bacteroides, Clostridium coccoides, Clostridium leptum and bifidobacteria, during and after EEN in CD children compared to controls, and correlated these changes to disease activity and intestinal inflammation. EEN had a significant effect on the composition of the predominant intestinal flora, which remained altered until 4 months after the dietary intervention. Changes of the gut flora have major effects on the bacterial fermentation in the intestine resulting in different levels of short-chain fatty acids, particularly butyrate. In animal models, butyrate was shown to have a strong effect on the epithelial cell signaling genes and alter in a concentration-dependent manner the secretion of IL-8 and IGF binding protein [33].

The mucosal immune system of the intestine and tissue gene expression may respond directly to nutrients or their metabolites or indirectly to alterations in the luminal environment, particularly the gut flora [33, 34]. The altered expression of signaling genes in enterocytes influences the mucosal immune response via release of different chemokines. The term nutrigenetics implies the (beneficial) effect of nutrients on gene expression and cytokine
response. However, the effect may not be due to a single dietary item or even a group of nutrients and may act differently in different patients.

Some beneficial cytokines such as transforming growth factor-β (TGF-β) may be delivered with the formula as a natural component of cow’s milk. A casein-based formula for EN with appreciable contents of TGF-β was claimed to have additional benefits for EEN in CD patients [35]. TGF-β has a broad spectrum of activities including mucosal regulation of tolerance induction, anti-inflammatory action, secretory IgA expression and downregulation of major histocompatibility complex class expression; all effects may be beneficial in the treatment of CD [36, 37]. However, so far an RCT is lacking to prove that the TGF-β-rich formulae are superior over other formulations for mucosal healing. In fact, elemental formulae apparently free of cytokines including TGF-β are as effective as whole-protein formulations.

**Immunonutrition and Pharmaconutrition**

Nutritional pharmacology is defined as the use of specific substances for effects beyond their nutritional role. The term pharmaconutrition seems more appropriate compared to the term immunonutrition, which refers to feeds including a mixture of ‘immune-enhancing’ substrates with beneficial effects such as improved immune parameters and clinical outcomes.

Particularly four nutrients have been the subject of recent research: glutamine, arginine, nucleic acids, and essential fatty acids, particularly n-3 fatty acids. Glutamine has been classified as conditionally essential amino acid, with special usefulness in critically ill patients. Immunomodulation, gut protection, and prevention of protein depletion are mentioned among its positive effects in such circumstances. In newborn rats, glutamine administration partially prevented the sepsis-induced fall in plasma glutamine levels and reduced the concentration of both proinflammatory and anti-inflammatory cytokines [38]. Most RCTs have been performed in adult patients with trauma, burns, cancer or in critically ill patients on intensive care units. A recent meta-analysis of studies in adults showed no significant benefit of immunomodulating diets on mortality, but lower acquisition rates of new infections compared to control [39]. This effect was evident in patients in intensive care units and with burns, but less so in trauma patients.

Several clinical trials have been performed in adult perioperative cancer patients evaluating nutritional pharmacologic interventions using an enteral formula with a mixture of ‘immune-enhancing’ substrates including arginine, nucleotide, and n-3 fatty acids. The methodology of these studies was very diverse, which limits the ability to determine the best timing for initiation of immune-enhancing EN. The 2009 guidelines of the American Society of Parenteral and Enteral Nutrition recommended that individuals undergoing gastrointestinal or major head and neck surgery in whom there is preexisting
malnutrition would benefit from 5–7 days of preoperative supplementation [40]. Fewer studies have examined supplementation with single nutrients. The data on the use of formulae with supplementation of a single nutrient such as arginine or glutamine are too limited to make recommendations.

Only a few RCTs have been performed with immune-enhancing EN in children (table 2). Briassoulis et al. [41] reported their results of a blinded RCT in children admitted to the pediatric intensive care unit because of sepsis, respiratory failure, and severe head injury and a need for mechanical ventilation of ≥5 days. EN was started within 12 h of admission. Fifty critically ill children were randomized to receive either an immune-enhancing formulation designed for adults containing glutamine, arginine, n-3 fatty acids, and antioxidants, or

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Subjects</th>
<th>Clinical outcome and results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briassoulis et al. [41]</td>
<td>Immune-enhanced formula for adults vs. pediatric standard formula</td>
<td>50 critically ill ventilated children on PICU 25 in each group</td>
<td>No change in mortality Decreased nosocomial infection rates and positive gastric aspirate culture rates More diarrhea in immune-enhanced formula</td>
<td>Immune-enhanced formula was not adapted to children</td>
</tr>
<tr>
<td>Briassoulis et al. [42]</td>
<td>Immune-enhanced formula for adults vs. pediatric standard formula</td>
<td>40 critically ill ventilated children with severe traumatic head injury, 20 in each group</td>
<td>No change in mortality, time on ventilator or PICU, decreased IL8 level and gastric colonization with immune-enhanced formula</td>
<td>Immune-enhanced formula was not adapted to children, most patients are included in 2005 study (not stated)</td>
</tr>
<tr>
<td>Barbosa et al. [43]</td>
<td>0.3 g/kg glutamine vs. 0.3 g/kg casein for 5 days</td>
<td>9 children &lt;2 years on PICU 5 glutamine 4 controls</td>
<td>Bacterial infection 75% (3/4) in placebo vs. 20% in verum group Deaths 2/4 vs. 0/5</td>
<td>Sample too small for conclusions</td>
</tr>
<tr>
<td>Ward et al. [44]</td>
<td>0.65 g/kg enteral glutamine for 7 days vs. no intervention</td>
<td>55 children, chemotherapy, randomized cross-over trial</td>
<td>Symptoms of mucositis n.s., with glutamine: fewer patients needed parenteral nutrition (7 vs. 15) with a shorter duration</td>
<td>No toxicity, poor taste of glutamine, possible bias due to no blinding</td>
</tr>
</tbody>
</table>
standard age-appropriate pediatric formulation. Both formulae were isocaloric. Enteral caloric intake with predicted energy expenditure was reached by day 4. The study did not show any differences in the main outcome parameters, although the authors report a decrease in nosocomial infection rates and positive gastric aspirate culture rates in the intervention group compared to standard formula group. The immunologically active formula was less well tolerated with more diarrheal episodes, which may be due to the higher osmolarity compared to the control formula (420 vs. 206 mosm/l). The same investigators reported their results of an RCT in 40 children with severe head injury using the same formulae and study design [42]. Although not particularly stated in the paper, this recent study seems to include a proportion of the previous study. Again, no difference with respect to mortality and length on ventilator or intensive care unit was noticed. IL8 levels were reduced and significantly less positive gastric cultures were noticed with the immune-enhanced formula. RCTs using enteral glutamine supplementation were performed in a pilot study including 9 seriously ill infants [43]. Improved outcomes were reported in the glutamine-supplemented group, but the numbers are too small for meaningful conclusions.

Glutamine supplementation has also been used in a randomized crossover study in 50 children who received at least two cycles of identical chemotherapy. Although the main outcome parameters, symptoms of mucositis, did not differ in relation to enteral glutamine application, parenteral nutrition was significantly less often required compared to the non-intervention, and in those who needed parenteral feeding, the duration was shorter. This could be an indirect sign that glutamine supplementation improved gut and barrier function during chemotherapy.

In conclusion, a normal functioning immune system is crucial to our health, and diet is one of the major exogenous factors modulating immune regulation and competence. Recently, nutrition research has focused on the role of foods or specific food components in enhancing immune response, improving health, reducing disease risks and even treating diseases and inflammatory processes. EN has a greater potential than providing optimal nutrition, since changes in luminal contents directly affects molecular pathways, cytokine expression resulting in decreased inflammation and expression of class II major histocompatibility complex.

References

Progress of Enteral Feeding


Dr. Greer: What is Modulen exactly and does anyone have any idea how it really works?

Dr. S. Koletzko: Modulen is a casein-based formulation which has been used in most studies in pediatric Crohn's patients. It contains high levels of TGF-β; however, we don't know whether this has any effect since we have no comparison between the same formulation without or with TGF-β. Modulen is - at least in Europe - the preferred and most commonly used formula for children with Crohn's disease. This may have historical reasons.

Dr. Ruemmele: We know roughly where the idea comes from. Unfortunately, in the past these patients, adult patients in the beginning, required surgery for Crohn's disease and as part of the preparation for surgery they had to improve their nutritional...
status and use parenteral nutrition or in those who tolerated it enteral nutrition. Surprisingly, after the preparation phase some of these patients did not require any surgery anymore, at least temporarily, and that was the beginning of this enteral nutrition story for Crohn's disease. So it was a surprise, it was not intended to improve the disease, just to improve the nutritional status.

**Dr. S. Koletzko:** The first studies were conducted back in the 1960s in Ireland by O'Morain and some surgeons [1, 2]. They used an elemental diet based on amino acids only. I can’t answer why Nestlé came up with an exclusively casein-based whole-protein formula for this purpose.

**Dr. Haschke:** There was a whole Nestlé Nutrition Workshop on this at the end of 1995 when this TGF-β-enriched formula was launched. The company made a lactose-free product based on casein which worked very well against diarrhea, and the idea came from the pediatricians to enrich it with TGF-β which they thought could be beneficial.

**Dr. S. Koletzko:** But the question remains, does the TGF-β content matter? Since we see the same remissions rates with elemental diets which do not contain TGF-β, I just wonder if this has any additional benefit or not? We just don’t know.

**Dr. Lentze:** I wanted to come back to Crohn’s disease and to nutrition. When I talk to my colleagues from adult gastroenterology, they are always astonished that we do this in children because they have studied this in detail and the number of adult patients studied in gastroenterology is much higher than the number of children. My question is what is the difference between the two groups, and could it be that we haven’t studied enough children?

**Dr. S. Koletzko:** First of all it also works in adults. The per protocol analyses in these old studies show almost the same efficacy. However, many adults in the nutritional treatment arm dropped out and as a consequence, the intention to treat analysis was in favor of steroids. Children have less choice; they are more compliant with the treatment. This is part of the answer. With respect to adults, there are recent results from Japan reporting the successful treatment of Crohn’s patients with exclusive enteral nutrition. Unfortunately, nutritional therapy is – as a medical treatment – more effective in newly diagnosed patients compared to patients with longer disease duration. At the pediatric IBD meeting in Paris in September 2009, Annemarie Griffiths presented the original data from the Canadian nutritional trial which unfortunately have never been published. The results showed that enteral nutrition is less effective in patients with longer disease duration. Therefore, to compare the efficacy in adults and children, they should be matched for disease duration.

**Dr. Singhi:** My question is about nutrition in critically ill children. Do we have any scientific basis for using enteral nutrition as we’ve done it until now, because there are no randomized trials available, except in immunonutrition. Are there any studies that deal with energy-dense enteral nutrition in these children? And have we attempted in any way to define the components of the increased catabolism or weight loss in these patients, and tried to incorporate them in the formula that we give in enteral nutrition?

**Dr. S. Koletzko:** The benefit of energy-dense formulations in critically ill children depends on the underlying disease. The beneficial effect has been shown in randomized controlled trials in infants with failure to thrive but a normal gut function. The situation may be different in infants with enteropathy or short gut. Increasing energy density means increasing osmolarity which is often not tolerated. Carbohydrate concentration is the limiting factor in most of these patients. However, if you have a normal gut function, energy-dense formulations are preferable compared to supplementation of a standard infant formula with polyglucose and fat.

**Dr. Singhi:** Do you have any studies to support all this?

**Dr. S. Koletzko:** Yes, I showed you two studies, one in infants with bronchopulmonary dysplasia which showed a significantly greater length, bone mineral content and
lean mass at 3 months with the energy-dense formula compared to a supplemented standard formula. Both formulae provided 1 kcal/ml [3]. The other randomized study was performed in infants with faltering growth; most of them had congenital heart disease [4]. Again, there was better weight gain and growth in the children with the energy-dense formula.

Dr. Shenoi: In our country, we don’t have special formulas for children with inborn errors of metabolism. Are there any studies on nutritional supplementation for these children?

Dr. S. Koletzko: Sorry, I am not the right person to answer this question. We give part of the protein as human milk and then supplement it with special amino acid mixtures, for example free of phenylalanine for phenylketonuria. Do you want to add anything, Dr. Koletzko?

Dr. B. Koletzko: This depends, of course, on the type of underlying metabolic disease. If the problem is protein restriction, then it is our standard practice to combine human milk with a disease-specific amino acid formulation. In infants with phenylketonuria, for example, we can usually provide half of the meals by breastfeeding and half of the meals by a phenylalanine-free infant formulation during the first months of life. If you have a more restricted tolerance to some amino acids than in phenylketonuria, or if you have critical reactions like in some children with organic acidemias or hyperammonemia, the dietary management becomes more complicated, and sometimes breast milk can only be given by bottle in strictly defined amounts. There are also disorders where no breastfeeding is possible, for example galactosemia and some forms of long-chain fatty acid β-oxidation disorders.

Dr. S. Koletzko: And is there an ideal human milk fortifier?

Dr. B. Koletzko: We have good human milk fortifiers for preterm babies, but I would not qualify any of them as ideal. There may be considerable room for improvement.

Klassen: My question is related to the use of extensively hydrolyzed formulas and the development of the gut. Since proteins are absorbed in the gut mainly as peptides and only in part as free amino acids, would you suspect that providing only very small peptides to the infant’s digestive tract could potentially have a long-term effect on gut development?

Dr. S. Koletzko: My preference is a formula based on hydrolyzed protein rather than an amino acid based formulation, because peptides may have a beneficial effect on gut barrier function and absorptive capacity and even on the gut flora. We also use hydrolyzed formulae in children with short gut because peptides have a better effect on the adaptation process compared to amino acids. In addition, the osmolarity is lower. However, with respect to maturation and long-term effect I think nobody looked at that.

References