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Advances in infant nutrition

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Summary. - Recent advances in the nutrition of low birth weight infants are discussed, with special emphasis on concepts and methods to establish parameters for the control of growth and nutrition. Furthermore, the recent developments of methods in the research on newborn nutrition, the problems related to the use of breast milk, the timing of feeding and the problems of the intravenous alimentation are discussed in some detail. Secondly, the effects of breast feeding on infant health are summarised, with particular emphasis on the long term consequences (occurrence of diseases later in life) and on the effects on some surgical diseases of infancy. Recent acquisitions in the field of enteral and parenteral nutrition are also mentioned, and the problems related to composition of the nutritive solutions and indications in pediatric age are covered in some detail. Finally, the dietary management of infant with cow's milk protein allergy or intolerance is discussed, with special regard to composition and indications of hydrolysed protein formulas (casein based, whey based, soy and collagen based), soy based formulas and aminoacid based formulas.

Key words: infant, enteral nutrition, premature, parenteral nutrition, breast feeding.

Riassunto *(Attualità nell'alimentazione del lattante)*. - Sono anzitutto discusse le recenti novità nel campo dell'alimentazione del neonato di basso peso. In particolare sono esaminati i concetti guida nella definizione di parametri da utilizzare per il controllo della crescita in relazione all'alimentazione. Dopo aver ricordato i recenti sviluppi di ordine metodologico nella ricerca sulla nutrizione del neonato, vengono discusse in maggior dettaglio le questioni riguardanti l'uso del latte materno, il momento dell'inizio dell'alimentazione e gli aspetti riguardanti l'alimentazione per via endovenosa. In secondo luogo vengono esaminati gli effetti dell'allattamento al seno sulla salute con particolare riguardo alle conseguenze a distanza sulla comparsa di malattie in età successiva, nonché in riferimento all'effetto su alcune malattie del lattante di interesse chirurgico. Vengono poi discussi i recenti sviluppi delle conoscenze in materia di alimentazione enterale e parenterale nel lattante e a questo riguardo vengono esaminate in dettaglio le questioni riguardanti la composizione delle soluzioni nutritive nonché le indicazioni dei due tipi di alimentazione in età pediatrica. Infine, nell'affrontare il problema del trattamento dietetico del lattante con allergia o intolleranza alle proteine del latte vaccino, sono discusse, in particolare, composizione e indicazioni degli idrolizzati parziali da caseina, da proteine del siero o da proteine della soia e del collageno, nonché delle formule a base di soia o a base di aminoacidi.

Parole chiave: lattante, nutrizione enterale, prematuro, nutrizione parenterale, allattamento al seno.

It is obvious that even a volume would be insufficient to explain in adequate detail all the recent advances in the field of infant nutrition. We have therefore selected a few specific topics as both particularly relevant from the practical point of view and rich of recent scientific advances. To some degree the choice is inevitably arbitrary and reflects the personal experience of the authors.

This review covers therefore the following fields: 1) the nutrition of the low birth weight infant; 2) the role of breast feeding in infant health; 3) some recent advances in clinical nutrition (in particular enteral and parenteral nutrition); 4) the formulas devised for managing infants with cow's milk protein allergy or intolerance.

Nutrition of the low birth weight infant (LBWI)

The modern cardiopulmonary techniques of life support have increased the survival rate of very LBWI. However, both short and long term outcomes of these infants appear strictly related to their nutritional management. While our understanding of nutrition for the preterm infant has grown over the last 20 years, many areas of uncertainty and controversy still remain.

Goal of nutrition

One of the most basic questions concerning nutrition of LBWI is what the goal of feeding should be. Although the primary objective of a nutritional regimen for preterm

infants is to support life and to guarantee a sufficient growth rate to fulfill the individual's genetic potential, there are many doubts on how this goal should be achieved.

Two lines of thought exist concerning the nutritional requirements of such infants: the first one suggests that the optimal diet should provide nutrients in order to achieve protein and mineral accretion rates and weight gains similar to those of the fetus of the same gestational age [1]; the second one considers that the preterm infant is a new biological entity characterized by the immaturity of many organs and functions and thus the optimal diet of these infants is the one that imposes the least stress on the developing digestive, metabolic and excretory systems, even if this may cause a slower growth rate than during fetal life [2].

New techniques in neonatal nutritional research

A number of techniques are used in neonatal nutrition research. Some of these are modern adaptations and refinements of well known methods, such as nutrient balances using new chemical, chromatographic and electronic methods which are particularly safe and accurate.

By indirect calorimetry combined with nutrient balance [3] a reasonably good understanding of the energy, carbohydrate, fat and protein intakes required to obtain optimal growth has been achieved. We are now entering a period when a highly detailed analysis of the metabolic fate of ingested nutrients will be possible.

Variations in metabolism due to feeding, activity, cyrcadian rhythm, sleep state, illness and therapeutic intervention (e.g. mechanically assisted ventilation) are still largely unknown and will require further investigation in the future.

Timing of feeding

Considerable controversy remains regarding the timing to start the enteral feeding in premature infants. The larger prematures (i.e. > 1500 g) without significant lung disease or a need for assisted ventilation, may be fed within the first 24 hours of life. On the other hand, in very LBWI (< 1500 g) the following conditions may preclude early enteral feeding: perinatal asphyxia, mechanical ventilation, umbilical artery catheterization, patent ductus arteriosus and sepsis [4].

Due to the concern that early full-enteral feedings may cause necrotizing enterocolitis, enteral feeding is not frequently started for the first several weeks of life. A lower incidence of cholestatic jaundice and osteopenia and a better tolerance to enteral feedings are frequently observed in babies who are slowly fed with hypocaloric enteral feeding rather than in those parenterally fed. Early administration of low volume enteral feeding resulted in improved tolerance of nutrients and significant stimulation of serum gastrin, an expression of maturation of the gastrointestinal tract [5].

Breast milk

Human milk, especially colostrum, may bring significant benefits to the very LBWI, due to several advantages over commercial formulas: growth factors, anti-infective factors, lypase and amylase enzymatic activity, low renal solute load. Interestingly, epidemiological studies on a large number of infants have suggested that human milk in premature infants reduces the incidence of necrotizing enterocolitis [6]. Further studies will be important to establish which components of human milk are responsible for this. Recent evidence demonstrates that infants fed preterm human milk have a substantial advantage in subsequent IQ evaluated at 7 1/2 to 8 years [7].

While the very LBWI exclusively fed human milk is at risk for osteopenia and poor growth, the supplementation can compensate for the inadequate protein, calcium and phosphorus contents of preterm human milk.

Intravenous alimentation

Premature infants represent probably the largest group of patients receiving parenteral nutrition in the pediatric setting. Since the progression of enteral feeding in the very LBWI is slow and since there may be multiple episodes of feeding intolerance, intravenous feeding with amino acids and lipid emulsion is frequently used to supplement the caloric intake. The exact duration of the parenteral supplement and, therefore, the technique to be used (central *vs* peripheral route) are not clear. Amino acids are well tolerated even in the first days of life. It is important to remember that amino acids will not be protein-sparing until the basal metabolic needs are met, that is, until the caloric intake reaches 40 to 50 kcal/kg/day. Usually amino acids intake is gradually increased up to reach 2.5 to 3.0 g/kg/day.

Intravenous lipids are also well tolerated in the first days of life. Hyperlipemia may occur in small infants, especially those with intrauterine growth retardation and for this reason lipids are usually started at 1 g/kg/day and gradually increased to a total of 3 g/kg/day.

In addition to total intake, the duration and rate of infusion, as well as increments in dosages, are factors affecting lipid tolerance. It has been recently found that the use of a 20% lipid emulsion allows infusion of large amounts of lipids with a smaller increase in triglycerides, phospholipids, and cholesterol in comparison to that observed with the use of a 10% lipid emulsion [8]. The reason for this improved tolerance is that there are more phospholipid liposomes in the 10% lipid emulsion than

in the 20% lipid emulsion. Excessive phospholipid liposomes inhibit the removal of triglycerides from the plasma by competing for lipase-binding sites, and consequently slow the triglyceride hydrolisis. As liposomes accumulate, they are able to extract cholesterol from the cell membranes, leading to increased plasma cholesterol levels. On this basis, it appears that the use of 20% emulsion may be more convenient than the use of a 10% emulsion.

New aspects of the role of breast feeding in infant health

There is general agreement about the advantages of breast feeding for infant health. The nutritional, economic and hygienic properties and the psychological effects are well established. Although some of the protective effects may result from potential confounding factors such as family income, education, crowding, birth weight, and smoking, the protection against diarrheal as well as respiratory diseases has been demonstrated both in industrialised and developing countries since a long time [9, 10]. More recently, data from several countries have suggested a protective role of breast feeding against paralytic poliomyelitis [11], bacteremia and meningitis [12], necrotizing enterocolitis in premature infants [6], urinary tract infection [13], botulism [14], and against allergic disorders [15]. Furthermore, recent research has brought to attention the relationship between infant feeding and diseases occurring later in life, and the role of breast feeding in some surgical diseases of infancy.

Breast feeding and diseases occurring later in life

During the last decade, a consistent association has been reported between bottle feeding and immune system disorders. Data from several countries have associated insulin-dependent diabetes [15], Crohn's disease [16], lymphomas [17], Schoenlein-Henoch purpura [18], multiple sclerosis [19] and appendicitis [20] with reduced breast feeding. As most of these observations are based on case-control studies, further confirmation is needed; nonetheless, their consistency points to the hypothesis that the immune system of the neonate and of the infant is "imprinted" by the presence (or absence) of human milk.

Also it was observed that human milk is poor in the initiators and mediators of inflammation and is rich in antinflammatory agents [21]. Many of these agents are resistant to digestive enzymes and therefore might be expected to remain active in the gastrointestinal tract of the infant. Thus, the hypothesis evolved that part of the defense provided by human milk was caused by antinflammatory agents such as epithelial growth factors, maturational (cortisol) and cytoprotective (prostaglandins E2, F2 alpha) substances, enzymes that degrade mediators, binders of enzymes, modulators of leucocytes, and antioxidants [22].

Breast feeding and some surgical diseases of infancy

The idea that the type of feeding could influence the occurrence, or the age of onset of some surgical conditions is fascinating, but few data are available in children. Three surgical conditions of infancy have been studied to evaluate a possible association with feeding: intussusception [23], inguinal hernia [24], and hypertrophic pyloric stenosis [25]. A case-control study showed that, when compared with infants who had never been fed human milk, breast-fed infants had a relative risk of intussusception of 6.0 when breast feeding at admission was exclusive and of 2.3 when it was partial. The authors attributed this increased risk to the different intestinal motility of breast-fed infants [23]. The stimulation of intestinal peristalsis by breast milk has also been supposed to be associated with a decreased incidence of gastroesophageal reflux in breast-fed infants [26]. Infants affected by inguinal hernia have been reported to be less breast-fed than healthy controls [24], and it has been hypothesized that hormones contained in human milk could promote the closure of the inguinal canal and the testicular descent by means of stimulation of neonatal testicular function. Finally, in a case-control study, 102 infants with pyloric stenosis were reported to have been breast-fed significantly less than healthy controls. The risk associated to being bottle fed and only partially breast fed at the age of one week was respectively 2.74 and 2.04; the association remained even after correction for potential confounders. The increased risk associated with bottle feeding can be due either to the presence of factors in human milk able to promote relaxation of pyloric musculature or to an increased gastrin and HCl secretion.

Recent advances in clinical nutrition

The nutrient deliveries alternative to the natural oral route include enteral and parenteral nutrition.

By enteral nutrition we mean the direct nutrient administration into the gastric or the intestinal tract via a tube passing through the nose. Parenteral nutrition is the administration of nutrient solutions via a catheter placed into a central vein.

The indications for enteral or parenteral nutrition include a broad spectrum of diseases, most belonging to the gastroenterological area. While the indications in adult patients are well established by the American Society of Parenteral and Enteral Nutrition [27], they are less clear in children. As a general statement, if a child is not able to receive a sufficient amount of food by mouth, or if he/she refuses it, the enteral nutrition should be considered, particularly in the conditions listed in Table 1.

Table 1. - Main indications for enteral nutrition in children

Prematurely born children
Cancer
Intractable diarrhea
Short bowel syndrome
Chronic renal diseases
Cystic fibrosis
Inflammatory bowel diseases
Biliary atresia
Bone marrow transplantation
Burns
Anorexia
AIDS

In most cases enteral nutrition is administered in a 24 hour continuous regimen; the advantage of the procedure being the attainment of an increase in food uptake, when this is decreased because of reduced intestinal absorptive surface.

Total parenteral nutrition (TPN) is indicated when enteral nutrition cannot or should not be provided, with the advantage of overcoming the uncertainty regarding the integrity of the digestive-absorptive intestinal processes and the bio-availability of nutrients in the gastrointestinal tract.

Scientific and technological progresses have been made in two important fields: the catheters used to deliver nutrients either in the gastrointestinal tract or intravenously and the nutrient solutions for either route. Novel biocompatible materials are now available that increase the halflife of a catheter, thereby overcoming the need of replacing it after a short time period. Parallel progresses have been made in surgical techniques related to catheter implantation and it is now possible to replace a catheter by gaining access to the same vein in which the catheter to be withdrawn is placed. This makes it possible to spare vascular accesses in children with long lasting TPN (it should be noted that in these patients the lack of vascular accesses represents a frequent cause of death). Progresses have also been made in the control of bacterial contamination of enteral feeds, which is now recognized as a major clinical problem affecting the outcome of patients. Recently the use of catheters incorporating antimicrobial agents has been proposed [28].

A body of evidence has showed the importance of specific nutrients such as short chain fatty acids, glutamine and trace elements to be added to the nutrient solutions.

The short chain fatty acids and their precursors (undigested starch and soluble fibers) function as the preferred fuel for colonic mucosa, as they possess an enhancing effect on the structure and function of the large intestine [29]. Moreover, preliminary results suggest that the intracolonic administration of short chain fatty acids may be effective in patients receiving clinical nutrition [30].

Evidence obtained both *in vitro* and *in vivo* suggested that glutamine acts as small bowel fuel. Several beneficial effects have been detected with either local or parenteral supplementation of glutamine, including a trophic effect on the enterocyte, an improvement of immune function and a proabsorptive effect on intestinal transport [31].

The need to add trace elements is now well established. There are at least 10 elements whose lack induces a consistent abnormality associated to a biochemical defect, which can be prevented or reversed by the addition of the element. These elements are therefore considered as essential, and include: Fe, Zn, Cu, Co, Cr, Se, Mo, Mn, Fl and I. In recent years, techniques to accurately measure the concentration of trace elements have become available and the importance of each element in clinical nutrition is now clear [32]. Consequently, preparations containing some or all the trace elements in an optimal ratio have also become available to be administered to patients on clinical nutrition [33].

Recently the indications for enteral nutrition have been extended to the pediatric AIDS. In HIV infection, 3 mechanisms are responsible for weight loss and may lead to cachexia: the reduced food intake, the intestinal malabsorption and the increased energy expenditure [34]. We have treated with enteral nutrition at home three children with HIV infection. The children received enteral administration of high caloric-low osmolal formula and they showed a catch up growth, as judged by the increase of body weight. In all cases the treatment was well tolerated and their mothers were able to administer the formula with a large volume syringe with no problems, after a brief training conducted during their hospital stay.

Since its introduction, in the late 60s and early 70s, the use of TPN has gained increasing success and has been proved to be life-saving in those conditions that temporarily prevent the use of the intestinal tract.

A list of diarrheal diseases, for which we have administered long term TPN is reported in Table 2. Patients were all in life-threatening conditions when TPN was started. In Table 2 they are grouped by the etiology of diarrhea and their outcome is reported. It can be seen that full and permanent recovery was obtained in most cases [35].

One question that remains unanswered is how long can an intestine rest without adversely affecting the patient's outcome. Indeed a number of side-effects of TPN are now well known, such as the immunosuppression, the alteration in the intestinal barrier function, abnormalities in neuroendocrine driven processes, hepatic failure and others. However the major risks of TPN are related to sepsis, mostly due to the catheter, followed by mechanical and by metabolic complications. For all these reasons, the duration of TPN should be the shortest possible, and attempts at giving oral food should be done as soon as possible.

Table 2. - Diarrheal diseases in children receiving long term total parenteral nutrition and their outcome

	Patients no.	Full recovery	On drug treatment	Persistent TPN	Dead
Enteric infection	19	15	-	-	4
Food intolerance	10	8	1	-	1
Eosinophylic enteropathy	2	1	-	-	1
Intestinal lymphangectasia	1	-	-	-	1
Intestinal pseudoobstruction	3	-	-	2	1
Autoimmune enteropathy	1	-	1	-	-
Crohn's disease	1	-	1	-	-
Familial microvillous atrophy	3	-	-	-	3
Short bowel syndrome	2	1	-	1	-
Unknown	3	1	-	-	2
Total	45	26 (57%)	3 (7%)	3 (7%)	13 (29%)

Dietary management of infant with cow's milk protein allergy or intolerance

Cow's milk protein allergy (CMPA) is defined as an adverse response to cow's milk (CM) due to an immune mechanism, essentially IgE-mediated reactions. The most common antigenic components found in CM are casein, alpha-lactalbumin, beta-lactoglobulin, bovine serum albumin, and gammaglobulin. Non immunological reactions following ingestion of CM are defined as cow's milk protein intolerance (CMPI). Although CMPA/CMPI is recognized with increasing frequency, the infants and children who have adverse reactions to CM are not a homogeneous group. In various studies the incidence ranged from 0.5% to 7.5% depending on age, symptomatology, and diagnostic criteria. Most affected infants develop adverse symptoms within 3 months after feeding with CM based formula.

Strict avoidance of CM proteins is the only proven therapy for CMPA/CMPI, leading in most cases to the development of clinical tolerance before three years of age.

Hydrolysed protein formulas

These formulas, called "hypoallergenic", are prepared by enzymatic hydrolysis of the protein source: bovine casein (casein hydrolysates), whey (whey hydrolysates), soy and collagen proteins (soy and collagen hydrolysates). The rationale behind the use of protein hydrolysates is that peptides with molecular weights of less than 1000-1500 Dalton are supposed not to be allergens. However, there are several evidences that these formulas may induce adverse reactions in infants with CMPA/CMPI. The term "hypoallergenic" therefore should be considered cautiously [36].

Hydrolysed casein-based formulas. - Nutramigen and Pregestimil are hydrolysed casein-based formulas widely used in infants with CMPA/CMPI. These hydrolysates are enzimatically degraded to molecular weight less than 1500 Dalton and they have little allergenicity and antigenicity left (less than 1% of their peptides have molecular weights greater than 1500 Dalton). A well established clinical experience confirms the effectiveness of casein hydrolysates in CMPA/CMPI and only a few cases of adverse reactions to hydrolysated casein-based formulas have been reported. The problems with these highly hydrolysed formulas are unpalatability and bitterness. While they are usually accepted by young infants, older infants rarely accept them.

Hydrolysed whey-based formulas. - More recently, partially hydrolysed infant formulas based on whey protein have been used. These products are obtained by less extensive hydrolysis (Alfare', Nutrilon pepti, Pepti-Junior) or by hydrolysis associated to ultrafiltration (Hypolac) to remove any residual high molecular weight fraction; nonetheless they contain more than 15% peptides with molecular weights > 1500 Dalton, which are responsible for more frequent adverse reactions than those observed in infant with CMPA/CMPI fed a casein hydrolysate. The better taste and lower cost make these products adequate in infants with CM sensitive non IgE-mediated enteropathy. Even though these formulas are not extensively recommended in CMPA/CMPI, Halken *et al.* [37] demonstrated that an ultrafiltrated whey formula was both tolerated and effective in 35 children with verified adverse reactions to CM protein and gastrointestinal and/or extraintestinal IgE-mediated reactions.

Hydrolysed soy and collagen-based formulas. - Pregomin is the only hydrolysate from soy and collagen proteins. Despite the peptides present in this product are of molecular weigths less than 5000 Dalton, the product should be regarded as containing potential antigenic proteins. In fact, measurable amounts of casein [38] and beta-lattoglobulin [39], probably due to the preparation of the bovine collagen fraction, have been detected.

Soy-based formulas

Except for carbohydrate (soy formulas are lactose free) and protein, soy protein formulas are similar in composition to the standard infant formulas. The protein source in soy formulas, a refined soy protein isolate, is heat-treated to enhance the protein digestibility and bioavailability. Zinc, however, appears to be less biologically available in soy formula, due to the presence of phytate. Since soy protein has a lower biologic value than casein and whey, methionine has been added to improve protein quality. Carnitine, which plays an important role in oxidation of long chain fatty acid, must also be added. Soy protein antigenicity is essentially analogous to that of CM protein and soy protein allergy/intolerance has been reported in 17-47% of infants with CMPA/CMPI. However, soy-based formulas should be safer than hydrolysates and recommended as substitute for milk-based formulas in infants with severe IgE-mediated CMPA or atopic dermatitis. Soy-based formulas are considerably less expensive if compared to extensively hydrolysed formulas, and they taste better.

Amino acid-based formulas

In infants or children allergic/intolerant to "hypoallergenic" formulas, or to soy formulas, or in infants with a multiple food allergy/intolerance, an amino acid-based formula may be tolerated. These "elemental" formulas are potentially less likely to cause sensitization than those based on peptides. However, they are unpalatable, expensive, nutritionally poor, and of high osmolarity. Thus, their use in infant must be considered with caution. Recently a new infant amino acid-based formula (Nutri-Junior) has been manufactured. The main characteristics of this product are the relatively low cost, the osmolarity less than 250 mOsmol/l, the nutritional adequacy. Because of no published clinical trials, its efficacy and tolerance remain to be ascertained.

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