0148-6071/00/2406-0351$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 24, No. 6
Printed in U.S.A.

Nasogastric Tube Feeding in Children with Cancer: The Effect of Two Different Formulas on Weight, Body Composition, and Serum Protein Concentrations

Eline den Broeder, MSc*; Robert J. J. Lippens, PhD*; Martin A. van 't Hof, PhD†; Jules J. M. Tolboom, PhD*; Robert C. A. Sengers, PhD*; Anneke M. J. van den Berg‡; Nicole B. M. van Houdt‡; Zandrie Hofman, IR§; and Wija A. van Staveren, PhD‖

*From the Department of *Pediatrics and ‡Dietetics, University Hospital Nijmegen; †Department of Medical Statistics, University of Nijmegen; §Numico Research, Wageningen; and ‖Division of Human Nutrition and Epidemiology, Wageningen University Center, The Netherlands*

ABSTRACT. *Background:* Treatment of cancer cachexia partly involves the administration of adequate amounts of energy. The aim of this study was to assess the tolerance and efficacy of two equal volumes of tube feeding, one with a standard (1 kcal/mL) and one with a high energy density (1.5 kcal/mL), during the intensive phase of treatment. *Methods:* Nutritional status was assessed weekly, in 27 children with a solid tumor, by measuring weight, height, midupper arm circumference, biceps and triceps skinfold, and serum proteins. Tolerance was assessed by recording the occurrence of vomiting and by expressing the administered volume as a percentage of the required volume. *Results:* Both formulas were equally well tolerated, leading to a significantly higher energy intake in the energy-enriched formula group. In both formula groups, all anthropometric variables increased significantly (range of mean increase, 5.2% to 25.5%; $p < .05$) during the first 4 weeks of intervention. Between 4 and 10 weeks, variables continued to increase significantly in the energy-enriched group, resulting in adequate repletion, in contrast to the standard formula group. The concentration of serum proteins, low at initiation of tube feeding, returned to the normal range within 2 to 4 weeks with no significant differences between the two groups. *Conclusions:* The energy-enriched formula was more effective in improving the nutritional status of children with cancer during the intensive phase of treatment than the standard formula. Intensive, protocolized administration of an energy-enriched formula should therefore be initiated as soon as one of the criteria for initiation of tube feeding is met. (*Journal of Parenteral and Enteral Nutrition* **24**:351–360, 2000)

Cachexia is common in children with cancer and is mainly caused by a reduced oral energy intake, relative to energy expenditure. It can be present at diagnosis or develop during the intensive anticancer treatment.[1–7] This complex metabolic syndrome is characterized clinically by a progressive, involuntary loss of weight, through an accelerated breakdown of adipose and muscle tissue, and by a decrease in visceral protein concentrations.[4,6–8] The negative implications of this condition include a reduced tolerance to therapy, an impaired immune response, an increased susceptibility to infections, a delayed growth and development, a reduced state of well-being and performance, and a poorer clinical outcome.[1,2,5,9,10] The need for prevention or reversal of cachexia in children with cancer, which involves the correction of the metabolic derangements and increasing the child's energy intake, is therefore of the utmost importance and has been emphasized repeatedly in literature.[1,4,5,10–14]

Intensive nutrition counseling alone, aiming to increase the oral energy intake of a child with cancer, is incapable of preventing or reversing the development of cachexia during the intensive phase of treatment.[1,2,15] Nasogastric tube feeding and total parenteral nutrition (TPN) therefore are often used and have shown to effectively maintain or improve the nutritional status of children with cancer during the intensive phase of treatment.[2,12,16–21] However, nasogastric feeding, which has shown to be acceptable in and tolerated by children with cancer soon after diagnosis, is considered a more physiologic, safer, simpler, and more economic intervention method, which allows for a more normal life style and play activity, than TPN.[2,10,21–23] Therefore, as long as the gastrointestinal tract function is adequate, nasogastric feeding is preferred to TPN.[2,10,23]

Many tube-feeding formulas, with varying composition and energy density, are available on the market to improve the energy intake of children with cancer.[24] Their efficacy mainly depends on the feasibility of meeting the patient's energy requirements. Previous studies have shown that these energy requirements often are not met because of low infusion rates during the initial days of feeding, feeding interruptions due to medical procedures and inadvertent extubation, gastrointestinal intolerance, and suboptimal prescribed

Received for publication, October 22, 1999.
Accepted for publication, June 22, 2000.
Correspondence: Eline den Broeder, MSc, Department of Pediatrics, KOC 921, University Hospital Nijmegen, St Radboud, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Electronic mail may be sent to e.denbroeder@ckskg.azn.nl

energy goals.[19,25–27] It was suggested that careful monitoring and protocolized administration of tube feeding might diminish the incidence of complications and increase energy intake or that the volume of tube feeding may simply be increased to compensate for feeding interruptions.[19,25] However, increasing the volume may lead to a persistent failure to infuse this volume because of gastrointestinal intolerance.[21,26] Increasing the energy density of the formula may, on the other hand, increase energy intake without increasing the volume. However, hypercaloricity or hyperosmolarity may also lead to gastrointestinal side effects, due to delayed gastric emptying, and, subsequently, to a reduction in the volume and amount of energy provided, even though data on this issue vary.[24,26,28]

This study was initiated to assess the effect of short- (4 weeks) and long-term (10 weeks) administration of two equal volumes of commercially available tube-feeding formulas, one with a standard (1 kcal/mL) and one with a high energy density (1.5 kcal/mL), on the nutritional status of children with a solid tumor during the intensive phase of treatment.

Five aspects, with respect to the energy-dense and standard formulas, were studied:

1. The effect on weight, reflecting the overall nutritional status.
2. The effect on body composition, reflected in changes in skinfold thicknesses, midupperarm circumference (MUAC), and arm muscle area (AMA).
3. The effect on several serum proteins, reflecting nutritional status.
4. The occurrence of vomiting and the volume administered as a percentage of the volume required, reflecting the tolerance of the formulas.
5. Protocol adherence and dose reductions.

MATERIALS AND METHODS

Study Design

The study was a prospective, randomized, double-blind clinical trial involving a tube-feeding formula of "standard" energy density (1.0 kcal/mL, slightly adapted Nutrison Pediatric Standard; Numico N.V., Zoetermeer, The Netherlands) and a formula of "high" energy density (1.5 kcal/mL, Nutrison Pediatric Energy; Numico). The composition of both formulas was equal and differed only in that the energy-enriched formula provided 1.5 times more of every nutrient, including protein. Fifteen patients per formula group were calculated to detect a difference in nutrition effect of 6% with an $\alpha = .05$ and a power of 80%, assuming an SD of 6%.[21] Thirty formulas were randomized in pairs (block randomization), and patients were assigned a formula number in the order of inclusion into the study, after which tube feeding was initiated. The study period started at the initiation of tube feeding (week 0) and ended after 10 weeks.

Patients

All children between 1 and 18 years of age, newly diagnosed with cancer at the University Hospital Nijmegen between March 1996 and April 1998, who were expected to receive cycles of cytotoxic chemotherapy or radiotherapy during the study period, were eligible for the study. Patients were included in the study when at least one of the inclusion criteria was met and when none of the exclusion criteria were applicable. The inclusion criteria were as follows: (1) a present state of malnutrition at diagnosis that failed to or was not expected to improve within 1 week; (2) weight loss after diagnosis that was >5% from the weight at diagnosis; and (3) oral energy intake that was <80% of total energy requirements (see below).

Excluded from the study were patients who were expected to receive corticosteroids in combination with chemotherapy for >7 days, patients with an energy requirement of >3000 kcal/d, patients who received nutrition therapy at diagnosis, relapsed patients who had participated in the study before, and patients who had been intolerant to tube feeding due to chemotherapy-related gastrointestinal problems within 2 weeks of initiation of tube feeding. Only 1 patient was excluded on the basis of the last criterion. His gastrointestinal tract was severely damaged by chemotherapy (methotrexate), and he had to resort to TPN.

In total, 29 patients were included in the study, but only 27 could be used in the analysis of data, because 2 patients withdrew and were lost for follow-up. The Medical Ethics Committee of the University Hospital Nijmegen approved the study. A written informed consent was obtained from the parents of each patient entering the study.

Tube Feeding Regimen

The total daily energy requirement of each child, in kilocalories per 24 hours, was calculated weekly using the following formula[29,30]: Basal metabolic rate × (Activity factor + Illness factor − 1) × Growth factor × Absorption factor.

Basal metabolic rate (kcal/24 h), according to age, weight, and sex, was determined using the Schofield formulas.[31] The child's physical activity was described by the parents and converted into an activity factor ranging from 1.2 to 1.7, according to data from the Department of Health (London),[32] and Jacobs et al.[33] The illness and absorption factors of the children in this study were considered to be 1.[2] The growth factor, used to correct for weight loss, was determined by dividing the child's target weight for height (WFH) by the actual weight. Target WFH was determined from the child's preillness growth data available from the municipal health services and the school physician. At every point in time, up to 0.5 years before diagnosis, weight was expressed as percentage of the standard WFH (P50) according to age- and sex-specific reference percentiles.[34] The mean of all preillness WFH percentages multiplied by the P50 of weight for the actual height at diagnosis was used as target weight.

The volume of tube feeding to be administered was set to provide each child with 100% of the total daily energy requirement. However, during the study period, it was unknown whether the child received the standard or the energy-dense formula. Therefore, the volume, in milliliters, was calculated under the

assumption that all patients received the standard formula (1 kcal/mL) and, thus, equaled the total daily energy requirements of the child. Patients, who were randomized to receive the energy-enriched formula, in fact, received 150% of their daily energy requirements.

The volume was built up to full strength in 3 consecutive days. Vomiting was carefully monitored, because intractable vomiting would indicate the need for transpyloric rather than nasogastric feeding, to reduce the risk of aspiration.[27] When a child would consistently vomit above a certain volume, feeding volume was reduced to the previously tolerated level and increased when tolerance improved. Vomiting in and around periods of chemotherapy was treated with antiemetics. Furthermore, promotility agents were used, when necessary, to reduce the occurrence of gastrointestinal side effects.[28] The formula was, however, never diluted. If a child had not responded sufficiently to these measures, transpyloric feeding would have been initiated.

Tube feeding was administered at home and during hospital admission via a small bore (9F), silicone duodenal feeding tube with a weighted tip (Vygon, Ecouen, France) that was inserted into the stomach, after which proper placement was verified by auscultation over the abdomen while injecting air into the tube. During hospital admissions, tube feeding was administered by continuous infusion over a 24-hour period in all patients. At home, the feeding routine was flexible and was tailored to individual needs and possibilities, but ultimately most patients preferred, best-tolerated, and thus received feedings overnight by continuous infusion over a 10- to 12-hour period, combined with a 2-hour period of continuous infusion during the day. Nocturnal feeding was started after dinner, in order to stimulate the child to eat during dinner. For the same reason, the daytime portion was preferably administered after lunch. In some of the older children, feeding was restricted to continuous nocturnal feeding, provided the required volume could be administered, because they preferred to remove the tube during the day-time and reinsert it in the evening, for social reasons. Oral feeding was permitted *ad libitum* but did not influence the volume of tube feeding administered. All oral intake was recorded daily in a food diary. The amount (±20% of total daily energy requirements) and composition of the oral energy intake will be described in the near future.

Much effort was spent on achieving the highest compliance possible in the administration of the prescribed volume. Parents were encouraged weekly to provide their child with the prescribed volume and were allowed to call at all times if any problems occurred. To maximally compensate for feeding interruptions due to planned medical procedures, the infusion rate was temporarily increased, when tolerated, or the period of tube feeding was extended by a few hours on the day(s) before the procedure. Furthermore, parents (and children), when willing, were taught how to insert the tube in order to minimize feeding time lost because of inadvertent extubation at home.

Tolerance of the Formulas

Tolerance was assessed by expressing the administered volume of tube feeding as a percentage of the required volume and by the occurrence of vomiting. Both were recorded daily in a diary by the parents. The recorded volume administered was not corrected for vomiting. The occurrence of vomiting was divided into therapy-related, infection-related, and other cause–related and was expressed in mean number of days per week. Only the number of days on which vomiting occurred was evaluated and not the frequency per day or the volume.

Weight and Height

Weight and height measurements were performed weekly from diagnosis onward by one observer using standard techniques. Height (length for children < 2 years of age) was measured to the nearest 0.1 cm using a stadiometer (Holtain Ltd, Crymych, United Kingdom) and weight (without clothes) was determined to the nearest 0.1 kg using an electronic scale (Berkel, Ridderkerk, The Netherlands). Weight for height was expressed as a *z*-score, according to the Dutch reference values,[34] and was corrected for the child's individual target *z*-score, derived from the child's target weight. *z*-Scores below zero indicated a deviation from the child's own growth percentile, indicating weight loss and malnutrition. Malnutrition at diagnosis was defined as a weight loss of >5% from preillness body weight.

Body Composition

MUAC, triceps skinfold (TSF) and biceps skinfold (BSF) thicknesses were measured at diagnosis and at weekly intervals thereafter by one observer using standard techniques.[35,36] Skinfolds were measured in threefold to the nearest 0.1 mm using a skinfold caliper (Holtain Ltd), and the MUAC was measured to the nearest 0.1 cm using a nonstretchable tape measure, both on the nondominant arm. Upper arm muscle area (AMA) was calculated from the TSF thickness and the MUAC according to Frisancho et al.[35] Measurements of MUAC, BSF, and TSF thicknesses were expressed weekly as percentages below or above the standard (P50) of a reference population.[37] The 10th percentile of MUAC and of BSF and TSF thicknesses was considered to be the cutoff point for malnutrition, but achieving the 50th percentiles of a reference population was the only measure considered to indicate adequate repletion.[15]

Serum Proteins

Serum prealbumin, transferrin, retinol-binding protein (RBP), and albumin concentrations were determined at diagnosis, at initiation of tube feeding, and every week thereafter during the study period. During periods of fever and infection (>38°C; ±4 days), no blood samples were taken, because these factors are known to influence serum protein concentrations.[17,18,38,39] Serum protein concentrations below the lower limit of the normal range were considered to

indicate protein depletion. The normal ranges were considered to be as follows: serum prealbumin, 0.17 to 0.42 g/L; RBP, 30 to 60 mg/L; transferrin, 2.2 to 3.6 g/L; and albumin, 35 to 50 g/L.[40]

All blood samples were measured in the same laboratory, by the same technique, under quality control standards. Prealbumin, RBP, and transferrin concentrations were determined by immunonephelometry using a Cobas Fara II analyzer (Hoffmann-La Roche, Basel, Switzerland) for prealbumin and a Hyland Disc 120 Nephelometer (Hyland, Bruges, Belgium) for the other two serum proteins. Albumin concentrations in serum were determined using a Hitachi 747 spectrophotometric analyzer (Hitachi, Tokyo, Japan) and the Brom-Cresol Green method. Prealbumin, RBP, and transferrin were calibrated against the Certified Reference Material 470 (CRM-470) of the International Federation of Clinical Chemistry.

Protocol Adherence and Dose Reductions

For each patient, the number of dose reductions and delays in therapy were recorded. Per formula group, the delays and reductions were expressed as the mean over the 10-week study period.

Statistical Analysis

The statistical program used to analyze data was the SPSS (SPSS Inc, Chicago, IL). If necessary, data were log transformed before further analysis to obtain "normality." Differences in baseline characteristics were tested for significance by a *t* test, to confirm that randomization had worked. To test significant differences between means, a *t* test or Mann Whitney *U* test was used, whichever was appropriate. Relative changes in anthropometric variables and changes in serum protein concentrations after 4 and 10 weeks, within and between groups, were tested for significance by repeated-measures ANOVA (RMA). To deal with missing values, the values of 2 subsequent weeks were averaged, with the exception of the value at initiation of tube feeding. If a value were missing in 1 week, the available value in the subsequent week was used.

RESULTS

Description of the Sample and Energy Intake

A summary of patients' characteristics at initiation of tube feeding is shown in Table I. Groups were similar on baseline characteristics, because no significant differences between the groups were found for age, distribution of sex, high tumor load Ewing sarcoma or disseminated disease, and any of the anthropometric and biochemical variables.

Energy Intake by Tube Feeding

Tube feeding was initiated 2.8 ± 3.8 weeks after diagnosis in the energy-enriched formula group and after 1.6 ± 2.6 weeks (*t* test; $p = .38$) in the standard formula group. The mean daily energy intake per week, expressed as a percentage of the total daily requirements, is shown in Figure 1. Energy intake was

TABLE I
Summary of patient characteristics at initiation of tube feeding

	Tube feeding formula	
	Standard (1.0 kcal/mL)	Energy enriched (1.5 kcal/mL)
No. of patients	12	15
Age (years)*	5.7 ± 3.8	6.5 ± 4.5
Sex		
Male	5	7
Female	7	8
Diagnosis		
Nephroblastoma	4	4
Rhabdomyosarcoma	1	2
Ewing sarcoma	1	2
Neuroblastoma	1	1
Osteosarcoma	0	2
Germ cell tumor	0	1
Hepatoblastoma	1	0
Brain tumor	4	3
Patients with high tumor load and/or with disseminated disease (%)	58	60
Z-score of WFH corrected for target weight*	−1.5 ± 1.1	−1.3 ± 0.9
MUAC (%)*†	−10.4 ± 10.1	−6.8 ± 10.9
Triceps skinfold (%)*†	−29.4 ± 25.0	−28.4 ± 35.9
Biceps skinfold (%)*†	−19.7 ± 27.4	−24.2 ± 38.9

MUAC, midupper arm circumference; WFH, weight for height.
*Values are means ± SD.
†Difference from reference population.

significantly higher in the energy-enriched formula group throughout the whole study period and sufficiently covered the child's daily energy requirements, in contrast to the standard formula. A mean daily energy intake by tube feeding of 84% ± 14% of requirements was achieved in the standard formula group compared with 112% ± 15% in the energy-enriched formula group (*t* test; $p < .001$). A mean daily protein intake of 1.27 g/kg body weight was observed in the standard formula group compared with 1.54 g/kg body weight in the energy-enriched formula group. The recommended daily allowance for protein was the same for both groups, namely 1.12 g/kg body weight. The daily intake of fluids (tube feeding + *ad libitum* [in mL]), recorded at home and during hospital admission, adequately met fluid requirements in both groups.

Tolerance of the Tube-Feeding Formulas

The administered volume of tube feeding, expressed as a percentage of the required volume, is shown in Figure 1. On average, patients in the standard formula group daily received 84% ± 14% of the required volume, whereas patients in the energy-enriched formula group received 75% ± 10% (*t* test; $p = .108$) of the required volume, during the study period.

The occurrence of vomiting and the percentage of patients in which the different types of vomiting occurred are shown in Table II. A high number of days does not necessarily imply a high frequency or large volume of vomiting, because only the number of days on which vomiting occurred was taken into account. In both groups, vomiting was mainly therapy-related, with no differences between the two groups. Therapy-related vomiting responded well to the use of antiemet-

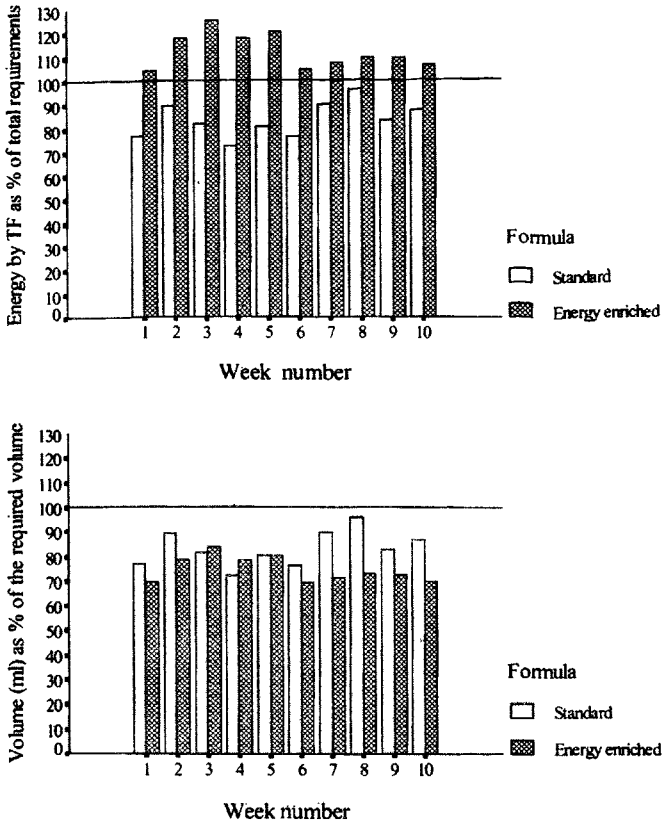

FIG. 1. Top: mean daily energy intake per week provided by tube feeding, expressed as a percentage of the total daily energy requirements; bottom: mean daily volume of tube feeding administered per week, expressed as a percentage of the required volume.

ics, and its occurrence was significantly higher than that of infection-related vomiting and vomiting related to other causes ($p \leq .001$). Only the occurrence of infection-related vomiting was significantly different between the two groups. The total occurrence of vomiting was not significantly different.

Diarrhea did not seem to be an adverse side effect of tube feeding in any of the children. In most children, however, stools were less solid than usual during the period of tube feeding. In the younger children (<3 years), diarrhea was present during the first weeks of administration, after which it disappeared.

TABLE II
The occurrence of vomiting, by cause, and the percentage of patients in which that type of vomiting was observed

Cause of vomiting	Formula	
	Standard	Energy enriched
Therapy related	2.2 ± 1.1 (100)	2.0 ± 0.6 (100)
Infection related	0.1 ± 0.2 (33)	0.5 ± 0.5 (73)*
Other	0.6 ± 0.6 (67)	0.7 ± 0.6 (80)

Values are the mean number of days per week, with the percentage of patients in parentheses. Only the number of days on which vomiting occurred were evaluated and not the frequency per day or the vomited volume.
*$p < .05$ (*t*-test).

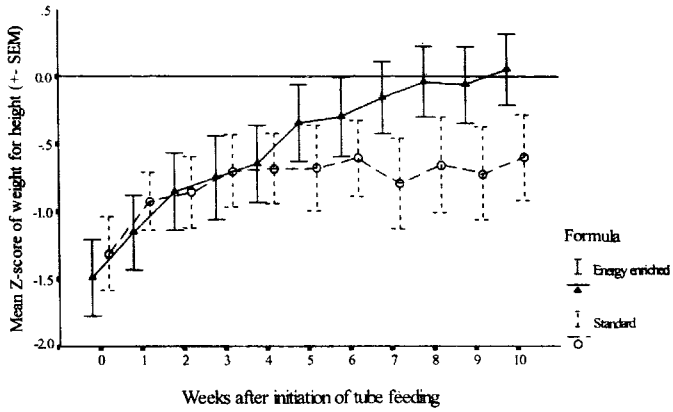

FIG. 2. Changes in *z*-score of weight for height in the standard and the energy-enriched tube-feeding formula group during 10 weeks of nasogastric tube feeding. The increase in *z*-score in the energy-enriched formula group was significantly higher than the increase in the standard formula group (repeated-measures ANOVA between groups: $p = .006$).

Weight

Changes in the *z*-score (±SEM) of WFH are illustrated in Figure 2. During the first 4 weeks of tube feeding, the *z*-score increased significantly in both formula groups (RMA; $p = .003$ and $p = .002$, in the standard and energy-enriched formula groups, respectively) with no significant difference between the two groups. Between 4 and 10 weeks, the *z*-score of WFH continued to increase significantly in the energy-enriched formula group (RMA; $p = .003$), whereas the increase in the standard formula group was no longer significant. This ultimately resulted in a significantly higher increase in *z*-score of WFH in the energy-enriched formula group, compared with the standard formula group after 10 weeks of tube feeding (RMA; $p = .006$). During these 10 weeks WFH "normalized" in the energy-enriched formula group but not in the standard formula group (Fig. 2). In the energy-enriched formula group, 11 (73%) of 15 patients increased their *z*-score from below to above zero, compared with 2 (17%) of 12 patients in the standard formula group.

Body Composition

Changes in MUAC and in BSF and TSF thicknesses, relative to the reference population, are shown in Figure 3. During the first 4 weeks of tube feeding a significant increase in MUAC, BSF, and TSF thicknesses (RMA; $p \leq .001$) was observed in both formula groups, with no significant differences between the two groups. Between 4 and 10 weeks of tube feeding, however, these variables continued to increase significantly in the energy-enriched formula group (RMA; $p \leq .001$), in contrast to the standard formula group, where BSF and TSF thicknesses remained stable or even decreased, and MUAC increased only slightly (RMA; $p = .05$). This ultimately resulted in a significantly higher increase in MUAC, BSF, and TSF thicknesses, in the energy-enriched formula group, compared with the standard formula group, after 10 weeks of tube feeding. In the energy-enriched formula group MUAC,

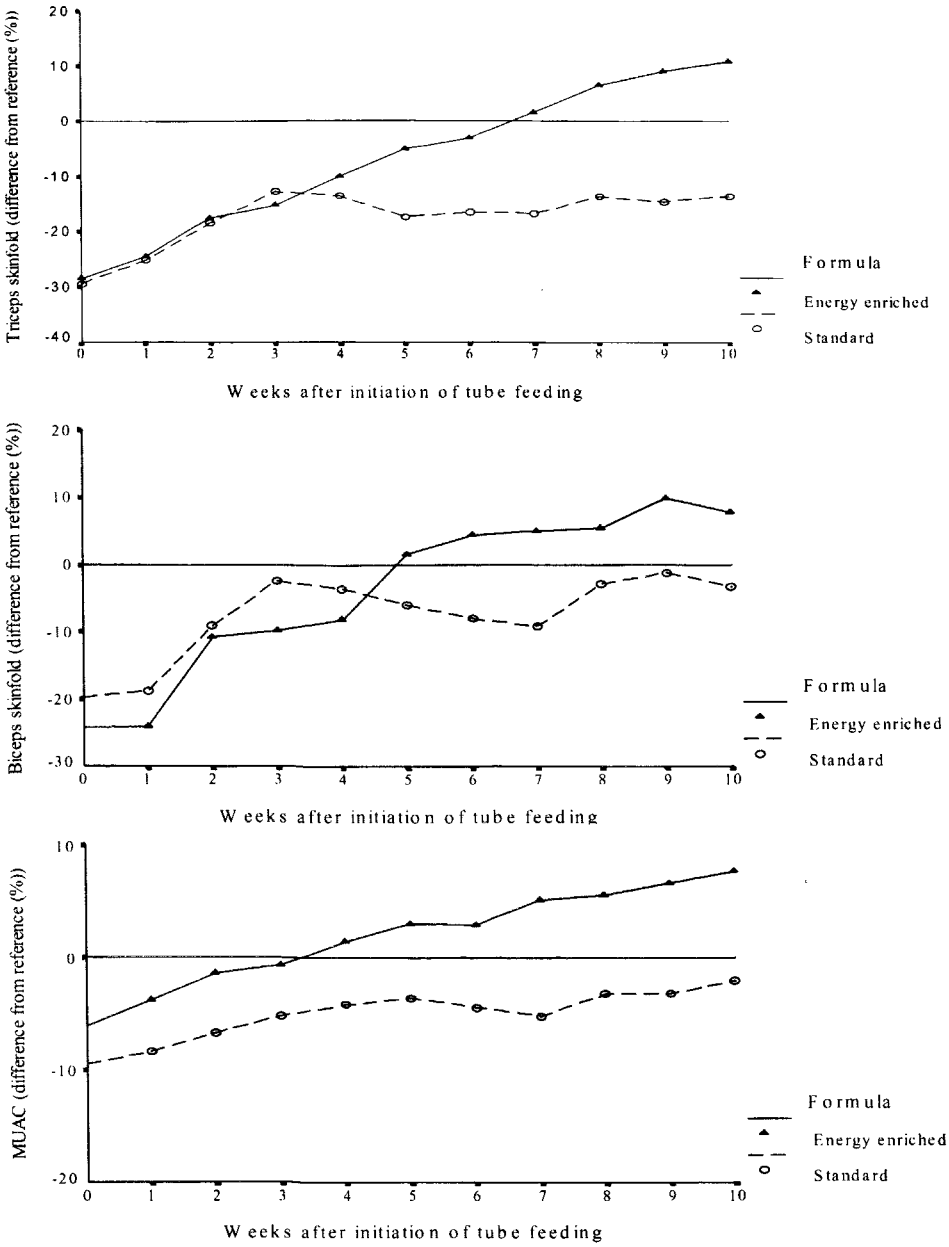

FIG. 3. Changes in triceps and biceps skinfolds (top and middle, respectively) and in midupperarm circumference (MUAC; bottom) in the standard and the energy-enriched tube-feeding formula group, during 10 weeks of nasogastric tube feeding, expressed as percentage under or above the reference value (P50). The increase of these three anthropometric variables were all significantly higher in the energy-enriched formula group, compared with the standard formula group (repeated-measures ANOVA between groups: $p = .002$, $p = .004$, and $p < .001$, respectively).

TSF, and BSF thicknesses normalized after 4, 7, and 5 weeks, respectively, whereas these variables all remained below the standard (P50) in the standard formula group.

TABLE III
Relative changes in arm muscle area in children with solid tumors after 4 and 10 weeks of nasogastric tube feeding

Time interval (weeks)	Relative change in AMA (%)		p^*
	Standard formula	Energy enriched formula	
0–4	8.4 ± 12.8†	12.8 ± 9.5†	.341
0–10	14.9 ± 10.1†	20.7 ± 8.4†	.013
4–10	6.5 ± 10.7	7.9 ± 6.8†	.923

Values are means ± SD. AMA, arm muscle area.
*p value repeated-measures ANOVA for difference between standard and energy-enriched formula.
†Significant increase within group (repeated-measures ANOVA; $p <$ .05).

Relative changes in AMA and their significance are shown in Table III. Significant increases were observed in both groups during the first 4 weeks and were followed by an additional significant increase, between 4 and 10 weeks, in the energy-enriched formula group. This was in contrast to the standard formula group in which only a borderline significant increase was observed ($p = .06$). Ultimately, after 10 weeks of tube feeding, the increase in AMA appeared significantly higher in the energy-enriched formula group.

Protocol Adherence and Dose Reductions

Delays in chemotherapy occurred in 3 (25%) of 12 patients in the standard formula group, compared with 6 (40%) of 15 patients in the energy-enriched formula group. The mean number of delays was not significantly different between the two groups. Dose reductions did not occur, during the study period, in any of

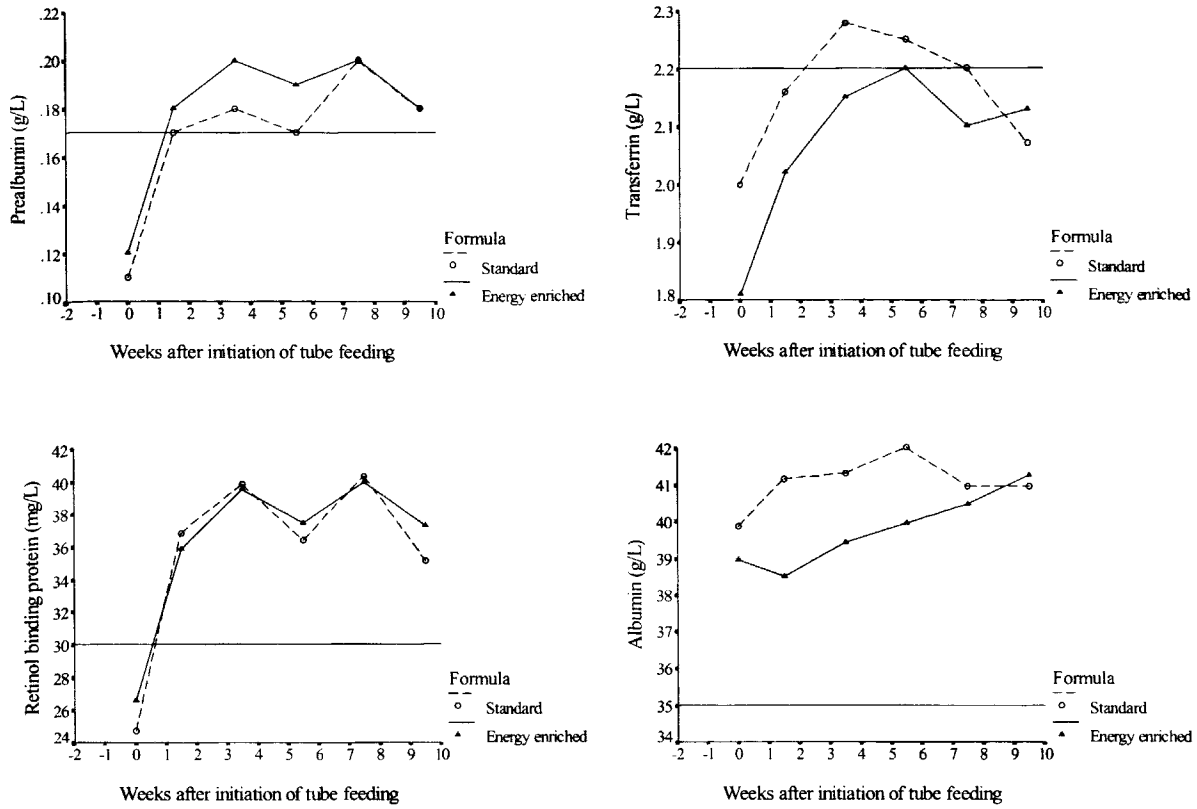

FIG. 4. Changes in serum prealbumin, transferrin, retinol binding protein and albumin concentrations in the standard and the energy-enriched formula group, during 10 weeks of nasogastric tube feeding. All serum proteins increased significantly during the first 2 to 4 weeks (RMA; $p < .05$) with no significant differences between the two groups. The lower limit of the normal range is shown for each serum protein (horizontal line).

the patients in the energy-enriched formula group and in only 1 patient in the standard formula group.

Serum Proteins

Changes in mean serum prealbumin, transferrin, RBP, and albumin concentrations during 10 weeks of nasogastric tube feeding are shown in Figure 4. Between the two formula groups, no significant differences were observed in the concentrations at initiation of tube feeding and in the changes of the serum proteins after initiation of tube feeding. At initiation of tube feeding serum prealbumin, transferrin, and RBP concentrations were below the lower limit of the normal range in both groups. During the first 2 weeks, serum prealbumin and RBP concentrations had increased into the normal range in both groups ($p < .02$), after which no significant changes occurred. Serum transferrin concentrations increased significantly within 2 weeks in the energy-enriched formula group and within 4 weeks in the standard formula group and continued to increase until 6 weeks after initiation of tube feeding. After this initial increase, serum transferrin concentrations decreased in both groups. Serum albumin concentrations increased in both groups, but the increase was within the normal range.

DISCUSSION

The results of this study show that long-term administration (10 weeks) of an energy-enriched tube-feeding formula (1.5 kcal/mL) is needed to adequately improve both weight and body composition in children with cancer during the intensive phase of treatment. To our knowledge no data are available comparing the effect of two different tube-feeding formulas on the nutritional status of children with cancer during this period. Because previous studies have shown that the absence of nutrition support will lead to a deterioration of nutritional status in most children with cancer,[1,2,15] a control group without nutrition support was not added for ethical reasons.

Because of the double-blind, randomized nature of the study, it was not possible to provide equal caloric levels, so equal volumes were provided. As was to be expected from previous studies,[19,25–27] a compliance of 100% of the prescribed volume was not achieved, despite careful monitoring and protocolized administration. These measures may, however, have increased compliance (and thus energy intake), because approximately 84% of the prescribed volume of standard (isotonic) formula was administered in this study, compared with 67% in a study by Keohane et al.[26] Furthermore, in a study by Abernathy et al,[25] only 61% of the required amount of energy was administered compared with approximately 98% (mean of both groups) in this study.

Compliance was not significantly different between the two groups (84% *vs* 75%). We may, therefore, conclude that, compared with the standard formula, the increased energy density of the energy-enriched for-

mula did not lead to an increase in gastrointestinal side effects, due to which the volume administered has to be significantly reduced. Together with the fact that the occurrence of vomiting was not significantly different between the two groups, our data confirm findings from Keohane et al,[26] which showed that no difference in gastrointestinal intolerance was appreciated between hyperosmolar and isotonic formulas. A hyperosmolar formula, therefore, led to a higher energy intake (when volumes are equal),[26] which, naturally, resulted in superior nutritional repletion (in this study).

Even though all types of vomiting (ie, therapy-related, infection-related, and other cause–related) occurred in the majority of patients, vomiting was not troublesome. This confirmed data from other studies that found nasogastric tube feeding to be acceptable in and tolerated by children with cancer, during intensive chemotherapy or bone marrow transplantation.[21,41] Vomiting responded well to antiemetic therapy, reductions in volume of feeding, and the use of promotility agents. We believed that vomiting was, by no means, intractable and did not significantly increase the risk of aspiration. Therefore, there was no need to initiate transpyloric feeding in any of the patients.[27]

Studies of body composition in cancer patients have demonstrated that body fat is the major component of weight loss[4,7,8,42] as compensatory mechanisms protect the body proteins, by reducing the need to use them as a source of energy, at the expense of body fat.[43] When fat stores are used up, protein wasting continues and becomes markedly accelerated with all the coinciding negative implications.[2,14,43,44] It is, therefore, imperative to maintain adequate body fat stores or to restore depleted body fat stores throughout the initial, intensive phase of treatment. Along with the achievement of a body weight greater than the child's target weight, this is one of the general goals of nutrition support in children with cancer.[2,9,11,45]

In the energy-enriched formula group both general goals of nutrition support were attained after 10 weeks. Energy and protein intakes were sufficient for metabolism, restoration of weight loss, repletion of fat stores, and an increase in muscle protein mass during the initial, intensive phase of treatment. The increase in skinfold thicknesses did not lead to excessive fat, inasmuch as skinfold thicknesses did not exceed the standard (P50) by >10%, which was considered extra energy storage during periods of intensive therapy. In the standard formula group both weight and fat reserves were not adequately restored after 10 weeks. Between 4 and 10 weeks of tube feeding, energy intake was not enough to meet metabolic demands, inasmuch as skinfolds decreased slightly. Apparently, fat stores were used as additional source of energy in order to spare the use of protein, even though protein intake was more than sufficient. This resulted in an increase in muscle protein mass concomitant with a decrease in fat stores, as can be concluded from the borderline increase in AMA and MUAC between 4 and 10 weeks. A similar observation was described by Fomon et al.[46] A low energy reserve due to insufficient repleted fat stores and a continuation of the slight decrease in fat stores would eventually lead to accelerated wasting of muscle proteins.

These data do not necessarily imply that the standard formula *per se* is inferior to the energy-enriched formula. A greater provision of nutrients by the standard formula, due to an increase in volume, might have resulted in a weight gain similar to the weight gain achieved by the energy-enriched formula. However, in this group of patients during this phase of treatment, the administered volume of standard formula was incapable of meeting energy requirements, indicating a maximum in the tolerated volume. Volume appears to be the main determinant of tolerance and not energy density, as has been assumed.[26] Therefore, increasing the energy intake via the standard formula by increasing the volume, would, with the current administration schedules, not be tolerated. Smith et al[21] also found that large volumes of isotonic nasogastric feedings were not well tolerated in children with cancer. The volume and efficacy of the standard formula might, however, increase during another phase treatment or in children with a disease other than cancer.

Continuation of tube feeding in the energy-enriched formula group after 10 weeks would probably result in an excess of weight and fat. It is, therefore, recommended to decrease the volume of energy-enriched tube feeding to the extent that the administered energy is able to maintain the child's individual WFH percentile, with corresponding body fat stores and muscle protein mass.

Because of the absence of reference data for AMA in Dutch children, it is difficult to comment on the degree of muscle protein depletion at initiation of tube feeding. American reference data, which are available, have to be applied with caution, because it is not known whether the body composition of American children resembles that of Dutch children. If, however, these reference values were applied to our data, these would show that, at initiation of tube feeding, the use of protein as an energy store had indeed been minimized at the expense of fat stores, because AMA was only slightly below the AMA of the reference population (data not shown) in the presence of considerably depleted skinfold thicknesses.

Because preillness data on weight and height were available for all the children in the study, we used the child's WFH percentile by history to determine weight loss at diagnosis and the target weight for nutrition support. We found this approach to be more accurate than using the 50th percentile of WFH of a healthy reference population for all children. Children who, for instance, have always been on the 10th or 90th percentile of WFH would be assigned a target weight above or below the target weight according to their individual growth percentile, and weight loss would not be accurately assessed. For MUAC, BSF, and TSF thicknesses, reference data from a healthy population were used to provide information on the degree of depletion, because no preillness data were available for these variables.

In children with cancer, body weight can be influenced by edema, fluid retention, and tumor mass.

These factors can mask the loss of fat and skeletal muscle.[3,47] The upper limb is not directly influenced by tumor mass or edema and can, therefore, be used as additional method to provide a more accurate and complete characterization of body composition. Biceps and triceps skinfold measurements provide an estimate of the body's fat reserves, whereas arm muscle area can serve as estimate of muscle protein reserves.[3,10,15,20,35–37,47] As in a study by Rickard et al[16] using parenteral nutrition, our data suggest that a combined evaluation of AMA and changes in skinfolds can provide important information on the efficacy of tube feeding.

Tumor mass may also influence (the rate of) changes in nutritional status through its influence on metabolism. It was, however, beyond the scope of this study to elaborate further on this issue. Because of the randomized nature of the study, it was assumed that tumor load was equally divided between the two formula groups and was, therefore, not considered responsible for the observed difference in efficacy. The effect of the tumor on basal metabolic rate (BMR) was, however, studied in another group of children with solid tumors, who were considerably older than the children in this study. These data, which showed BMR to be increased at diagnosis, will be described elsewhere.

Data from other studies suggest that nutrition support may attenuate bone marrow suppression and improve chemotherapy tolerance. Furthermore, it may improve immune competence and reduce the occurrence of infections.[2,48] In this study, however, no difference in treatment delays and dose reductions was observed between the two formula groups, and occurrence, in general, was low. This may be explained by the fact that most patients were included in the study during the first stage of therapy, whereas treatment delays and dose reductions are more likely to occur during the later stages of therapy after a number of chemotherapy courses have been administered. This is confirmed by the fact that patients with treatment delays had already received more bone marrow suppressive chemotherapy courses before being entered into the study than patients in which no treatment delays were observed. Patients in whom treatment delays did occur were included into the study, approximately 5.0 $\pm$ 3.9 weeks after diagnosis, whereas patients without treatment delays were included after 1.0 $\pm$ 1.8 weeks ($p < .05$).

Serum proteins are generally considered to be sensitive indicators of protein energy malnutrition. Several studies have shown serum prealbumin, transferrin, and RBP to be low in children with cancer.[12,17,18] With their short half-lives, these serum proteins react rapidly to changes in protein or energy intake,[1,18,38] and they have been shown to increase in response to TPN and nasogastric tube feeding.[12,17,18] Because no difference was found between the two formula groups in the response of the serum proteins, it can be concluded that the amount of energy required to replete serum proteins is less than the amount needed to replete anthropometric variables. The additional energy that is provided by the energy-enriched formula compared with the standard formula does not contribute to an additional increase in serum protein concentrations.

As the general effects of malnutrition in patients with cancer are no different from those seen in noncancer patients, malnutrition should be prevented in all groups of patients. These data might, therefore, be of use in children who are malnourished because of causes other than cancer. Children with the human immunodeficiency virus, for instance, have increased energy requirements compared with healthy children. A study assessing the effects of nasogastric tube feeding in this group of children showed that tube feeding was able to improve weight and arm fat area but was unable to significantly increase AMA even though tube feeding was administered over a mean period of 8.5 months.[49] Administration of the energy-enriched formula in these patients might result in a more rapid improvement of nutritional status, including a significant improvement of muscle proteins.

It is concluded from this study that during intensive anticancer treatment, the tolerance of an energy-enriched tube-feeding formula is not significantly different from that of a standard formula. However, the tolerated volume of standard formula was not able to provide the child with its total daily energy requirements. Because of the increased energy density, the same volume of energy-enriched formula was able to meet the child's energy requirements and compensate for energy lost because of feeding interruptions and intolerance. The long-term administration of an energy-enriched formula (1.5 kcal/mL) is, therefore, more effective than a standard formula (1 kcal/mL) in improving the nutritional status of children with cancer during the intensive phase of treatment, as this study clearly demonstrates. We, therefore, recommend that intensive, protocolized administration of an energy-enriched tube-feeding formula, calculated at 150% of the child's total daily energy requirements, is initiated and continued for at least 10 weeks in children with solid tumors as soon as one of the inclusion criteria is met.

ACKNOWLEDGMENTS

We thank Numico Research BV for their financial support and for the preparation and distribution of the nasogastric tube-feeding formulas.

REFERENCES

1. Eys van J: Malnutrition in children with cancer. Cancer 43:2030–2035, 1979
2. Mauer AM, Burgess JB, Donaldson SS, et al: Special nutritional needs of children with malignancies: A review. JPEN 14:315–324, 1990
3. Smith DE, Stevens MCG, Booth IW: Malnutrition at diagnosis of malignancy in childhood: Common but mostly missed. Eur J Pediatr 150:318–322, 1991
4. Kern KA, Norton JA: Cancer cachexia. JPEN 12:286–298, 1988
5. Andrassy RJ, Chwals WJ: Nutritional support of the pediatric oncology patient. Nutrition 14:124–129, 1998
6. Grant MM, Rivera LM: Anorexia, cachexia, and dysphagia: the symptom experience. Semin Oncol Nurs 11:266–271. 1995
7. Keller U: Pathophysiology of cancer cachexia. Support Care Cancer 1:290–294, 1993
8. Toomey D, Redmond HP, Bouchier-Hayes D: Mechanisms mediating cancer cachexia. Cancer 76:2418–2426, 1995

9. Rickard KA, Loghmani ES, Grosfeld JL, et al: Short- and long-term effectiveness of enteral and parenteral nutrition in reversing or preventing protein-energy malnutrition in advanced neuroblastoma. Cancer 56:2881–2897, 1985
10. Lukens JN: The use of nutritional therapy. J Pediatr Hematol Oncol 3:261–265, 1984
11. Rickard KA, Coates TD, Grosfeld JL, et al: The value of nutrition support in children with cancer. Cancer 58:1904–1910, 1986
12. Rickard KA, Jaeger Godshall B, Loghmani ES, et al: Integration of nutrition support into oncologic treatment protocols for high and low nutritional risk children with Wilms' tumor. Cancer 64:491–509, 1989
13. Tyc VL, Vallelunga L, Mahoney S, et al: Nutritional and treatment-related characteristics of pediatric oncology patients referred or not referred for nutritional support. Med Pediatr Oncol 25:379–388, 1995
14. Coates TD, Rickard KA, Grosfeld JL, et al: Nutritional support of children with neoplastic diseases. Surg Clin North Am 66:1197–1212, 1986
15. Rickard KA, Grosfeld JL, Coates TD, et al: Advances in nutrition care with neoplastic diseases: A review of treatment, research, and application. J Am Diet Assoc 12:1666–1676, 1986
16. Rickard KA, Corcoran Becker M, Loghmani E, et al: Effectiveness of two methods of parenteral nutrition support in improving muscle mass of children with neuroblastoma or Wilms' tumor. Cancer 64:116–125, 1989
17. Howanietz H, Thun-Hohenstein L, Haschke F, et al: Protein-malnutrition bei padiatrischen patienten mit onkologischen erkrankungen. Klin Padiatr 199:73–76, 1987
18. Young VR, Sergio Marchini J, Cortiella J: Assessment of protein nutritional status. J Nutr 11:1496–1502, 1990
19. Broeder den E, Lippens RJJ, van 't Hof MA, et al: Effects of naso-gastric tube feeding on the nutritional status of children with cancer. Eur J Clin Nutr 52:494–500, 1998
20. De Vries EGE, Kreumer WMT, Schippers DL, et al: Tube feeding of cancer patients treated with chemotherapy. Med Oncol Tumor Pharmacother 2:219–224, 1985
21. Smith DE, Handy DJ, Holden CE, et al: An investigation of supplementary naso-gastric feeding in malnourished children undergoing treatment for malignancy: Results of a pilot study. J Hum Nutr Diet 5:85–91, 1992
22. Mainous MR, Block EFJ, Deitch EA: Nutritional support of the gut: How and why. New Horiz 2:193–201, 1994
23. Leite HP, De Carvalho WB, Grandini S: Nasoduodenal feeding of the critically ill child. Rev Paul Med 110:124–130, 1992
24. Culpepper-Morgan JA, Kim K, Floch MH: Using enteral nutrition formulas. Gastroenterologist 1:143–157, 1993
25. Abernathy GB, Heizer WD, Holcombe BJ, et al: Efficacy of tube feeding in supplying energy requirements of hospitalized patients. JPEN 13:387–391,1989
26. Keohane PP, Attrill H, Love M, et al: Relation between osmolality of diet and gastrointestinal side effects in enteral nutrition. Br Med J 288:678–680, 1984
27. Fuchs GJ: Enteral support of the hospitalized child. IN Textbook of Pediatric Nutrition, 2nd ed., Suskind RM, Lewinter-Suskind L (eds). Raven Press, Ltd, New York, 1993, pp 239–246
28. Bowling TE, Silk DBA: Enteral feeding—problems and solutions. Eur J Clin Nutr 48:379–385, 1994
29. Hohenbrink K, Nicol JJ: Pediatrics. IN Nutrition Support Dietetics, 2nd ed., Gottschlich MM, Matarese LE, Shronts EP (eds). American Society for Parenteral and Enteral Nutrition, Silver Spring, MD, 1993, pp 163–197
30. Peterson KE: Failure to thrive. IN Handbook of Pediatric Nutrition, Queen PM, Lang CE (eds). Aspen Publishers, Gaithersburg, MD, 1993, pp 366–383
31. Schofield WN: Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 39(S):5–41, 1985
32. Department of Health: Report on Health and Social Subjects. Dietary reference values for food, energy and nutrients for the United Kingdom. HMSO, London, 1991
33. Jacobs DO, Albina FE, Bernard MA: Energy requirements. IN Atlas of Nutritional Support Technique, Rombeau JL, Caldwell MD, Forlaw L (eds). Little, Brown and Company, Boston, 1989, pp 54–57
34. Fredriks AM, van Buuren S, Burgmeijer RJF, et al: Continuing positive secular growth change in The Netherlands 1955–1997. Pediatr Res 47:316–323, 2000
35. Frisancho AR, Tracer DP: Standards of arm muscle by stature for the assessment of nutritional status of children. Am J Phys Anthropol 73:459–465, 1987
36. Frisancho AR: New norms of upper limb fat and muscle areas for the assessment of nutritional status. Am J Clin Nutr 34:2540–2545, 1981
37. Gerver WJM, de Bruin R: Paediatric Morphometrics: A Reference Manual. Bunge, Utrecht, 1996
38. Ingenbleek Y, van den Schrieck HG, De Nayer P, et al: Albumin, transferrin and the thyroxine binding prealbumin/retinol-binding protein (TBPA-RBP) complex in the assessment of malnutrition. Clin Chim Acta 63:61–67, 1975
39. Merritt RJ, Kalsch M, Roux LD, et al: Significance of hypoalbuminemia in pediatric oncology patients: Malnutrition or infection? JPEN 9:303–306, 1985
40. Uderzo C, Rovelli A, Bonomi M, et al: Nutritional status in untreated children with acute leukemia as compared with children without malignancy. J Pediatr Gastroenterol Nutr 23:34–37, 1996
41. Pietsch JB, Ford C, Whitlock JA: Naso-gastric tube feeding in children with high-risk cancer: A pilot study. J Pediatr Hematol Oncol 21:111–114, 1999
42. Heymsfield SB, McManus CB: Tissue components of weight loss in cancer patients. A method of study and preliminary observations. Cancer 55:238–249, 1985
43. Jeejeebhoy KN, Meguid MM: Assessment of nutritional status in the oncologic patient. Surg Clin North Am 66:1077–1090, 1986
44. Yoshida SH, Keen CL, Ansari AA: Nutrition and the immune system. IN Modern Nutrition in Health and Disease, 9th ed, Shils ME, Olson JA, Shike M (eds). Lippincott, Williams and Wilkins, Baltimore, 1999, pp 725–747
45. Daley SE, Pearson ADJ, Craft AW, et al: Whole body protein metabolism in children with cancer. Arch Dis Child 75:273–281, 1996
46. Fomon SJ, Filer LJ, Ziegler EE, et al: Skim milk in infant feeding. Acta Pediatr 66:17–30, 1977
47. Heymsfield SB, Baumgartner RN, Pan S: Nutritional assessment of malnutrition by anthropometric methods. IN Modern Nutrition in Health and Disease, 9th ed, Shils ME, Olson JA, Shike M (eds). Lippincott, Williams and Wilkins, Baltimore, 1999, pp 903–921
48. Broeder den E, Lippens RJJ, van 't Hof MA, et al: Association between the change in nutritional status in response to tube feeding and the occurrence of infections in children with a solid tumour. Pediatr Hematol Oncol 17:1–9, 2000
49. Henderson RA, Saavedra JM, Perman JA, et al: Effect of enteral tube feeding on growth of children with symptomatic human immunodeficieny virus infection. J Pediatr Gastroenterol Nutr 18:429–434, 1994