

Transplantation in children

Energy expenditure in children undergoing hematopoietic stem cell transplantation

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Summary:

Prior studies suggest that patients undergoing hematopoietic stem cell transplantation (HSCT) for malignancy have nutritional needs that are greater than their estimated needs. To determine whether energy estimation equations accurately predict energy expenditure of pediatric patients undergoing HSCT, we prospectively compared the estimated energy expenditure (EEE) and measured energy expenditure (MEE) of 40 patients at four time-points. We also investigated whether energy requirements changed during the transplant period. MEE was determined by indirect calorimetry. Data from 34 patients (autologous HSCT = 10, allogeneic HSCT = 24) were sufficient for analysis. The World Health Organization equation adequately approximated MEE only on day 14 after HSCT. At all other time-points, measured energy expenditure was significantly less than estimated energy expenditure obtained by using the WHO equation (applicable to all patients), the Seashore equation (for patients <15 years of age; $n = 19$), or the Harris-Benedict equation (for patients ≥ 15 years of age; $n = 15$). The median measured energy expenditure varied significantly over the study period and was greatest on day 14 after HSCT. Until accurate equations have been identified for estimating these patients' needs, the use of indirect calorimetry may be medically warranted.

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Medical nutrition therapy is an important part of the management of hematopoietic stem cell transplantation (HSCT) in children. During the transplant period, numerous factors can alter nutritional requirements. First, the intense chemotherapy and, in some cases, radiation given before transplantation may cause tissue damage, mucositis, nausea and vomiting, and diarrhea, any of which may increase caloric requirements or lead to protein catabolism.^{1–3} Second, graft-versus-host disease (GVHD), which often follows allogeneic HSCT, may increase energy requirements and lead to a negative nitrogen balance.⁴ Third, the energy requirements of children are increased by the demands of physical growth. Therefore, the goals of medical nutrition therapy in this patient population are to restore or maintain lean body mass, to provide the nutrients needed for recovery of the hematopoietic and immune systems, and to facilitate normal growth and development.⁵

Prior studies, most of which were conducted in adults undergoing HSCT, revealed that energy needs change throughout the course of transplantation and that patients appear to expend more energy than is estimated by standard predictive equations.^{4,6,7} Energy expenditure may be determined by standard estimation equations and through the use of indirect calorimetry. Indirect calorimetry can be extremely useful in the daily nutritional management of hospitalized patients who are at risk for nutritional depletion and who may be suffering from catabolic stress as a result of infection, trauma, or treatment complications.⁸ To date, the energy requirements of pediatric patients undergoing HSCT have not been systematically studied. We prospectively compared the estimated resting energy expenditure (EEE) of these patients to their measured resting energy expenditure (MEE) at four time-points during the transplant period to determine whether the standard methods used to estimate caloric needs are adequate for this patient population. We also investigated whether energy requirements changed during the transplant period.

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Patients and methods

Patients

This study was approved by the St Jude Children's Research Hospital Institutional Review Board. All patients undergoing autologous or allogeneic hematopoietic stem cell transplantation (HSCT) at St Jude between July 1993 and July 1996 were eligible for the study. Patients were randomly recruited prospectively depending upon availability of staff and the indirect calorimetry equipment, while attempting to include a variety of preparative regimens and donor types. Patients who were unable to comply with the indirect calorimetry procedures (maintain a steady state of breathing through the mouth apparatus), who required respiratory support or supplemental oxygen, or who had a Karnofsky/Lansky Performance Score <70 were excluded.

Autologous transplantation

During the period of this study, all patients at our institution who had acute myelogenous leukemia (AML) and who lacked an HLA-identical sibling donor received induction chemotherapy followed by autologous HSCT in first remission. Patients with recurrent chemosensitive non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD) also underwent autologous HSCT. At the time of stem cell collection, patients had no detectable marrow disease. Bone marrow (more than 1.0×10^8 nucleated cells/kg) was harvested from bilateral posterior iliac crests. Patients with AML or HD received a pretransplant regimen of 16×1 mg/kg doses of busulfan (total dose 16 mg/kg) and four 50 mg/kg doses of cyclophosphamide (total dose 200 mg/kg) with mesna uroprotection.⁹ Patients with NHL received three 700 mg/m² doses of carboplatin (total dose 2100 mg/m²) and three 500 mg/m² doses of etoposide (total dose 1500 mg/m²).¹⁰

Allogeneic transplantation

Patients received a pretreatment regimen of six 3 g/m² doses of cytarabine (total dose 18 g/m²) and two 45 mg/kg doses of cyclophosphamide (total dose 90 mg/kg), with 9 mg/kg mesna administered before and 3, 6, 9 and 12 h after each dose of cyclophosphamide (total dose 45 mg/kg).¹¹ They also received total-body irradiation in eight fractions, to a total dose of 12 Gy (matched sibling donor) or 14 Gy (unrelated or haploidentical family member donor). Antithymocyte globulin was administered to enhance immunosuppression in five patients whose donors were unrelated or were mismatched family members. Bone marrow from mismatched family members or unrelated donors was depleted *ex vivo* of approximately 1.5 logs of T lymphocytes by use of monoclonal antibodies to CD6 and CD8 plus rabbit complement.¹⁰ Two days before transplantation, all recipients began receiving cyclosporin A, at dosages adjusted to produce plasma levels of 200–350 ng/ml. Patients who had matched sibling donors received additional GVHD prophylaxis with pentoxifylline or a short course of methotrexate. Engraftment was considered

to have occurred on the first of 3 consecutive days of an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9/l$. Acute and chronic GVHD were graded according to standard criteria.¹²

Estimation and measurement of resting energy expenditure

Energy expenditure was estimated and measured after admission to the hospital, 3 or fewer days before transplantation. Energy expenditure was also measured on days +7, +14 and +21 after transplantation. Estimated energy expenditure remained constant during this period, because the variables used in the equations (age, sex and weight) did not change. EEE was estimated by using the Seashore equation (SEA)¹³ for patients <15 years of age and the Harris-Benedict (HB) equation¹⁴ for patient's ≥ 15 years of age. The World Health Organization (WHO) equations¹⁵ were used for all patients. Energy expenditure was measured by indirect calorimetry with an MGS System 2001 breath-by-breath analyzer (Medical Graphics Corporation, St Paul, MN, USA). Energy measurements were obtained in the patients' rooms between 7:00 and 8:00 a.m. by the same certified pulmonary clinician. Measurements were obtained during a 15- to 30-min steady-state period. Patients were awake and lying supine. At least 2 h had elapsed since ingestion of any nutrients or change in parenterally delivered nutrients, and at least 1 h had elapsed since the completion of activities such as chest physiotherapy, physical therapy, and nursing procedures. While patients breathed through the mouthpiece, the volume and the oxygen (O₂) and carbon dioxide (CO₂) concentration of expired air were measured. The respiratory quotient (RQ), which is ratio of CO₂ expired to the amount of oxygen inspired, was measured by indirect calorimetry at the time resting energy expenditure was obtained. RQ was used as an indicator of appropriate calorie intake.^{16,17} Patients were considered to be overfed (ie to be receiving excessive calories) if the RQ was >1 at the time MEE was obtained and the total calorie intake was greater than the MEE.^{16,17}

Nutrition support assessment

Oral nutrient intake was estimated from dietary intake records by using the CBORD Diet Analyzer, version 3.0.4 (CBORD Group, Ithaca, NY, USA). Parenteral nutrition support was initiated when oral intake was <50% of estimated needs on 3 consecutive days. Parenteral nutrition was initiated and managed on the basis of the institution's Metabolic Infusion Support Service guidelines. Nutrient intake (total calories and grams of protein per day consumed or provided parenterally) was recorded on each day MEE was obtained. The nutritional status of each patient was determined before the first measurement and at the time of the last measurement of resting energy expenditure, and the results were compared to detect changes in nutritional status. Patients were classified as adequately nourished if they met two of the following criteria: 90% ideal body weight, serum albumin >35 g/l, weight loss <5%. They were considered depleted or inadequately nourished if they met two of the following criteria: 81–90% of ideal body

weight, serum albumin 32–35 g/l, weight loss 5–10%. They were considered severely depleted or severely inadequately nourished if they met two of the following criteria: <80% ideal body weight, serum albumin <32 g/dl, weight loss >10%.¹⁸

Statistical analysis

We used the exact one-sample binomial test¹⁹ to assess the extent of agreement between MEE and EEE obtained by using the predictive equations. An EEE value was considered acceptable if it fell within ±10% of the MEE in at least 50% of all observations. The exact McNemar test for paired binary responses was used to compare the ability of the standard Seashore and HB equations with that of the WHO equation to estimate energy expenditure within ±10% of MEE.²⁰

To determine whether energy expenditure varied during the HSCT course, we used the PROC MIXED software (SAS Institute, Cary, NC, USA) to compare changes in MEE across four time-points.²¹ An unstructured covariance matrix was used because the standard Pearson’s correlation showed no pattern. The choice of unstructured covariance was supported by the Akaike information criterion, a standard statistical criterion for assessing the appropriate covariance structure.²² The exact Wilcoxon signed-rank test was performed to detect statistically significant differences in MEE at pairs of time-points.²³

Results

Patients

During the time period of this study, 111 patients underwent allogeneic HSCT for malignant (*n* = 93) or non-malignant (*n* = 18) diseases. Sixty-seven patients underwent 83 autologous transplant procedures for AML (*n* = 22), lymphomas (*n* = 13), or solid tumors (*n* = 32). Of 40 patients initially enrolled on the study, six were unable to complete the first scheduled energy expenditure measurement because of medical complications, such as mouth pain. The median age of the remaining 34 patients was 14 years (range, 6–22 years). Diagnoses included acute lymphoblastic leukemia (ALL, *n* = 7), AML (*n* = 12), chronic myelogenous leukemia (CML, *n* = 5), myelodysplastic syndrome (MDS, *n* = 4), Hodgkin’s disease (HD, *n* = 5), and non-Hodgkin’s lymphoma (NHL, *n* = 1). Ten patients underwent autologous HSCT and 24 allogeneic HSCT. Eight patients received bone marrow from matched siblings; eight patients, from matched unrelated donors (matched at five or six HLA loci) and eight from haploidentical family members. Some of these patients had complications that prevented the measurement of energy expenditure at all of the four planned time-points. Patient characteristics are summarized in Table 1.

Comparison of MEE and EEE

When the estimated energy expenditure was obtained by standard methods (the Seashore or Harris-Benedict

Table 1 Patient characteristics

| Type of HSCT | Autologous (<i>n</i> = 10) | Allogeneic (<i>n</i> = 24) |
|-----------------------|--------------------------------|--------------------------------|
| Donor | Not applicable | |
| HLA-identical sibling | | 8 |
| Matched unrelated | | 8 |
| Mismatched related | | 8 |
| Race | | |
| African-American | 1 | 1 |
| Hispanic | 1 | 1 |
| Caucasian | 8 | 18 |
| Other | 0 | 4 |
| Age: median (range) | 14 (9–22) years | 14 (6–21) years |
| Sex | | |
| Male | 6 | 15 |
| Female | 4 | 9 |
| Diagnosis | | |
| ALL | 0 | 7 |
| AML | 4 | 8 |
| CML | 0 | 5 |
| MDS | 0 | 4 |
| HD | 5 | 0 |
| NH | 1 | 0 |

ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; MDS = myelodysplastic syndrome; HD = Hodgkin’s disease; NHL = non-Hodgkin’s lymphoma.

equation), the proportion of patients whose EEE fell within ±10% of the MEE was statistically significantly different from 50% at all four time-points (Table 2). These results indicate that the standard estimation methods do not accurately reflect energy expenditure in this patient group. The upper limit of the 95% confidence interval at each time-point was <50%; therefore, MEE was adequately estimated for less than 50% of the patients by using these standard equations.

When EEE was obtained by using the WHO equation, the proportion of patients whose EEE was within ±10% of MEE was significantly different from 50% at all time-points except day 14 after HSCT (Table 2). EEE on day

Table 2 Accuracy of energy expenditure estimates obtained from standard (Harris-Benedict and Seashore) and World Health Organization equations for pediatric patients undergoing HSC

| Time-point | Estimation method | Proportion (%) within ±10% of MEE | 95% CI | P value |
|------------|-------------------|-----------------------------------|----------------|---------|
| Pre-HSCT | Standard | 5.88 | (0.72, 19.68) | <0.0001 |
| | WHO | 11.76 | (3.30, 27.45) | <0.0001 |
| Day +7 | Standard | 20 | (6.83, 40.70) | 0.0041 |
| | WHO | 16 | (4.54, 36.08) | 0.0009 |
| Day +14 | Standard | 25 | (8.66, 49.10) | 0.0414 |
| | WHO | 30 | (11.89, 54.28) | 0.1153 |
| Day +21 | Standard | 22.22 | (6.41, 47.64) | 0.0309 |
| | WHO | 11.11 | (1.38, 34.71) | 0.0013 |

CI = confidence interval; HSCT = hematopoietic stem cell transplantation; MEE = measured energy expenditure.

+14 was within $\pm 10\%$ of MEE in 30% of the patients (95% confidence interval, 11.9–54.3%). Therefore, the WHO equation met our criterion for adequate estimation of energy needs on day +14.

Comparison of equations used to estimate energy expenditure

McNemar's test showed no statistically significant difference between the standard estimation equations and the WHO equation in the proportion of patients whose estimated values fell within $\pm 10\%$ of MEE ($P \geq 0.625$). In more than 77% of cases, EEE obtained by either method differed from the MEE by more than 10%. Thus, the standard methods and the WHO equation offered statistically equivalent results but unsatisfactory accuracy in the estimation of caloric needs.

Changes in energy requirements

The median measured energy requirements of the patients varied significantly ($P = 0.0215$) during the transplant course. The MEE on day 14 after transplantation was significantly higher than both the pretransplant MEE ($P = 0.029$) and the MEE on day 7 after transplantation ($P = 0.023$). No significant difference was seen between MEE values at other pairs of time-points ($P > 0.326$).

Adequacy of nutrition support

Nutritional status did not change significantly between the time of the first (before HSCT) and last (21 days after HSCT) measurements of energy expenditure ($P > 0.99$). Nine of the 10 patients undergoing autologous HSCT were adequately nourished at both time-points, and one was depleted at both time-points. Of the patients who underwent allogeneic HSCT, three (12%) were considered to be depleted at both time-points, and 88% ($n = 21$) were adequately nourished at both time-points. One patient (who received autologous HSCT) received oral nutrition throughout the study period. The remaining 33 patients were placed on parenteral nutrition support before the HSCT infusion and remained on that support during the study period.

We used the respiratory quotient to confirm that patients were being overfed. A total of 102 energy expenditure measurements were obtained during the study period. Of these, 30 (29%) showed a caloric intake $>MEE$ and a respiratory quotient >1 . The proportions (95% CI) of patients whose caloric intake was $>MEE$ and whose RQ was >1 were 11/34 (17.4–50.5%) before HSCT, 7/30 (9.93–42.3%) on day +7, 7/20 (15.4–59.2%) on day +14, and 5/18 (9.69–53.5%) on day +21. Thus, at any point in the transplant period, between 10% and nearly 50% of our patients were likely to have a caloric intake $>MEE$ and an RQ >1 .

Discussion

The guidelines currently used for nutrition assessment in bone marrow transplantation support the use of energy expenditure equations to estimate energy needs and suggest that patients require nutrition in excess of these estimates.^{1,24} For pediatric patients, 140% of the EEE obtained by the Harris Benedict equation is suggested.¹ However, in our study, the three most commonly used energy estimation equations did not accurately estimate the needs of children undergoing HSCT. All three equations overestimated patients' needs in comparison to their measured energy expenditure. Taveroff *et al*²⁵ proposed that during the transplant process, therapy-induced changes in membrane function may limit nutrient utilization and that parenteral nutrition during HSCT should therefore meet only the basal energy requirements as calculated by the Harris-Benedict equation. Their recommendation was based on findings indicating that patients who receive fewer calories experience fewer electrolyte disturbances and have higher serum albumin concentrations.²⁵

Our results differ from those of several other investigators. Szeluga *et al*⁴ reported that the energy requirements of the six children they studied increased during HSCT. Hutchinson *et al*²⁶ reported an average energy requirement 5% above that estimated by the Harris-Benedict equation, with individual patients' needs ranging from 79% to 121% of the estimate. Others report that individuals undergoing HSCT have energy requirements 1.3 to 1.5 times those obtained by using the Harris-Benedict equation.^{27–29} We were unable to find differences in MEE between the two patient groups, allogeneic and autologous specifically. None of the commonly reported side-effects, fever and acute graft-versus-host disease (GVHD), were associated with an increased MEE. However, our study only evaluated MEE up to day +21. This was not an adequate time-frame to evaluate the effect of these complications and their effect on energy requirement because many patients had not yet engrafted or developed GVHD. Patients who were enrolled on this study and who developed severe mucositis were unable to complete the energy studies. The impact that this makes on our results is unknown, but this may have inadvertently resulted in omission of some patients with higher metabolic needs. In addition, our results are limited to children from ages 5–21 years, due to the issues associated with ability to comply with the indirect calorimetry procedure.

Our respiratory quotient analysis indicated that use of the estimation equations to set caloric goals for parenteral nutrition support could result in overfeeding. The RQ can be used to tailor a nutrition support regimen to a specific patient's needs. In general, an RQ greater than 1.0 indicates that the total calorie load should be decreased.^{16,17} In our study group, patients often had high respiratory quotients, which confirmed that their estimate-based nutrition support exceeded their MEE. Of 72 RQ measurements performed in this group, 22 (30%) indicated overfeeding.

To our knowledge, ours is the first study to use indirect calorimetry to measure energy expenditure in pediatric patients undergoing HSCT. Our findings suggest that the equations currently in use provide consistent results, but overestimate the energy needs of these patients. It is diffi-

cult to say on the basis of our study whether this overestimation is clinically significant. However, patients undergoing HSCT who receive excessive calories are more likely to experience metabolic or electrolyte complications.²⁵ Numerous complications, such as fluid and electrolyte imbalances, have been reported with the use of parenteral nutrition support.³⁰ Another major complication, overfeeding, can cause complications of the liver, lungs and other organs that may already be compromised by chemotherapy and radiation therapy.³¹ In addition, overfeeding of oncology patients may increase the risk of enhanced tumor growth and increase infection rates.³²

Other energy estimation equations should be tested in a larger population of children undergoing HSCT to identify those most appropriate for use. Additional research is also needed to characterize the unique impact of transplantation regimens on energy requirements. Nutritional support that is adequate to prevent protein loss but that does not supply excessive calories and cause fat accumulation is essential to the survival of patients undergoing transplantation. Until accurate equations have been identified for estimating these patients' needs, the use of indirect calorimetry may be medically warranted.

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