Accuracy of Prediction Formulae for the Assessment of Resting Energy Expenditure in Hospitalized Children

*Carlo Agostoni, †Alberto Edefonti, ‡Edoardo Calderini, §Emilio Fossali, ||Carla Colombo, ¶Alberto Battezzati, ¶Simona Bertoli, §Gregorio Milani, ||Arianna Bisogno, †Michela Perrone, ‡Silvia Bettocchi, ‡#Valentina De Cosmi, *Alessandra Mazzocchi, and *¶Giorgio Bedogni

ABSTRACT

Background and Aim: The resting energy expenditure (REE) of ill children is commonly estimated from prediction formulae developed in healthy children. The aim of the present study was to evaluate the accuracy of commonly employed REE prediction formulae versus indirect calorimetry in hospitalized children.

Methods: We performed a cross-sectional study of 236 infants, children, and adolescents consecutively admitted to the Intermediate Care, Nephrology, Intensive Care, Emergency, and Cystic Fibrosis Units of the De Marchi Pediatric Hospital (Milan, Italy) between September 2013 and March 2015. REE was measured by indirect calorimetry and estimated using the World Health Organization (WHO), Harris-Benedict, Schofield, and Oxford formulae.

Results: The mean (standard deviation) difference between the estimated and measured REE was: −1 (234) kcal/day for the WHO formula; 82 (286) kcal/day for the Harris-Benedict formula; 2 (215) kcal/day for the Schofield-weight formula; −2 (214) kcal/day for the Schofield-weight and height formula; and −5 (221) kcal/day for the Oxford formula. Even though the WHO, Schofield, and Oxford formulae gave accurate estimates of REE at the population level (small mean bias), all the formulae were not accurate enough to be employed at the individual level (large SD of bias).

Conclusions: The WHO, Harris-Benedict, Schofield, and Oxford formulae should not be used to estimate REE in hospitalized children.

Key Words: adolescents, children, equations, indirect calorimetry, infants, resting energy expenditure

(*JPGN* 2016;63: 708–712)

What Is Known

- Indirect calorimetry is the reference method for the assessment of resting energy expenditure.
- Indirect calorimetry is not available for routine clinical use and the resting energy expenditure of ill children is often estimated using formulae developed in healthy children.

What Is New

- We evaluated the accuracy of commonly used resting energy expenditure prediction formulae (World Health Organization, Harris-Benedict, Schofield, and Oxford) against indirect calorimetry in hospitalized children.
- The World Health Organization, Schofield, and Oxford formulae were accurate at the population level but all formulae were not accurate enough at the individual level.

Malnutrition is common among hospitalized children and is associated with increased length of stay and complications (1,2), especially in intensive care units (ICU) (3).

The estimation of total energy expenditure, the first step of tailoring nutritional support, usually starts from the measurement or the estimation of basal or resting energy expenditure (REE) (4–6). REE can be measured using indirect calorimetry (IC) but is more commonly estimated using prediction formulae (7). As pointed out by recent reviews, REE formulae have not undergone an extensive evaluation in heterogeneous clinical populations (4,6).

Most clinical validation studies of REE formulae have been performed in mechanically ventilated children (8). Even if the measurement of REE in such children may be especially reliable (9), the findings obtained in mechanically ventilated children cannot be generalized to spontaneously breathing children (6). The 5 most commonly employed REE prediction formulae are the World Health Organization (WHO) formula, the Harris-Benedict formula, the Schofield formula based on weight, the Schofield formula based on weight and height (7), and the Oxford formula (10). Although these formulae have been validated with variable results in healthy children, their accuracy in ill children is largely unknown (4,6).

The aim of the present study was, therefore, to evaluate the accuracy of the WHO, Harris-Benedict, Schofield, and Oxford

Received January 14, 2016; accepted March 29, 2016.

From the *Pediatric Medium Intensity Care Unit, Department of Clinical Science and Community Health, Università degli Studi di Milano, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, the †Pediatric Nephrology and Dialysis Unit, the ‡Pediatric Intensive Care Unit, the §Pediatric Emergency Unit, the ||Cystic Fibrosis Center, Fondazione IRCCS Cà Granda-Ospedale Maggiore Policlinico, University of Milan, the ¶International Center for the Assessment of Nutritional Status, University of Milan, and the #Laboratorio di Statistica Medica, Biometria ed Epidemiologia 'G.A. Maccacaro' Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

Address correspondence and reprint requests to Carlo Agostoni, Clinica Pediatrica, Fondazione IRCCS Cà Granda-Ospedale Maggiore Policlinico, Dipartimento di Scienze Cliniche e di Comunità, Università di Milano, Via della Commenda 9, 20122 Milan, Italy (e-mail: carlo.agostoni@unimi.it).

The study was partially supported by a grant from the Italian Ministry of Health (Progetto Ricerca Corrente 2016 850/01—Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico).

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000001223

formulae in a large series of acutely and chronically ill children cared as inpatients at an Italian Pediatric Hospital.

PATIENTS AND METHODS

Study Design

We performed a cross-sectional study of 236 infants, children, and adolescents consecutively admitted to the Intermediate Care, Nephrology, Intensive Care, Emergency, and Cystic Fibrosis Units of the De Marchi Pediatric Hospital (Milan, Italy) between September 2013 and March 2015. Patients from all Units were excluded from the study in the presence of respiratory quotient (RQ) <0.67 or >1.3; need of supplemental oxygen; and inability to maintain the fasting state for at least 4 hours. Values of RQ between 0.67 and 1.3 were used as marker of validity of the IC measurements following McClave et al (11). Patients from the Nephrology Unit were excluded from the study in the presence of nephrotic syndrome; treatment with intravenous methylprednisolone; kidney transplantation with circulating antidonor antibodies; and hemodialysis or peritoneal dialysis with acute disease, for example, influenza. Patients from the Emergency Unit were excluded from the study in the presence of gas leaking >10% and fraction of inspired oxygen (FIO_2) >40%. Patients with $FIO_2 > 40\%$ were excluded from the study because, even if the inspired oxygen will contribute to the measured REE, such contribution is expected to substantially distort the measure at values of $FIO_2 \geq 60\%$ (12). The study was approved by the Ethical Committee of the De Marchi Pediatric Hospital and the parents of the children gave their written informed consent.

Anthropometry

Weight, length (age <2 years), or height (age ≥2 years), arm circumference, and triceps skinfold were measured following international guidelines (13). Body mass index (BMI) was calculated as weight (kg)/length or height $(m)^2$. Standard deviation scores (SDS) of weight, length, height, weight-for-length, weight-for-height, BMI, arm circumference, and triceps skinfold were calculated using the WHO reference data (14,15). WHO SDS could be calculated for the following intervals of age and anthropometric dimensions: weight-for-age from age 0 to 10 years; length-for-age from age 0 to 2 years; height-for-age from age 2 to 18 years; weight-for-length for length 45 to 110 cm; weight-for-height for height 65 to 120 cm; arm circumference-for-age from age 0.25 to 5 years; and triceps skinfold-for-age from age 0.25 to 5 years.

Measurement of Resting Energy Expenditure

REE was measured in thermoneutral conditions using an open-circuit indirect calorimeter (Vmax 29, Sensor Medics, Yorba Linda, CA). An 8-hour fasting period was recommended for all patients, but a fasting period of at least 4 hours was acceptable for patients ages 2 years or younger. In spontaneously breathing patients, a canopy was positioned around the patient's head and the expired air was drawn from the hood at a fixed rate (16). In patients requiring mechanical ventilation, the calorimeter was connected to the ventilator (Babylog VN500, Dräger, Andover, MA). No changes in the ventilator settings were done for at least 1 hour before the REE measurement. Steady state was defined as at least 5 minutes with <5% variation in RQ, <10% variation in oxygen consumption, and <10% variation in minute ventilation (11). After the steady state was reached, the REE measurement was performed for at least 30 minutes. REE was obtained from oxygen uptake and carbon dioxide output using Weir's equation (17).

Estimation of Resting Energy Expenditure

REE was estimated using the 5 most commonly employed formulae: the WHO formula (7), the Harris-Benedict formula (7), the Schofield formula based on weight (7), the Schofield formula based on weight and height (7), and the Oxford formula (10).

Statistical Analysis

Most variables were not Gaussian distributed and all are reported as 25th, 50th, and 75th percentiles. Bland-Altman plots of the bias (estimated REE − measured REE) versus the average [(estimated REE + measured REE)/2] and of the percent bias [(estimated REE − measured REE)/measured REE] versus the average were used to evaluate the presence of proportional bias (18,19). The association between the bias and the average was evaluated using the Pearson product-moment correlation coefficient. Because proportional bias was detected in all cases, the Bland-Altman limits of agreement were not calculated (20). The absolute bias was Gaussian distributed, as determined by using kernel density plots and the Shapiro-Wilk test. The comparison of the measured and estimated values of REE was performed using Student *t* test for paired data. The percent bias was not Gaussian distributed. We evaluated the association of the percent bias of the Schofield-weight formula with sex, age, weight, and respiratory insufficiency (RI) using multivariable median regression (21). The response variable was percent bias (continuous, %) and the predictors were sex (discrete, 0 = female; 1 = male), age (continuous, years), weight (continuous, kg), and RI (discrete, 0 = no; 1 = yes). The continuous predictors were in linear relation with the outcome, as detected by using multivariable fractional polynomials (22). Statistical analysis was performed using Stata 14.1 (Stata Corporation, College Station, TX).

RESULTS

Clinical, Anthropometric, and Metabolic Features of the Patients

A number of 236 consecutive patients (200 Caucasians 85% and 123 boys 52%) aged 0.04 to 17.7 years were studied. Among them, 210 (89%) were spontaneously breathing. The reasons for hospitalization were (in order of frequency) the following: RI (n = 81); kidney disease (n = 51); rheumatic disease (n = 32); cystic fibrosis (n = 18); blood disease (n = 17); gastrointestinal disease (n = 16); neurological disease (n = 12); infectious disease (n = 6); and slow growth (n = 3).

The anthropometric and metabolic measurements of the patients are given in Table 1.

The measurements of weight and length or height were available in all 236 patients, those of arm circumference in 223 (95%), and those of triceps skinfold in 219 (93%). The median SDS of weight-for-age, length-for-age, height-for-age, weight-for-length, weight-for-height, and BMI-for-age were negative, signaling values always below the 50th percentile. In detail, the median BMI-for-age was −0.33 SDS, corresponding to the 37th percentile and 28 children (12%) had a BMI-for-age <2 SDS. The median (interquartile range) REE was 895 (419–1315) kcal/day.

Accuracy of the Prediction Formulae

Table 2 gives the absolute and percent bias of the WHO, Harris-Benedict, Schofield, and Oxford formulae.

Figure 1 shows the presence of negative proportional bias for all formulae, especially for the Harris-Benedict formula.

TABLE 1. Anthropometric and metabolic measurements of the study children

	N	P_{50}	P_{25}	P_{75}
Age (years)	236	6.6	0.8	11.4
Weight (kg)	236	19.7	7.9	36.7
Weight-for-age (SDS WHO*)	152	−0.74	−1.67	0.16
Length (cm)	79	62.0	57.0	72.0
Length-for-age (SDS WHO*)	79	−0.55	−1.70	0.41
Height (cm)	157	135.0	116.0	152.0
Height-for-age (SDS WHO*)	157	−0.72	−1.49	0.12
Weight-for-length (SDS WHO*)	79	−0.43	−1.56	0.80
Weight-for-height (SDS WHO*)	49	−0.16	−1.06	0.34
Body mass index (kg/m^2)	236	15.9	14.7	18.5
Body mass index-for-age (SDS WHO*)	236	−0.33	−1.20	0.69
Arm circumference (cm)	223	17.0	14.0	21.0
Arm circumference-for-age (SDS WHO*)	72	−0.34	−1.62	0.68
Triceps skinfold (mm)	219	9.6	7.7	12.7
Triceps skinfold-for-age (SDS WHO*)	71	−0.01	−0.42	1.19
Resting energy expenditure (kcal/day)	236	895	419	1315
Resting energy expenditure (kcal/kg weight)	236	40	32	53

P_x = Xth percentile; SDS = standard deviations scores; WHO = World Health Organization.

*WHO SDS could be calculated for the following intervals of age and anthropometric dimensions: (1) weight-for-age from age 0 to 10 years; (2) length-for-age from age 0 to 2 years; (3) height-for-age from age 2 to 18 years; (4) weight-for-length for length 45 to 110 cm; (5) weight-for-height for height 65 to 120 cm; (6) arm circumference-for-age from age 0.25 to 5 years; (7) triceps skinfold-for-age from age 0.25 to 5 years.

TABLE 2. Absolute and percent bias associated with the estimation of resting energy expenditure from the WHO, Harris-Benedict, Schofield, and Oxford formulae

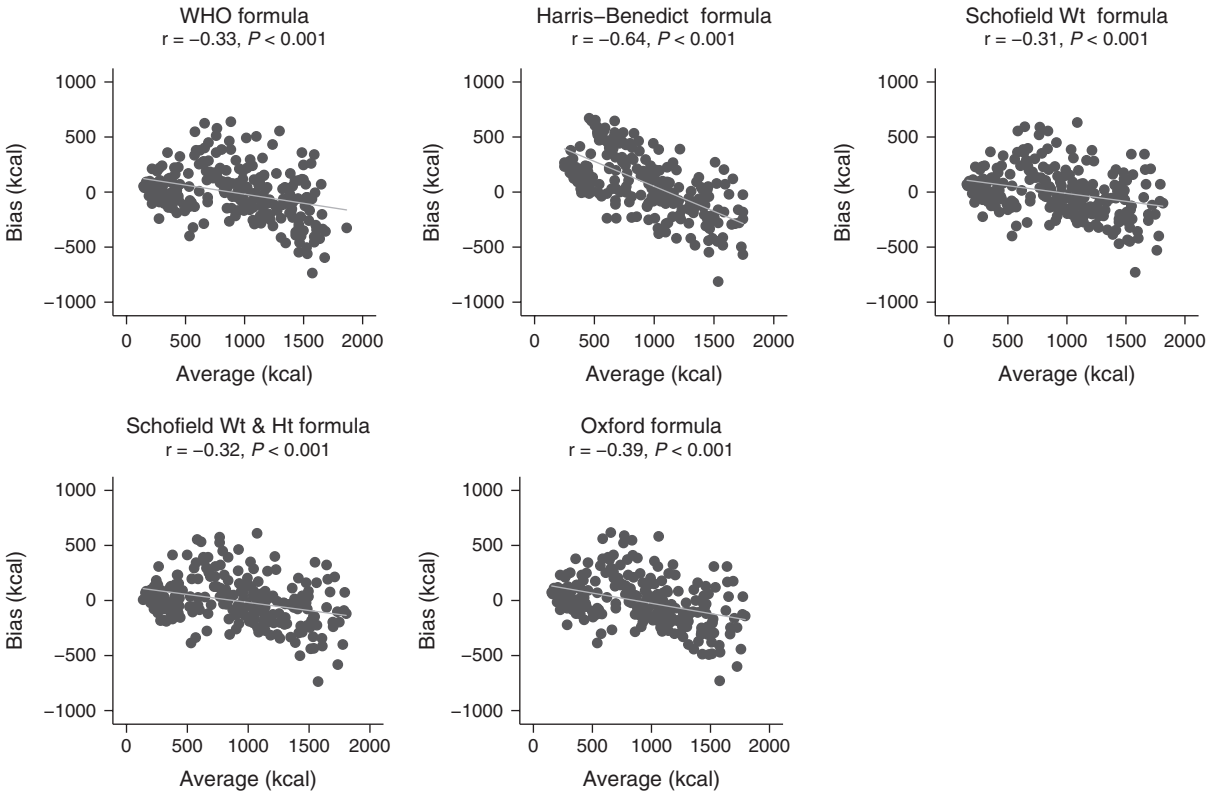
	n	Mean	SD	P_{50}	P_{25}	P_{75}
Bias-WHO (kcal)†	236	−1	234	−11	−134	117
Bias-WHO (%)‡	236	—	—	−2	−16	25
Bias-Harris-Benedict (kcal)†	236	82*	286	76	−103	270
Bias-Harris-Benedict (%)‡	236	—	—	8	−9	65
Bias-Schofield weight (kcal)†	236	2	215	−11	−129	125
Bias-Schofield weight (%)‡	236	—	—	−1	−14	25
Bias-Schofield weight & height (kcal)†	236	−2	214	−18	−134	120
Bias-Schofield weight & height (%)‡	236	—	—	−2	−14	22
Bias-Oxford (kcal)†	236	−5	221	−14	−130	121
Bias-Oxford (%)‡	236	—	—	−2	−14	24

P_x = Xth percentile; SD = standard deviation; WHO = World Health Organization.

*$P < 0.001$ (Student t test for paired data).

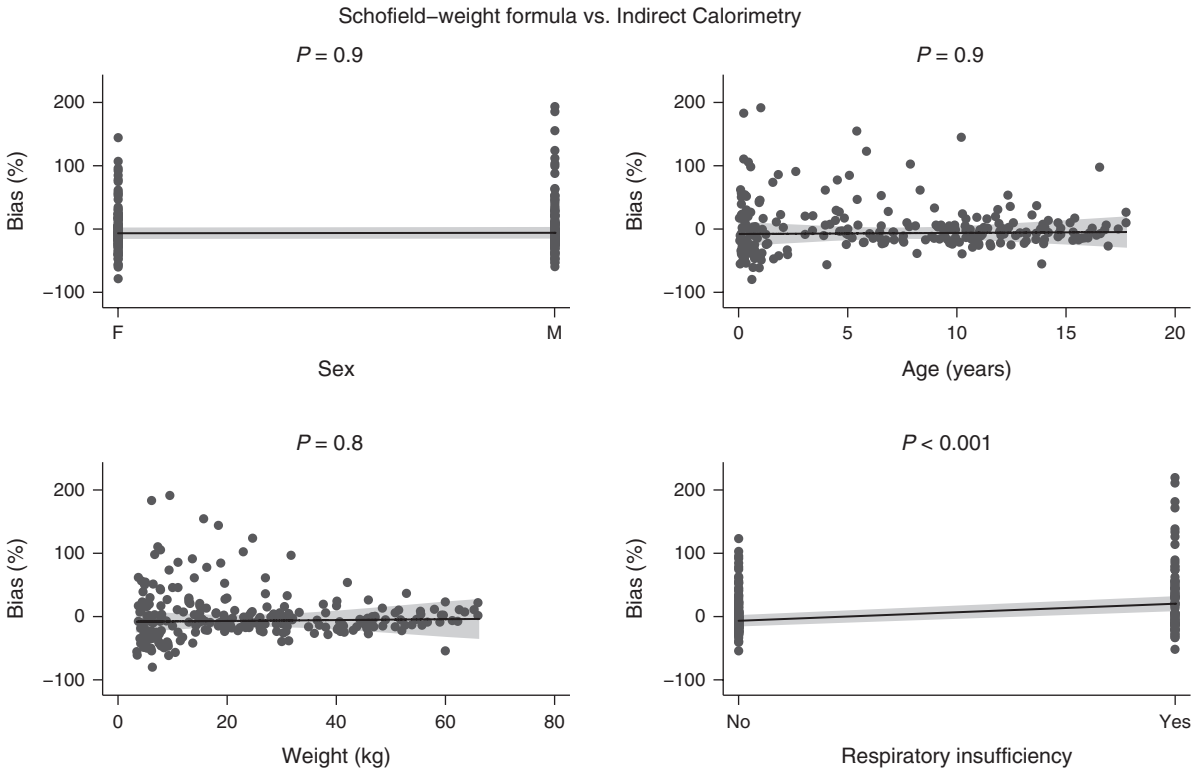
†Absolute bias was calculated as (estimated resting energy expenditure − measured resting energy expenditure). Absolute bias was Gaussian-distributed and Student t test for paired data was used to compare estimated and measured values.

‡Percent bias was calculated as [(estimated resting energy expenditure − measured resting energy expenditure)/measured energy expenditure)]. Percent bias was not Gaussian-distributed.



Bias = (estimated resting energy expenditure – measured resting energy expenditure).
Average = [estimated resting energy expenditure + measured resting energy expenditure)/2.]
Wt = weight; Ht = height

FIGURE 1. Bland-Altman plots of the bias versus the average for the WHO, Harris-Benedict, Schofield, and Oxford formulae.



Bias = (estimated resting energy expenditure – measured resting energy expenditure) / measured resting energy expenditure.
Graphs are partial residual plots obtained from multivariable median regression.
Gray bands are 95% confidence intervals.

FIGURE 2. Association of the percent bias of the Schofield-weight formula with age, weight, and respiratory insufficiency (multivariable median regression).

Because proportional bias was detected also for percent bias (not shown), limits of agreement were not calculated. Because IC is a reference method, the values reported in Table 2, however, do accurately quantify the prediction error and its interindividual variability.

The estimated REE was <80% and >120% of measured REE in 16% and 28% of patients using the WHO formula; 10% and 41% using the Harris-Benedict formula; 15% and 27% using the Schofield-weight formula; 14% and 26% using the Schofield-weight and stature formula; and 14 and 28% using the Oxford formula. This offers a rough but clinically useful measure of how many children would be underfed or overfed using these formulae (5). Using a stricter criterion (23), the estimated REE was <90% and >110% in 35% and 36% of patients using the WHO formula; 22% and 46% using the Harris-Benedict formula; 35% and 35% using the Schofield-weight formula; 35% and 33% using the Schofield-weight and stature formula; and 33% and 33% using the Oxford formula.

Figure 2 plots the joint contribution of sex, age, weight, and RI to the percent bias of the Schofield formula (multivariable median regression).

Sex ($P = 0.9$), age ($P = 0.9$), and weight ($P = 0.8$) were not associated with the percent bias but RI was (35%, 95% CI 23–46, $P < 0.001$).

DISCUSSION

Most of the available clinical validation studies of REE formulae have been performed in mechanically ventilated children (4,6). In the present study, we evaluated the accuracy of the most commonly employed REE prediction formulae (WHO, Harris-Benedict, Schofield, and Oxford) (7,10) in a large sample of hospitalized children.

All formulae except the Harris-Benedict formula gave accurate estimates of REE at the population level (small mean bias) but were not accurate enough to be employed at the individual level (large SD of the bias). This finding has important implications for the treatment and prevention of hospital malnutrition (1). Our results highlight the risk of underfeeding or overfeeding in hospitalized children whose energy prescription is based on REE estimated from commonly used prediction formulae.

In order to evaluate how REE formulae perform in a ''mixed'' pediatric hospital setting, we chose to study a heterogeneous population of hospitalized children. An obvious limitation of this approach is that, for most of the diseases that we studied, we do not reach a sufficient number of children to test whether purposely developed REE population-specific formulae perform better than traditional REE formulae. Further studies should be performed to test whether population-specific formulae can improve the accuracy of REE estimation in the pediatric hospital setting. Moreover, in the present study, we did not evaluate the contribution of nutritional rehabilitation (24) and of the ebb and flow phases of trauma (25) to the bias of estimated REE. These are clinically important modifiers of REE worthy of further clinical investigation.

The mean bias of the WHO (−1 kcal), Schofield-weight (2 kcal), Schofield-weight and height (−2 kcal), and Oxford (−5 kcal) formulae was much lower than the mean bias of the Harris-Benedict

(82 kcal) formula. If one considers the large SD of the bias shown by all formulae, it is, however, clear that none of these formulae can be applied satisfactorily at the individual level. The greater absolute and proportional bias associated with the Harris-Benedict formula was not unexpected, owing to the fact that its development sample included only adults. The similar accuracy of the Schofield and Oxford formulae was also not unexpected because most of their development sets consisted of common subjects. Our findings about the accuracy of the Schofield formulae agree with those of other researchers who studied mechanically ventilated children or children recovered in ICU (8,26). It is also worth noting that, in a clinical population made mostly of children with failure to thrive (27), the Schofield-weight formula proved slightly better than the Harris-Benedict formula.

Interestingly, despite the highly variable age and weight of our children, we found that these factors were not associated with the percent bias of the Schofield-weight formula. The contribution of RI to the bias of the Schofield-formula was, however, clinically relevant and shows that the presence of RI should be always taken into account by studies investigating the accuracy of estimated REE in the clinical setting. Our conclusion that REE formulae should not be used in hospitalized children, be they under mechanical ventilation or not, is the same offered by most studies of mechanically ventilated children (8,9,28).

In conclusion, the WHO, Harris-Benedict, Schofield, and Oxford formulae should not be used to estimate REE in hospitalized children. Further studies are needed to test whether population-specific formulae can improve the accuracy of REE estimation in the hospital setting and to test whether factors such as nutritional rehabilitation can affect the ability of IC to estimate REE in hospitalized children.

REFERENCES

1. Agostoni C, Fossali E, Calderini E, et al. Nutritional assessment and risk of malnutrition in hospitalised children in northern Italy. *Acta Paediatr* 2014;103:e416–7.
2. Hecht C, Weber M, Grote V, et al. Disease associated malnutrition correlates with length of hospital stay in children. *Clin Nutr* 2015;34:53–9.
3. Van der Kuip M, Oosterveld MJS, Van Bokhorst-de van der Schueren MA, et al. Nutritional support in 111 pediatric intensive care units: a European survey. *Intensive Care Med* 2004;30:1807–13.
4. Carpenter A, Pencharz P, Mouzaki M. Accurate estimation of energy requirements of young patients. *J Pediatr Gastroenterol Nutr* 2015;60:4–10.
5. Mehta NM. Energy expenditure: how much does it matter in infant and pediatric chronic disorders? *Pediatr Res* 2015;77:168–72.
6. Sion-Sarid R, Cohen J, Houri Z, et al. Indirect calorimetry: a guide for optimizing nutritional support in the critically ill child. *Nutrition* 2013;29:1094–9.
7. Koletzko B, Goulet O, Hunt J, et al. 2. Energy. *J Pediatr Gastroenterol Nutr* 2005;41:S5–11. Erratum J Pediatr Gastroenterol Nutr 2013; 56(4): 460.
8. Meyer R, Kulinskaya E, Briassoulis G, et al. The challenge of developing a new predictive formula to estimate energy requirements in ventilated critically ill children. *Nutr Clin Pract* 2012;27:669–76.
9. Smallwood CD, Mehta NM. Accuracy of abbreviated indirect calorimetry protocols for energy expenditure measurement in critically ill children. *J Parenter Enteral Nutr* 2012;36:693–9.
10. Henry CJK. Basal metabolic rate studies in humans: measurement and development of new equations. *Public Health Nutr* 2005;8: 1133–52.
11. McClave SA, Lowen CC, Kleber MJ, et al. Clinical use of the respiratory quotient obtained from indirect calorimetry. *J Parenter Enteral Nutr* 2003;27:21–6.
12. Haugen HA, Chan L-N, Li F. Indirect calorimetry: a practical guide for clinicians. *Nutr Clin Pract* 2007;22:377–88.
13. Lohman TG, Roche AF, Martorell R. Anthropometric Standardization Reference Manual. Champaign, IL: Human Kinetics Books; 1988.
14. Van den Broeck J, Willie D, Younger N. Child Growth Standards: Head Circumference-for-Age, Arm Circumference-for-Age, Triceps Skinfold-for-Age and Subscapular Skinfold-for-Age: Methods and Development. *Eur J Pediatr* 2009;168:247–51.
15. Van den Broeck J, Willie D, Younger N. Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development. *Eur J Pediatr* 2009;168:247–51.
16. Isbell TR, Klesges RC, Meyers AW, et al. Measurement reliability and reactivity using repeated measurements of resting energy expenditure with a face mask, mouthpiece, and ventilated canopy. *J Parenter Enteral Nutr* 1991;15:165–8.
17. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. 1949. *Nutrition* 1990;6:213–21.
18. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999;8:135–60.
19. Carstensen B. Comparing Clinical Measurement Methods: A Practical Guide Chichester, West Sussex: John Wiley & Sons; 2010.
20. Dewitte K, Fierens C, Stöckl D, et al. Application of the Bland Altman plot for interpretation of method-comparison studies: a critical investigation of its practice. *Clin Chem* 2002;48:799–801.
21. Koenker R. Quantile Regression. Cambridge, UK: Cambridge University Press; 2005.
22. Royston P, Sauerbrei W. Multivariable Model-Building: A Pragmatic Approach to Regression Analysis Based on Fractional Polynomials for Modelling Continuous Variables Chichester, UK: Wiley; 2008.
23. Lazzer S, Bedogni G, Lafortuna CL, et al. Relationship between basal metabolic rate, gender, age, and body composition in 8,780 white obese subjects. *Obesity* 2010;18:71–8.
24. Arrowsmith FE, Allen JR, Gaskin KJ, et al. Nutritional rehabilitation increases the resting energy expenditure of malnourished children with severe cerebral palsy. *Dev Med Child Neurol* 2012;54: 170–5.
25. Finnerty CC, Jeschke MG, Qian W-J, et al. Determination of burn patient outcome by large-scale quantitative discovery proteomics. *Crit Care Med* 2013;41:1421–34.
26. Framson CMH, LeLeiko NS, Dallal GE, et al. Energy expenditure in critically ill children. *Pediatr Crit Care Med* 2007;8:264–7.
27. Kaplan AS, Zemel BS, Neiswender KM, et al. Resting energy expenditure in clinical pediatrics: measured versus prediction equations. *J Pediatr* 1995;127:200–5.
28. Oosterveld MJS, Van der Kuip M, De Meer K, et al. Energy expenditure and balance following pediatric intensive care unit admission: a longitudinal study of critically ill children. *Pediatr Crit Care Med* 2006;7:147–53.