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INVITED REVIEW

Determining energy and protein needs in critically ill pediatric patients: A scoping review

Corinne Jotterand Chaparro PhD, RD[1,2] | **Céline Pabion MSc, RD**[1] | **Lyvonne Tume PhD, RN**[1,3] | **Nilesh M. Mehta MD**[4] | **Frédéric V. Valla PhD, MD**[5] | **Clémence Moullet MSc, RD**[1]

[1]Geneva School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland, Geneva, Switzerland

[2]Bureau d'Echange des Savoirs pour des praTiques exemplaires de soins (BEST): A JBI Centre of Excellence, Lausanne, Switzerland

[3]Faculty of Health, Social Care and Medicine, Edge Hill University, Ormskirk, UK

[4]Department of Anesthesiology, Critical Care and Pain Medicine, Division of Critical Care Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[5]Pediatric Intensive Care Unit, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Lyon, France

Correspondence
Corinne Jotterand Chaparro, PhD, RD, Department of Nutrition and Dietetics, Geneva School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland, Geneva, Rue des Caroubiers 25, 1227 Carouge, Switzerland.
Email: corinne.jotterand@hesge.ch

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Abstract

Introduction: In critically ill pediatric patients, optimal energy and protein intakes are associated with a decreased risk of morbidity and mortality. However, the determination of energy and protein needs is complex. The objective of this scoping review was to understand the extent and type of evidence related to the methods used to determine energy and protein needs in critically ill pediatric patients.

Methods: An international expert group composed of dietitians, pediatric intensivists, a nurse, and a methodologist conducted the review, based on the Johanna Briggs Institute methodology. Two researchers searched for studies published between 2008 and 2023 in two electronic databases, screened abstracts and relevant full texts for eligibility, and extracted data.

Results: A total of 39 studies were included, mostly conducted in critically ill children undergoing ventilation, to assess the accuracy of predictive equations for estimating resting energy expenditure (REE) ($n = 16$, 41%) and the impact of clinical factors ($n = 22$, 56%). They confirmed the risk of underestimation or overestimation of REE when using predictive equations, of which the Schofield equation was the least inaccurate. Apart from weight and age, which were positively correlated with REE, the impact of other factors was not always consistent. No new indirect calorimeter method used to determine protein needs has been validated.

Conclusion: This scoping review highlights the need for scientific data on the methods used to measure energy expenditure and determine protein needs in critically ill children. Studies using a reference method are needed to validate an indirect calorimeter.

Frédéric V. Valla and Clémence Moullet contributed equally to this study.

decisions, content, or writing of this supplement.

KEYWORDS
children, critical illness, energy expenditure, pediatric intensive care unit, pediatrics, protein requirements

INTRODUCTION

In critically ill pediatric patients, optimal nutrition support, especially adequate amounts of energy and protein, has been associated with a lower risk of morbidity and mortality.[1–3] Estimation of energy and protein requirements in healthy children is difficult because these requirements change with age, growth velocity, modifications in body composition, and physical activity.[4] The task is even more complex in pediatric intensive care units (PICUs) and neonatal ICUs (NICUs), in which nutrition needs may be influenced by dynamic clinical factors, treatments, and hospital conditions.[5]

To determine energy requirements in critically ill children, scientific societies recommend measuring resting energy expenditure (REE) using a validated indirect calorimeter or estimating REE by Schofield predictive equations[6] while highlighting the risk of underestimation or overestimation of this method.[7–9] Worldwide and European surveys[10–12] showed that only a minority of PICUs (7%–17%) had access to an indirect calorimeter, and as a result, clinicians estimated REE in critically ill children using a variety of predictive equations that were developed using data from healthy children.[13] Furthermore, the recommended use of a validated calorimeter is challenging, as the Deltatrac II (Datex-Ohmeda, Helsinki, Finland), the reference device to determine REE, which has been validated in critically ill adults and children,[14,15] is no longer manufactured. Other indirect calorimeters, including the M-COVX (Datex-Ohmeda, Finland), CCM Express (Medical Graphics Corp, UK), Quark RMR, or the Q-NRG (COSMED, Italy), have been commercialized, but research development, including clinical studies and approval, has been mainly restricted to adults.[16–19] In addition, these devices can only be used in children weighing >10–15 kg, which excludes much of the PICU population. Because of these constraints, there is a paucity of trials that have examined the impact of indirect calorimetry–guided energy prescription on clinical outcomes.

The doubly labeled water method measures total EE, which includes EE during activity, for ≥5 consecutive days.[4] This method requires the use of isotopes and strict data collection, which may not be available in most centers and has been rarely used clinically in critically ill children.[20,21]

To determine protein needs, there is no simple method that can be used in daily practice. The classical method is the assessment of nitrogen balance, which requires the measurement of daily urinary nitrogen[22] and is used for research purposes. Urine collected over a shorter time may provide an estimate of 24-h nitrogen excretion but lacks accuracy. Based on limited data in critically ill children and neonates,[23,24] it is recommended to consider an enteral protein intake of ≥1.5 g/kg/day to avoid negative protein balance in this population.[7–9] Clinical trials describing the optimal amount of protein that improves clinical outcomes have not yet been reported.

The determination of energy and protein needs in critically ill pediatric patients requires specific knowledge of the methods available to determine REE, total EE, and protein needs in terms of their accuracy and limitations. A preliminary search conducted in MEDLINE, Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis provided two systematic reviews in this field. One systematic review, published in 2018, assessed the accuracy of predictive equations for estimating REE in critically ill children.[13] The second published in 2019 reviewed the patient and clinical factors associated with REE in critically ill patients, including children and neonates.[5] In addition to these works, we are not aware of systematic or scoping reviews that have synthetized data on both the determination of energy and protein needs in critically ill pediatric patients.

Therefore, the objective of our scoping review was to understand the extent and type of evidence related to the methods used to determine energy and protein needs in critically ill pediatric patients, including medical and surgical patients. We included the available evidence and discussed the following specific topics: (1) indirect calorimetry to measure EE or other measurement methods, (2) predictive equations to estimate REE, (3) clinical factors that may affect EE determination, and (4) methods used to determine protein needs in critically ill pediatric patients.

REVIEW QUESTIONS AND CRITERIA

Review questions

The two main review questions addressed in this scoping review were as follows:

1. "Which methods used to determine energy needs have been assessed in critically ill pediatric patients,

including medical and surgical patients, and what are the findings?"
2. "Which methods used to determine protein needs have been assessed in critically ill pediatric patients, including medical and surgical patients, and what are the findings?"

Considering the amount of scientific data on energy needs in critically ill pediatric patients, three subquestions were defined to clarify the presentation of data:

a. Which measurement methods of EE (either total EE or REE), including various indirect calorimeters, have been assessed in critically ill pediatric patients, and what are the findings?
b. Which estimation methods of REE, including various predictive equations, have been assessed in critically ill pediatric patients and what are the findings?
c. Which clinical factors play a role in EE determination in critically ill pediatric patients?

Inclusion and exclusion criteria

- Population: this review considered studies conducted in critically ill pediatric patients, including preterm neonates, term neonates (born at ≥37 weeks of gestation up to 1 month of age), infants (aged 1–23 months), and children and adolescents (aged 13–18 years) admitted to the PICU or NICU. Patients admitted for a medical or surgical reason, including cardiac patients, were eligible.
- Concept: This review considered studies that assessed the methods used to determine energy or protein needs in critically ill pediatric patients. For energy, it included measurements of total EE or REE, using calorimetry, total doubly labeled water, or predictive equations. For protein, measurements or estimation methods were considered. Studies that aimed to determine the clinical factors that may affect the determination of EE were eligible. The following studies were excluded: those that estimated REE with predictive equations but without control measurement of EE and those that compared energy needs and energy prescriptions.
- Context: This review considered studies conducted in the PICU or NICU settings. Studies that included patients outside of the PICU or NICU were excluded.
- Types of studies: This review considered both experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort, case-control, and analytical cross-sectional studies, were considered for inclusion. This review also considered descriptive observational study designs, including descriptive cross-sectional studies. To provide an overview of available data, systematic reviews that met the inclusion criteria were also considered depending on the research question, including the two identified systematic reviews.[5,13] Editorial abstracts from conferences, case reports, qualitative studies, text and opinion articles, reviews, and guidelines were also excluded.

METHODS

An international expert group of six members was established, composed of pediatric intensivists, dietitians, a nurse, and a methodologist, to conduct this scoping review based on the JBI methodology for scoping reviews.[25] The study protocol was registered in the Open Science Framework (doi:10.17605/OSF.IO/7SVXM).

Search strategy

The search strategy focused on the identification of published studies. A 3-step search strategy was used. An initial limited search of MEDLINE PubMed was performed to identify articles published within the selected time period. We adapted full-search strategies for MEDLINE, previously developed for a systematic review on the accuracy of predictive equations in critically ill children[13] and European guidelines on nutrition support in critically ill children.[9] The final full-search strategy for MEDLINE, developed in collaboration with a specialized librarian from the University of Applied Sciences and Arts of Western Switzerland Institution, Geneva, is shown in Appendix A. The search strategy, including all identified keywords and index terms, was adapted for Web of Science. In addition, the reference lists of all included sources of evidence were screened for additional studies, including references from existing systematic reviews on the topic. Studies published between January 2008 and the present (the last 15 years) in English and French were included. This limitation date was selected to focus on the most recent data, considering the addition of at least two major guidelines on this topic in the early 21st century.[26,27]

Study selection

After the search, we collated and uploaded all identified citations to the reference manager software Zotero and removed duplicates. After a pilot test, two independent reviewers screened the titles and abstracts for assessment against the inclusion criteria using the Rayyan software.[28] Any disagreements between the reviewers at each stage of the selection process were resolved through discussion or through an additional reviewer. Two independent reviewers assessed the full text of the selected citations based on the inclusion criteria. Reasons for exclusion of sources of evidence in the full text that did not meet the inclusion criteria were recorded. The results of the search and the study inclusion process were reported in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram.[29]

Data extraction

Data were extracted from the studies included in the scoping review by one reviewer using a data extraction tool developed by the researchers and pretested before embarking on full data. The data extracted included specific details about the participants (number, sex, age, nutrition status, etc), concept (aim of the study, test method, reference method used for the comparison), context (PICU or NICU), study methods, and key findings relevant to the review questions and subquestions.

Data analysis and presentation

Data were presented with a narrative summary, accompanied by tabulated and/or charted results, and how the results relate to the review's objective and subquestions on energy were described. The presentation of results was organized under the main research questions and subresearch questions and included details from the data extraction table. As we included two systematic reviews[5,13] identified for subquestions 1b and 1c, we narratively compared their results with those of subsequently published studies to avoid redundant results. The results of the studies included in these two systematic reviews were presented in tables to provide an overview of the available evidence for each subquestion. A diagrammatic synthesis was provided to show the data available on the main research question and subquestions.

RESULTS

Included studies for the main questions and subquestions

The literature search identified 472 articles and 398 after removing duplicates. Of these, 229 were published after December 2007 and eligible for screening (Figure 1). After abstract and full-text screening, a total of 39 articles were included. The PRISMA-ScR[29] is shown in Figure 1. Most studies assessed the accuracy of predictive equations to estimate REE ($n = 16$; 41%) and the impact of clinical factors on EE ($n = 22$; 56%) (Figure 2). Tables 1–4 summarize the study characteristics and findings for the three subquestions on energy and the main question on protein. Five studies were included for both subquestions 1b and 1c on energy needs.

Methods of measurement of EE (subquestion 1a)

Only two studies were included in which REE measurement methods were assessed in critically ill children in the PICU[30,31] (Table 1). The first study compared the indirect calorimeter E-COVX (GE Healthcare, Waukesha, WI) with the Vmax Encore Metabolic Cart (Carefusion, San Diego, CA) in 19 children undergoing mechanical ventilation (mean age: 6.9 ± 5.8 years).[30] The authors did not consider any of these devices as reference methods. The Bland-Altman limits of agreement were outside the clinically acceptable range and were on either side of the mean bias, with no discernible pattern. The authors concluded that these devices cannot be used interchangeably in this population.

A second study assessed the influence of different ventilator modes on carbon dioxide production (VCO_2), oxygen consumption (VO_2), respiratory quotient (RQ), and REE, measured by the E-COVX, in 11 critically ill children (mean age: 7.8 ± 4.9 years).[31] No reference method has been used for the determination of REE. The VCO_2, VO_2, and REE measurements did not differ among the three ventilator modes; however, their SDs varied widely. There were no significant differences between repeated measurements. This group concluded that the influence of ventilator modes was not significant and that E-COVX was suitable for repeated measurements in children undergoing ventilation with stable respiratory patterns.

Methods of estimation of REE (subquestion 1b)

In total, 16 studies assessing the estimation methods of REE in critically ill pediatric patients were included: one systematic review published in 2018,[13] six studies already included in the systematic review, and six published thereafter, as shown in Table 2. They assessed either standard predictive equations, equations developed

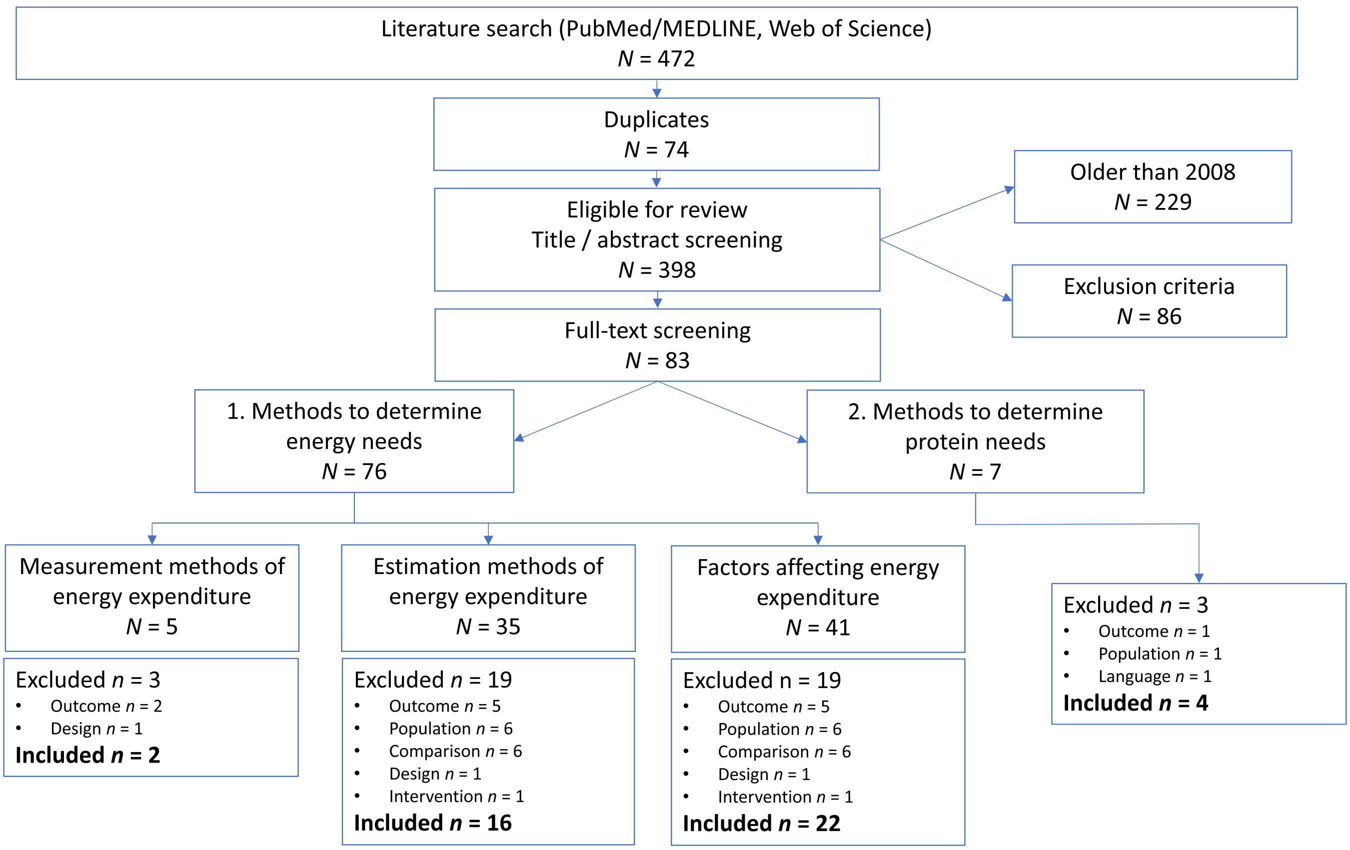

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart showing the inclusion and exclusion of studies.

specifically for critically ill children, or a novel simplified metabolic equation that uses a measured VCO_2 value and a fixed RQ of 0.89.[41]

The systematic review included 1102 critically ill children from 22 studies, most of whom measured REE using Deltatrac II.[13] The Schofield equations[6] and Talbot tables,[65] which were the least inaccurate, predicted REE within ±15% of the measured REE in ~50% of the observations, and the Schofield equations predicted REE within ±10% in 34%–38% of the observations. The Harris-Benedict (HB)[66] equation overestimated REE in two-thirds of the patients. The authors concluded that a newly validated indirect calorimeter and more precise predictive equations were urgently needed in this population.

Studies published after 2018 have reported similar findings, although none measured REE using the Deltatrac II but used other devices, including the Vmax 29, the E-COVX, the Quark RMR, and the AMIS 2000 (Table 2). In 40 children with severe sepsis (median age: 7 years), the FAO/WHO/UNU[22] and Schofield equations estimated REE within ±10% of the measured REE in 30% of observations and HB in 25%, with underestimation or overestimation of REE.[37] In 107 children undergoing cardiopulmonary bypass (median age: 5 months), all tested equations overestimated REE by adding a stress factor of 1.2 to the predicted values.[36] The FAO/WHO/UNU and Schofield equations and an allometric equation with an RQ of 0.8 had the least discrepancy, and the HB equation and dietary reference intake had the largest overestimation. In 95 children undergoing ventilation (median age: 17 months), all tested equations underestimated REE except for the FAO/WHO/UNU equation.[35] The Schofield equation, with weight and height, showed the best performance for the entire group and subgroups according to age, sex, nutrition status, and organ failure. Among 16 tested equations in 153 children (median age: 7.5 years),[32] the majority, especially the Recommended Dietary Allowances, overestimated REE measured by E-COVX. In contrast to the above findings, the Schofield weight and height equation overestimated REE with one of the highest bias, and the HB equations had a smaller bias but still had wide limits of agreement.

Several studies have assessed the equations of White et al.[67] and Meyer et al.[44] developed specifically for critically ill children undergoing ventilation and

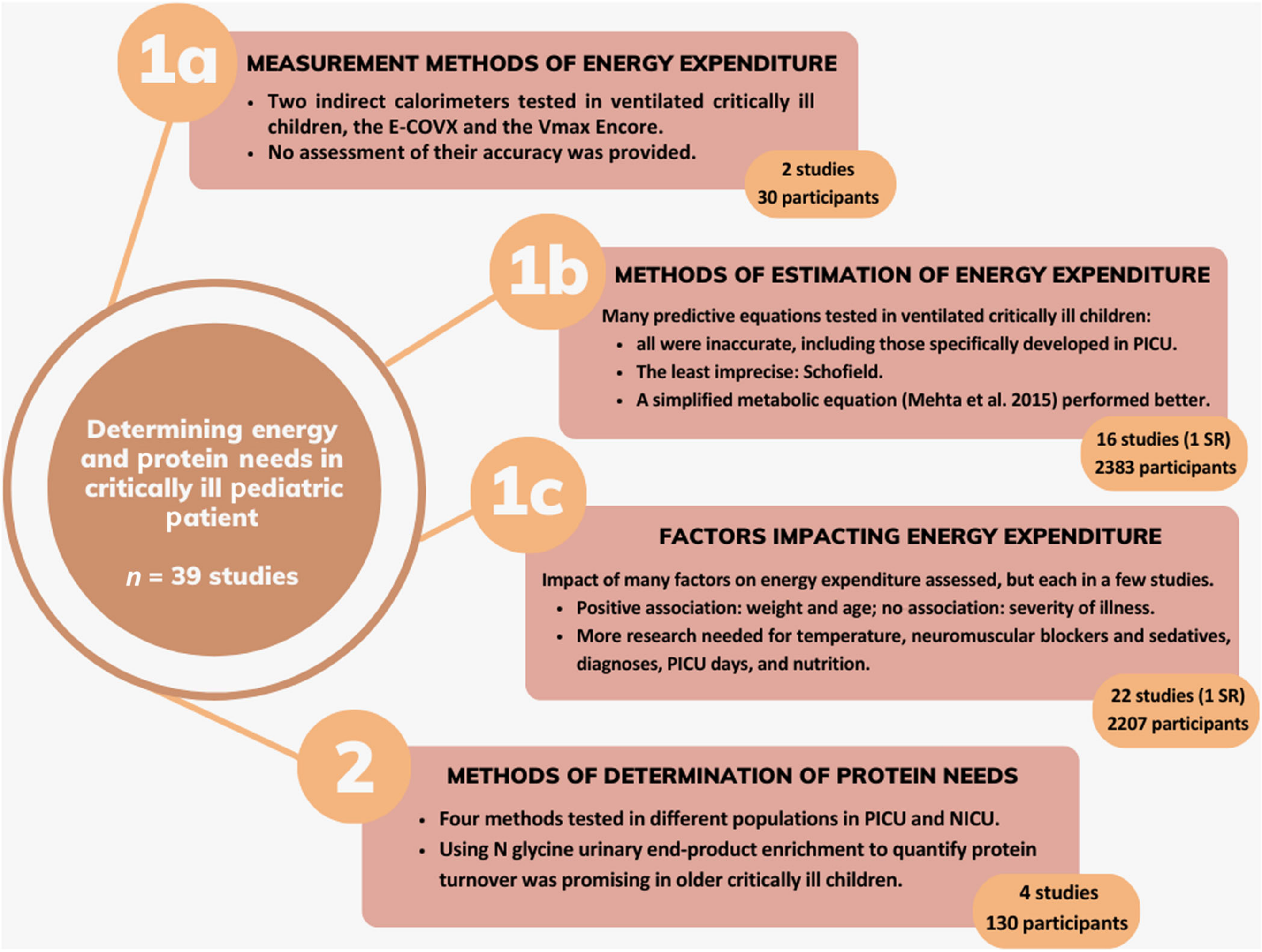

FIGURE 2 Literature search and main findings for the main research questions and subquestions. NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; SR, systematic review.

observed that they did not perform better than standard predictive equations, or worse.[32,39,45] Among the three equations developed by Meyer et al., one (equation A) performed better in two studies[35,44] but still did not predict REE within a clinically accepted range.

Several studies[13,33,34,38–40] assessed the simplified metabolic equation, which was developed by Mehta et al. in 2015, in a derivation group of critically ill children undergoing ventilation, followed by a validation study.[41] Around 50% of estimations fell within ±10% of measured REE, and the remaining observations were an underestimation of REE.[33,39,40] This metabolic equation was the most accurate among several tested equations in critically ill children based on 475 and 275 indirect calorimetry measurements, respectively.[34,39] The most important determinant of bias was the RQ, with a smaller error in patients with an RQ between 0.8 and 1.[40]

In terms of factors that may affect the accuracy of predictive equations, two recent studies, involving one-third of overweight or obese patients, showed that apart from age, inaccuracy of the equations was not correlated to factors such as the presence of overweight or obesity, diagnostic categories including trauma, or disease severity.[32,33]

Factors impacting EE (subquestion 1c)

In total, 22 studies assessing clinical factors that may have a role in EE determination in critically ill pediatric patients were identified. It includes one systematic review conducted in critically ill adults, children, and neonates published in 2019,[5] eight studies already included in this systematic review, and 11 studies published thereafter, as described in Table 3.

The systematic review found 95 clinical factors evaluated, with 352 evaluations performed mostly in adults.[5] Based on at least two evaluations, factors in children that were positively correlated with EE included

TABLE 1 Findings related to subquestion 1a: Measurement methods of EE in critically ill pediatric patients.

References	Study design	Objective	Population	Measurements	Key findings and authors conclusions
Smallwood and Mehta[30]	Prospective observational study	To compare VO_2, VCO_2, REE, and RQ in children using mechanical ventilation, obtained by two devices using distinct gas sampling methods	$n = 19$ (15 girls) children using ventilator, PICU Mean age: 6.9 ± 5.8 years	$n = 19$ tests 1. E-COVX 2. Vmax Encore Neither device served as a gold standard	The mean percentage bias for VO_2, VCO_2, REE, and RQ values between the two methods was 0.2 (−41.8 to 42.3), −0.8 (−21.8 to 20.1), −2.2 (−33.9 to 29.6), and 1.9 (−21 to 24.9), respectively. Bland-Altman analysis showed wide limits of agreement that were outside the clinically acceptable range and that were on either side of the mean bias, with no discernible pattern. The two devices should not be used interchangeably in children using mechanical ventilation
Briassoulis et al.[31]	Cross-sectional pilot study	To assess (1) the influence of different ventilator modes on VCO_2 and VO_2 using a compact modular metabolic monitor (E-COVX) and its impact on calculated RQ and REE in critically ill children; (2) the reproducibility of measurements, in adequately sedated patients, in each ventilator mode	$n = 11$ (7/4) children undergoing ventilation, PICU Mean age ± SD: 7.8 ± 4.9 years	$n = 3960$ pulmonary 1-min gas exchange measurements Modular metabolic monitor E-COVX Continuous measurements sequentially at three ventilator modes	The VO_2, VCO_2, and REE did not differ among the ventilator modes, but their SDs varied widely. The Bland-Altman analysis showed that the average paired differences between the pressure-regulated volume-controlled ventilation, synchronized intermittent mandatory ventilation, and biphasic intermittent positive airway pressure/airway pressure release ventilation were, respectively, – REE: −0.6%, −2.2%, and −3.5% – VO_2: −0.2%, −1.6%, and −2.7% – VCO_2: −2.2%, −2.6%, and −5.5% – With a 95% confidence interval that varied from 34.4% to 27.1% The influence of different ventilator modes on VO_2 and VCO_2 measurements in adequately sedated critically ill children is not significant. The E-COVX metabolic module is suitable for repeated measurements in well-sedated children undergoing mechanical ventilation with stable respiratory patterns using three modes of ventilation

Abbreviations: PICU, pediatric intensive care unit; REE, resting energy expenditure; RQ, respiratory quotient; VCO_2, carbon dioxide production; VO_2, oxygen consumption.

TABLE 2 Findings related to subquestion 1b: Estimating methods of REE in critically ill pediatric patients.

References	Study design	Population	Measurements	Predictive equations	Key findings and author conclusion
Briassoulis et al.[32]	Cross-sectional study	$n = 153$ (108 boys/45 girls) children undergoing ventilation, 27% trauma, PICU Median age: 7.5 (IQR, 5–12.5) years Underweight: 20% Overweight: 11% Obese: 25%	$n = 153$ Indirect calorimeter: E-COVX	16 predictive equations for children or adults including PICU-specific White and Meyer	The estimated REE was either underestimated (median 606 kcal/day; IQR, 512–784 kcal/day) or overestimated (1340 kcal/day; IQR, 1126–929) REE_{IC} compared with IC: 1239 kcal/day (IQR, 928–651 kcal/day). Commonly used predictive equations for calculating energy needs are inaccurate for individual patients. The equations' reliability was consistent across subcohorts of patients with obesity, overweight, and underweight.
Briassoulis et al.[33]	Cross-sectional study	$n = 107$ (75 boys/32 girls) children undergoing ventilation, 22% trauma, PICU Mean age: 9.2 ± 5.3 years Underweight: 22% Overweight:9% Obese: 25%	$n = 107$ Indirect calorimeter: E-COVX	VCO_2-based equation: REE(VCO_2)	The calculated REE(VCO_2) resulted in a mean bias of −73 kcal/day (95% limits of agreement, −322 to 176 kcal/day); 51% of the calculations fell outside the ±10% accuracy rate. REE(VCO_2) derived from RQ 0.80 or 0.85 did not improve accuracy. None of the patients' demographics, BMI nutrition status (overweight, obesity), diagnostic category, severity of illness, temperature, heart rate, blood gases, or CRP level was independently associated with the REE (VCO_2)–measured REE difference. REE(VCO_2) cannot be recommended as an alternative to IC in children undergoing mechanical ventilation.
Spolidoro et al.[34]	Cross-sectional prospective study	$N = 257$ (145 males) children, PICU Median age: 2.4 years Wasting: $n = 2$ No obesity	$N = 257$ Indirect calorimeter: Vmax 29	Artificial neural networks, Talbot tables VCO_2-REE, HB, Schofield-W, Schofield-HW, FAO/WHO/UNU, and Oxford equations	The artificial neural networks considered demographic and anthropometric data to model REE, which was good but not better than Talbot tables. After adding vital signs and biochemical values, it became superior to all equations. Including measured VCO_2 by IC increased the accuracy to 90%, superior to the Mehta equation. All equations, except Mehta equation, overestimated REE, mostly for lowest values. The largest differences were observed for the HB equations.
Jhang and Park[35]	Single-center retrospective study	$n = 95$ (32 boys/38 girls) children undergoing ventilation, PICU Median age: 17.4 (0.5–205) months Malnutrition: 46%	IC: E-sCAiOVX gas exchange module	Schofield-W; Schofield-HW; Oxford-W; Oxford-HW; FAO/WHO/UNU; Meyer A, B, and C	All equations underestimated REE, except the FAO/WHO/UNU equation. The Schofield-HW equation showed the best performance for the entire cohort (least bias, −68 kcal/day) and in subgroup analysis by age, sex, nutrition status, and organ failure. A newly developed equation showed better performance.

TABLE 2 (Continued)

References	Study design	Population	Measurements	Predictive equations	Key findings and author conclusion
Roebuck et al.[36]	Observational longitudinal prospective study	$n = 107$ children undergoing ventilation after cardiopulmonary bypass, PICU Median age: 5.2 (0.8–10.7) months Nutrition status: ∅	$n = 5$ per patient (median) Respiratory mass spectrometry	Dietary reference intake, Schofield, FAO/WHO/UNU, HB, and novel allometric equations; stress factor of 1.2 (1.2 × REE)	All equations overestimated REE, especially the dietary reference intake, the HB equation, and the use of stress factor (1.2). The FAO/WHO/UNU and Schofield equations, and the allometric equation with a RQ of 0.8, had the least discrepancy from measured REE.
Ismail et al.[37]	Observational longitudinal prospective study	$n = 40$ (24 boys) children undergoing ventilation and severe sepsis, PICU Median age: 7 (5.2–10) years Underweight: 18% Obese: 3%	$n = 176$ Indirect calorimeter: Quark RMR	Schofield, HB, and FAO/WHO/UNU	Predictive equations estimated REE within ±10% of measured REE in 30% of measurements when using the Schofield and FAO/WHO/UNU equations, and 25% using HB. Predictive equations are inaccurate compared with IC.
Jotterand Chaparro et al.[13]	Systematic review	$n = 1102$ critically ill children, PICU $n = 22$ included studies Nutrition status: ∅ Children with severe burns excluded	$n = 2326$	21 equations: mostly HB, FAO/WHO/UNU, Schofield-W, Schofield-HW, Talbot tables, White, Fleisch, Mehta (VCO_2-REE)	No equation predicted REE within ±10% of measured REE in >50% of observations. The HB equation overestimated REE in two-thirds of patients. The Schofield equations and Talbot tables predicted REE within ±15% of measured REE in ~50% of observations. The HB equation was highly inaccurate. The Schofield equations and Talbot tables were the least inaccurate.
Kerklaan et al.[38]	Observational prospective study	$N = 41$ (56% male) children undergoing ventilation, PICU Median age: 2.3 years Nutrition status: ∅	$n = 411$. Deltatrac II 2. VCO_2 from Servo-I ventilator	VCO_2-based equation, Schofield, FAO/WHO/UNU	Large difference and limits of agreement between VCO_2 measured by IC and Servo-I. Difference ≤10% observed in 44% of children overall, and 70% in children weighing ≥15 kg. The limits of agreement were narrowest for the REE based on VCO_2 (Servo-I) compared with Schofield and FAO/WHO/UNU equations. The VCO_2 method was not sufficiently accurate for children weighing <15 kg.
Jotterand Chaparro et al.[39]	Observational longitudinal prospective study	$n = 75$ (43/32) children undergoing ventilation, PICU Median age: 21 (5–35) months Normal nutrition status: 51% Malnutrition: 49%	$n = 407$ Indirect calorimeter: Deltatrac II	HB; HB infant; Henry-W; Henry-HW; Fleisch; Meyer A, B, and C; Schofield-W; Schofield-HW; Talbot; White 1;	The tables of Talbot, Henry, and Schofield equations had the smallest biases but underestimated or overestimated REE for low values. The Mehta equation had a bias of −8% (95% CI, −17% to −3%) at 200 kcal/day that gradually decreased to reach zero bias at 1000 kcal/day. Equations of White 1 and 2, Fleisch, and HB should not

(Continues)

TABLE 2 (Continued)

References	Study design	Population	Measurements	Predictive equations	Key findings and author conclusion
				White 2; WHO; Mehta (VCO_2-REE)	be used in young critically ill children. No equation was accurate for the range of 200–1000 kcal/day
Mouzaki et al.[40]	Observational longitudinal study	$n = 104$ (56/48) children undergoing ventilation after cardiopulmonary bypass, PICU Median age: 5.1 (0.6–10) months Nutrition status: ∅	$n = 575$ paired REE measurements Indirect calorimeter: AMIS 2000	1. REE by the standard Weir equation 2. VCO_2-based equation: REE(VCO_2)	Median values for REE and REE(VCO_2) were 54 kcal/kg/day ($P = 0.48$). REE(VCO_2) was within 10% of REE in 49% of measurements. The equation using VCO_2 is appealing for critically ill patients. However, it is of limited value in the immediate postoperative period after cardiopulmonary bypass owing to wide variation in RQ.
Mehta et al.[41]	Observational transversal 2-center study	Children undergoing ventilation, PICU Derivation group: $n = 79$; median age: 2.3 years Validation group: $n = 94$; median age: 0.5 years Nutrition status: ∅	1. REE by Vmax Encore 2. REE by Deltatrac II	VCO_2-based equation REE(VCO_2), Schofield	The bias and limits of agreement for the VCO_2 based equation were −0.7% (−14% to +13%). No error in predicting REE when the actual RQ was 0.9. For an RQ of 0.7–1.2, the percentage expected error ranged from −20% to +20%, respectively. The mean bias for Schofield was 0.09% (40%–41%). The equation using VCO_2 values was superior to standard equation.
Mtaweh et al.[42]	Observational longitudinal study	$n = 13$ (8 males) children undergoing ventilation, PICU Age: 9.8 ± 1.4 years Nutrition status: ∅	$n = 32$ Indirect calorimeter: not specified	HB, Schofield-HW	REE was 70% ± 4% of estimated REE for all participants, and only 5 of the REE values were greater than expected from the HB equation. When measured, REE was compared with estimated REE as determined by the Schofield equation; the mean was 69% ± 5%, with 3 measurements greater than expected.
Smallwood et al.[43]		$n = 34$ (12 males) children undergoing ventilation, PICU Nutrition status: ∅	$n = 45$ Indirect calorimeter: Vmax Encore	Schofield-HW	No agreement between measured and predicted REE by the Schofield equation. The mean bias was −127 kcal/day (−25%), and limits of agreement were −418 to 1176 (−85% to 142%).
Meyer et al.[44]	Observational prospective longitudinal study	$n = 30$ (17/13) children undergoing ventilation, PICU Median age: 52 months Nutrition status: ∅	$n = 30$ Indirect calorimeter: Deltatrac II	Meyer A, B, C; Schofield; White 2; FAO/WHO/UNU	The White formula performed less well. Schofield and FAO/WHO/UNU equations had a better statistical predictive value. Meyer equation A performed better than others. No equation predicted REE within a clinically accepted range.

TABLE 2 (Continued)

References	Study design	Population	Measurements	Predictive equations	Key findings and author conclusion
De Wit et al.[45]	Observational transversal study	$n = 21$ (17/4) children undergoing ventilation; PICU 7.3 ± 10.27 months No obesity	$n = 21$ Indirect calorimeter: Deltatrac II	White 2, FAO/WHO/UNU, Schofield	Significant difference between measured REE and the Schofield ($P = 0.006$), FAO/WHO/UNU, ($P = 0.002$), and PICU-specific equations ($P < 0.0001$). None predicted REE within an acceptable clinical range.
Sy et al.[46]	Observational prospective study	$n = 31$ (18 males) Mean BMI: 19 ± 5, 16 ± 4, and 19 ± 5	$n = 31$ Bicarbonate dilution kinetics	Schofield, FAO/WHO/UNU	The mean bias and limits of agreement between the bicarbonate method and Schofield and FAO/WHO/UNU equations were, respectively, 6.6 (−21 to 34) and 26 (−31 and 83) kcal/kg/day. The FAO/WHO/UNU and Schofield equations overestimated and underestimated measured REE, respectively.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FAO/WHO/UNU, Food and Agriculture Organization of the United Nations/World Health Organization/United National University; HB, Harris-Benedict; Henry-HW, Henry equation using height and weight; Henry-W, Henry equation using weight; IC, indirect calorimetry; Oxford-HW, Oxford equation using height and weight; Oxford-W, Oxford equation using weight; PICU, pediatric intensive care unit; REE, resting energy expenditure; RQ, respiratory quotient; Schofield-HW, Schofield equation using height and weight; Schofield-W, Schofield equation using weight; VCO_2, carbon dioxide production; VO_2, oxygen consumption; ∅, information not provided.

weight, age, anthropometrics, percentage of body surface area burned, respiratory disease, and multiorgan failure. Additional factors, including temperature, cardiopulmonary bypass, neuromuscular blockade, inotropes, vasopressors, and cytokine levels, were significantly correlated with EE in the majority but not in all measurements. In neonates, age, heart rate, and caloric intake positively correlated with EE.

Similar to this systematic review, three recent studies[34,35,52] observed a positive association between weight and EE in children. One study found a positive association between age and EE.[34]

A recent study also observed a positive association between EE and the presence of multiorgan failure, but the causes of PICU admission and underlying disease were not correlated with EE.[35] The systematic review[5] and three recent studies[32,35,37] showed no correlation between the disease severity and EE. Most studies have reported a positive association between body temperature and EE. Day in the PICU was not correlated with EE in the systematic review,[5] similar to a recent study,[32] whereas a positive correlation was observed in another study.[52]

Among recent studies, one study[52] also showed that neuromuscular blockers and sedatives had a negative association with EE in critically ill pediatric patients, and three studies did not find an association.[32,35,53]

Methods of determination of protein needs (main question 2)

Four studies on the methods of determining protein needs were included,[61–64] all testing various methods in different populations (Table 4).

In 2010, one study investigated the blood urea nitrogen method in 86 low-birth-weight preterm infants, and no significant association with protein intake was observed throughout time on parenteral nutrition.[64] In 2011, a study evaluated the balance of phosphate and rate of creatinine excretion as a method to monitor cell catabolism in 11 children undergoing ventilation after cardiac surgery.[63] Balance of phosphate was a useful and early tool for monitoring cell breakdown, whereas creatinine excretion rate is not a good marker of catabolism in children with major changes in glomerular filtration rate.

More recently, a study assessed the variability in the 24-h appearance of amino acids, representing protein and arginine metabolism, using stable isotopes in eight critically ill children.[62] The 24-h protein and arginine metabolism showed high intraindividual variability in the continuously fed children. The last study published

TABLE 3 Findings related to subquestion 1c: Factors that may impact EE in critically ill pediatric patients.

References	Study design	Population	Measurements	Key findings and author conclusions
Ewing et al.[47]	Prospective observational pilot study	$n = 7$ children undergoing extracorporeal membrane oxygenation, PICU Median age: 5 (0.5–11) years Median BMI: 15	$N = 16$ Indirect calorimeter: Vmax Encore	Highest EE in patients with septic shock
Briassoulis et al.[32]	Cross-sectional study	$n = 153$ (108 boys/45 girls) children undergoing ventilation, 27% trauma, PICU Median age: 7.5 (5–12.5) years Underweight: 20% Overweight: 11% Obese: 25%	$n = 153$ Indirect calorimeter: E-COVX	Only a younger age was significantly associated with EE. BMI nutrition status (overweight, obesity), severity of illness, diagnostic category, outcome, temperature, heart rate, lactate, vasoactive drugs, neuromuscular blockade, and energy intake were not independently associated with EE.
Spolidoro et al.[34]	Cross-sectional prospective study	$N = 257$ (145 males) children, PICU Median age: 2.4 years Z score BMI: −0.7 (2), including patients with obesity	$N = 257$ Indirect calorimeter: Vmax 29	VO_2, VCO_2, height, weight, and age were highly correlated with EE. In other cases (systolic blood pressure; diastolic blood pressure; CRP; oxygen saturation, blood glucose, temperature, heart rate, hemoglobin, etc), the Pearson R value was low.
Perrone et al.[48]	Cross-sectional study	$n = 50$ very low-birth-weight infants, NICU Mean age: 36.5 ± 0.85 weeks	$n = 50$ Indirect calorimetry: Quark RMR	No differences were found in EE of infants with human milk vs prevalent formula diet
Zaher et al.[49]	Observational prospective pilot study	$n = 42$ (57% boys) children undergoing ventilation, PICU Median age: 4.5 (2–11) years Malnourished: 12% Overweight: 9.5%	$n = 21$ Indirect calorimetry: Ultima CCM	GLP-1 had a poor association with REE and a good association with metabolic index. This suggests that rather than predicting overall REE, GLP-1 was associated with variation in REE induced by critical illness.
Zhang et al.[50]	Randomized trial	$n = 38$ infants with complex cardiac heart disease Weight-for-age Z score: −2.5 ± 0.9; −2.6 ± 1.3; and −2.8 ± 1.5	$n = 38$ Indirect calorimeter: Vmax Encore	CRP was positively correlated with EE when adjusted to group and time
Jhang and Park[35]	Retrospective study	$n = 25$ (14 boys/11 girls) children undergoing ventilation, PICU Median age: 24.4 (3.7–214) months Malnutrition: 46%	$n = 25$ Indirect calorimeter: E-sCAiOVX gas exchange module	EE was positively associated with weight and height and positively or negatively associated with several organ failures (negative for neurologic and positive for hematologic). Underlying disease, causes of PICU admission, disease severity, vasoactive-inotropic score, and the use of vasoactive-inotropic agents or sedatives were not associated with EE.
Pereira-da-Silva et al.[51]	Observational prospective study	$n = 29$; 15 preterm and 14 term infants, NICU	$n = 317$	Among all infants, preterm and term, no significant associations were found between EE and sex, binary gestational age at birth,

TABLE 3 (Continued)

References	Study design	Population	Measurements	Key findings and author conclusions
		Median gestational age: 35 and 38 weeks	Indirect calorimetry: Deltatrac II	postmenstrual age, weekly measured body weight, or daily total energy intake
Mtaweh et al.[52]	Retrospective study	$n = 239$ (57% boys) children undergoing ventilation, 10% burn and 8% trauma, PICU Median age: 4.7 (0.7–12) years Nutrition status: ∅	$n = 279$ Indirect calorimetry: Vmax Encore	EE was significantly associated with weight, heart rate, diastolic blood pressure, PICU day, minute ventilation, vasoactive-inotropic score, opioids, chloral hydrate, dexmedetomidine, inhaled salbutamol, and propofol dose
Ismail et al.[37]	Observational prospective study	$n = 40$ (24 boys) children undergoing ventilation and severe sepsis, PICU Median age: 7 (5.2–10) years Underweight: 18% Overweight: 13% Obese: 3%	$n = 176$ Indirect calorimeter: Quark RMR	None of the severity indices showed any correlation with EE. Mean EE was significantly higher in underweight group compared with non-underweight group.
Mtaweh et al.[5]	Systematic review	$n = 103$ articles included 42 articles on children and adolescents $n = 1869$ children and neonates	$n = 2646$ Indirect calorimetry used in 98% studies, Deltatrac II in 44% of studies,	Weight, age, anthropometrics, body surface area burn, respiratory disease, and multiorgan failure were positively associated with EE. In neonates, age, heart rate, sepsis, caloric intake, nutrition support, and stimulants had a positive association with EE.
Mortamet et al.[53]	Observational prospective study	$n = 20$ (10 boys) children undergoing ventilation, 15% neurologic disorder, PICU Median age: 5.5 (2–64) months Nutrition status: ∅	$n = 20$ Indirect calorimetry: Vmax Encore	EE and VO_2 did not differ according to the COMFORT behavior scale and sedation score
Jotterand Chaparro et al.[24]	Observational prospective study	$n = 74$ children undergoing ventilation for >72 h, PICU Median age: 21 months Normal nutrition status: 51% Malnutrition: 46%	$n = 402$ Indirect calorimetry: Deltatrac II	EE was affected by the use of neuromuscular blocking drugs, which decreased it by 6%, and by body temperature, which increased it by 8% per degree
Floh et al.[54]	Observational prospective study	$N = 111$ (55% boys) children post–cardiac surgery, PICU Median age: 5.3 (0.8–10.5) months Nutrition status: ∅	$n = 111$ Indirect calorimetry: AMIS 2000	EE was positively associated with plasma interleukin-6 and inversely associated with preoperative methylprednisolone use. Increase in cardiac output was also associated with higher EE. Age had a weak, but statistically significant, inverse association with EE.
Mehta et al.[55]	Observational prospective study	$n = 26$ (62% boys) children undergoing ventilation after cardiac surgery, cardiac PICU and PICU	$n = 26$ Indirect calorimetry: Vmax Encore	Mean values of VO_2 and EE did not change within the first 24 h after surgery. Concentrations of serum CRP showed a significant increase between EE baseline and 24 h postoperatively but did not correlate with EE at 8 h.

(Continues)

TABLE 3 (Continued)

References	Study design	Population	Measurements	Key findings and author conclusions
		Mean age: 3.6 ± 2.6 years Mean weight-for-age Z score: −0.94		
Meyer et al.[44]	Observational prospective study	$n = 175$ children undergoing ventilation, PICU Median age: 54 (1–191) months Central nervous system failure: $n = 48$ Nutrition status: ∅	$n = 369$ Indirect calorimetry: Deltatrac II	Only weight and diagnosis influenced EE significantly. Neuromuscular blockade, temperature, severity of disease, CRP, and PICU day did not have a significant impact on EE.
Bauer et al.[56]	Observational prospective study	$n = 32$ preterm neonates Mean gestational age: 35 ± 1 weeks	$n = 32$ Indirect calorimetry: Deltatrac II	EE in the moderately preterm infant group was significantly increased compared with the group of infants appropriate for gestational age
Botràn et al.[57]	Observational prospective study	$n = 46$ postsurgical and medical children undergoing ventilation, PICU Median age: 7.5 (3.8–25.8) months <10th percentile for age: 76%; <3rd percentile: 63%	$n = 46$ Indirect calorimetry: E-COVX	No relationship between EE and clinical severity, anthropometric nutrition status and biochemical alterations; no differences in EE between children with heart disease and those with other conditions
De Wit et al.[45]	Observational prospective study	$n = 21$ children undergoing ventilation after surgery for congenital heart disease, PICU Mean age: 7.3 ± 10.27 months No obese	$n = 21$ Indirect calorimetry: Deltatrac II	Cardiopulmonary bypass had a significant influence on EE after surgery. Children who were malnourished preoperatively had greater EE postoperatively.
Feferbaum et al.[58]	Observational prospective study	$n = 19$ neonates with sepsis, NICU Mean age: 27.3 ± 17.2 days	$n = 19$ Indirect calorimetry: developed by Hamamoto	EE was significantly increased during recovery compared with the acute phase of sepsis phase
Moreira et al.[59]		$n = 51$ very low-birth-weight newborns, 23 small and 28 appropriate for gestational age	$n = 51$ Indirect calorimetry: Deltatrac II	No statistical difference in EE between small- and appropriate-for-gestational-age very low-birth-weight newborns after reaching corrected at-term age
Nydegger et al.[60]	Observational prospective study	$n = 91$ neonates with congenital heart disease Median age: 16 (0–352) days Nutrition status: ∅	$n = 11$ paired measurements of REE preoperatively and postoperatively Indirect calorimetry: Deltatrac II	EE was increased before cardiac surgery compared with healthy controls. EE normalized within 1 week after surgery (not significantly), independently of age at operation, underlying heart defect, arterial blood saturation, pulmonary flow, or sex.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; EE, energy expenditure; GLP-1, glucagon-like peptide 1; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; REE, resting energy expenditure; VCO_2, carbon dioxide production; VO_2, volumetric oxygen consumption; ∅, information not provided.

TABLE 4 Findings related to main question 2: Methods used to determine protein needs in critically ill pediatric patients.

References	Study design	Objective	Population	Measurements	Key findings and author conclusions
Fullerton et al.[61]	A pilot study	To examine (1) the feasibility of using N-glycine urinary end-product enrichment to quantify protein turnover in children after thoracic surgery and (2) the correlation between protein balance obtained by this method and urinary urea nitrogen method	$n = 19$ (7/12) children; PICU Median age: 13.8 (12.2–15.1) years Body mass index *Z* score for age: −0.02 (−0.91 to 1.13)	15 N enrichment of ammonia and urea was measured in mixed urine after 12 and 24 h, respectively, and protein synthesis, breakdown, and net balance was determined	Protein synthesis and breakdown by N enrichment were 7.1 (5.5–9) and 7.1 (5.6–9) g/kg/day with ammonia (12 h) as the end product, and 5.8 (3.8–6.7) and 6.7 (4.5–7.6) g/kg/day with urea (24 h), respectively. Net protein balance by the N-glycine and urinary urea nitrogen methods were −0.34 (−0.47 to −0.3) and −0.48 (−0.65 to −0.28) g/kg/day, respectively. Protein balance obtained by the two methods was significantly correlated The single-dose oral administration of N-glycine stable isotope with measurement of urinary end-product enrichment is a feasible and noninvasive method to investigate whole-body protein turnover in children.
De Betue et al.[62]	Observational prospective study	To assess the variability in 24-h appearance of amino acids, representing protein and arginine metabolism, using stable isotopes, in critically ill children	$n = 8$ critically ill children, PICU and cardiac PICU Median age: 0.40 (0.1–9.9) y No overweight or obesity	24-h stable isotope tracer protocol Arterial blood was sampled every hour	Coefficients of variation, representing intra-individual variability, of the amino acid appearances of phenylalanine, tyrosine, leucine, arginine, and citrulline were high. The pattern and overall 24-h level of whole-body protein balance differed per individual. 24-h protein and arginine metabolism showed a high intra-individual variability in continuously fed critically ill children. When performing stable isotope tracer studies, this should be kept in mind.
Teixeira-Cintra et al.[63]	Prospective observational cohort study	To evaluate whether balance of phosphate and rate of creatinine excretion would be useful to monitor cell catabolism	$n = 11$ (8 boys) children undergoing ventilation after cardiac surgery, PICU No obesity	24-h urine collections were obtained postoperatively for creatinine measurement and nitrogen and phosphate balance	Phosphate balance was greater on days with anabolism compared with that on days with catabolism. Daily creatinine excretion did not correlate with protein balance. Balance of phosphate was a useful and early tool to monitor cell breakdown. Creatinine excretion rate was not a good marker of catabolism in patients with major changes in glomerular filtration rate.
Roggero et al.[64]	Prospective, longitudinal,	To investigate the relation between protein intake and	$n = 86$ preterm infants Mean gestational age (SD): 30 (2) weeks	Protein intake: 24-h period before blood	No correlation between protein intake and blood urea nitrogen during parenteral nutrition. Moderate positive correlation was observed on full enteral feeding.

(Continues)

TABLE 4 (Continued)

References	Study design	Objective	Population	Measurements	Key findings and author conclusions
	observational study	blood urea nitrogen during parenteral and enteral nutrition	Small for gestational age: 31%; extremely low birth weight: 30%	urea nitrogen collection Blood urea nitrogen: venipuncture on days 2, 5, and 15 of parenteral nutrition, and day of full enteral feeding	Blood urea nitrogen was not significantly associated with protein intake throughout the entire duration of parenteral nutrition.

Abbreviation: PICU, pediatric intensive care unit.

in 2018 in 19 critically ill children after thoracic surgery (median age, 14 years) showed that a single-dose oral administration of N-glycine stable isotope with measurement of urinary end-product enrichment was a feasible and noninvasive method to investigate whole-body protein turnover.[61] The protein balance obtained using the isotope and urinary urea nitrogen methods was significantly correlated.

DISCUSSION

This scoping review aimed to understand the extent and type of evidence in relation to the methods used to determine energy and protein needs in critically ill pediatric patients. Studies on the accuracy of predictive equations to estimate REE and the roles of clinical factors on EE were considerable, whereas only a few studies assessed methods of measurements of EE and of determination of protein needs.

Measurement of EE

We could only include two studies on the measurement methods of EE, which used indirect calorimetry in 30 critically ill children undergoing ventilation.[30,31] The first compared two indirect calorimeters, that is, E-COVX (GE Healthcare, Datex-Ohmeda) and Vmax Encore,[30] and the second assessed the impact of ventilator modes on the values obtained with E-COVX.[31] As no reference method was used, we could not draw conclusions regarding their accuracy.

The E-COVX is a gas exchange module developed to replace the Deltratrac II, which measures gas flow and concentrations via an adapter connected to the endotracheal or tracheostomy tube. The Vmax Encore is a breath-by-breath method similar to the mode of action of the Deltatrac II. Gas is sampled at the humidifier and ventilator exhaust to measure O_2 and CO_2 concentrations, and flow is measured at the ventilator exhaust.

In vitro pediatric studies and adult clinical studies have assessed the accuracy of these devices. The E-COVX and another new gas exchange module, the E-sCAiOVX-00 (GE Healthcare, Datex-Ohmeda), were tested for VCO_2 and VO_2 between 20 and 100 ml/min, which corresponded to patients weighing ~5–16 kg.[39] The E-COVX had wide bias and limits of agreement for VO_2 and VCO_2 that were not clinically acceptable, in contrast to the E-sCAiOVX, except for VCO_2 and VO_2 at 20 ml/min. Similarly, studies that compared the E-COVX or M-COVX (similar to the E-COVX) with the Deltatrac II in adults undergoing ventilation showed large limits of agreements.[19,68,69] These findings show the risk of inaccuracy when measuring REE with the E-COVX in critically ill children undergoing ventilation.

The Vmax Encore was tested in vitro for EE between 50 and 2000 kcal/day.[70] The predicted and actual VO_2 and VCO_2 data were strongly correlated; however, the simulation model represented spontaneously breathing critically ill patients. In another pediatric simulation, the CCM Express (MGC Diagnostics, Saint Paul, MN) and the volumetric capnography device NM3 (Philips Healthcare, Eindhoven, Netherlands), which measures VCO_2, showed a small mean bias for VCO_2 and acceptable limits of agreement.[71] The simulation values of VO_2 and VCO_2, corresponded to children older than 8 years and weighing >35 kg[72]; therefore, future research is needed for younger children, as they are highly represented in the PICU.

Estimation of REE

For this subquestion, we found 16 eligible studies performed in the PICU, including a systematic review,[13] concluding that none of the predictive equations developed in healthy or critically ill children were satisfactory for estimating REE in the PICU.

Most studies[13,35–37,39] observed that the Schofield equation, which predicted REE within ±10% of the measured REE in 30%–38% of observations only,[13,37] was one of the least inaccurate. The direction of accuracy differed among studies, with underestimation and overestimation of REE,[13,37] mainly an underestimation,[35,46] or an overestimation.[31,34,36] One study[39] showed that the bias of the Schofield equation differed along the REE range of values, resulting in the underestimation of REE in young children and the overestimation in older children, which may explain these differences. It is difficult to extrapolate the error introduced when estimating REE using this equation in critically ill children.

The FAO/WHO/UNU equation was also one of the least inaccurate equations in recent studies, but still had large limits of agreement.[32,36,37] Equations specifically developed for critically ill children did not perform better than the standard equations, especially the White equation.[67] These findings are in line with nutrition guidelines, which recommend that REE measurement using a validated indirect calorimeter should be considered to guide nutrition support in critically ill pediatric patients after the acute phase of the disease.[7–9] If not feasible, the guidelines suggest the use of the Schofield or FAO/WHO/UNU equations, using an accurate weight.

A recent study confirmed overestimation of REE when adding a stress factor of 1.2 to the predicted REE[36]; similarly, most included studies revealed an overestimation of REE using the HB equation and the Dietary Reference Intakes. Again, these are in line with nutrition guidelines,[7,9] which recommend not using the HB equation, not using Dietary Reference Intakes, and not adding a stress factor. Our findings do not provide guidance on which predictive equations should be used in specific subgroups of patients, including those with burns or trauma, or the increasing number of overweight or obese patients. Apart from age, no correlation was observed between these factors and the accuracy (or inaccuracy) of the predictive equations tested.[32,33]

The simplified metabolic equation, which uses a fixed RQ of 0.89 and a measured VCO_2, developed for critically ill children, was assessed by several studies,[13,33,34,38–40] which observed that ~50% of measurements fell within ±10% of measured REE.[32,40] This method, which is neither a simple predictive equation of REE nor a classical measurement of REE, performed better than the other equations.[34,39] This is promising for the future; however, this still requires an accurate measurement of VCO_2, especially in children weighting <15 kg.[38]

Clinical factors impacting EE determination

Studies that assessed the impact of clinical factors on EE are quite frequent, including a recent systematic review.[5] They assessed various factors related to the patients (age, weight, sex, respiratory rate, heart rate, etc), treatment, diseases, and PICU days. However, each of these factors has been evaluated in a few studies, and the findings were not consistent except for weight and age.

As expected, the available data showed positive correlations between weight and EE and age and EE.[5,32,34,35,44] These variables are included in most, if not all, of the standard predictive equations of REE for children and adults. Among the dynamic clinical factors, there was good agreement for the severity of illness among the included studies, concluding in the absence of an association with EE.[5,35,37,44,57] Similarly, most studies did not show a correlation between PICU days and EE. The relationship between EE and diagnosis remains indeterminate, but several studies do not show an association.[32,35,57] These findings may explain why predictive equations specifically developed for critically ill children, that is, the equations of Meyer et al.[45] and White et al.,[67] which integrate diagnosis categories and/or PICU days, are often more inaccurate than traditional predictive equations. Other factors, such as minute ventilation or heart rate, assessed in recent studies, could better represent the physiological state at different times of illness and be more useful in predicting EE.

Findings regarding sedation, neuromuscular blockade, inotropes, vasopressors, and caloric intake were not completely consistent. Most studies have observed a positive correlation between body temperature and EE and a negative association for neuromuscular blockade and sedation. These factors deserve further consideration for inclusion in predictive equations for estimating REE in critically ill pediatric patients.

These findings confirm that when estimating REE with a predictive equation in critically ill children, additional factors are not needed during the acute phase of disease on sedation and mechanical ventilation. This is in agreement with the guidelines, which recommend providing energy intake not exceeding REE during the acute phase and taking into account energy debt, physical activity, rehabilitation, and growth thereafter.

Determination methods of protein needs

We could only include four studies on the methods used to determine protein needs that assessed four different methods in various populations. These included the blood urea nitrogen method, balance of phosphate and the rate of creatinine excretion, use of stable isotopes, and administration of N-glycine stable isotopes with measurement of urinary end-product enrichment. The latter was promising in 19 older critically ill children to assess whole-body protein turnover[61] and needs further investigation in larger samples of younger children.

The classical method to determine protein needs in healthy and sick patients is the nitrogen balance method,[22] which requires an accurate assessment of both nitrogen intake and all nitrogen losses, especially urinary nitrogen losses, over several consecutive days. Only a few studies have used this method in critically ill children,[23,73] and an easier method is necessary for clinical practice and research. The recommendations for protein intake are still based on studies that measured urinary nitrogen losses and showed higher losses than reference values in healthy children. Based on these data, it is recommended to provide ≥1.5 g/kg per day and 57 kcal/kg per day to equilibrate the nitrogen balance in critically ill children.[7,9,73]

Limitations of the scoping review

This scoping review has some limitations. The measurement of EE differed among the included studies. Although the studies included in the systematic reviews mainly used the Deltatrac II, more recent studies used different devices, that is, the E-COVX, E-sCAiOVX, Quark RMR, Vmax Encore, the AMIS 2000, or respiratory mass spectrometry. As none of these indirect calorimeters has been validated in critically ill children, this may affect the findings of this scoping review and explain some observed discrepancies. Nevertheless, the global findings were quite similar among studies, except for one study, which used the E-COVX and had findings contrasting with previous studies regarding the Schofield and HB equations.[32] Other factors such as the included population may also explain this discrepancy. Thus, the device used should also be considered when interpreting the findings of each included study. In addition, the population of the included studies was quite heterogeneous, especially with respect to various ages and diagnoses. Finally, various studies performed in neonates on the topics were excluded from this scoping review, as they were conducted outside the NICU. As a result, most of the eligible studies were performed in the PICU and not in the NICU.

CONCLUSION

This scoping review revealed a considerable amount of data on predictive equations to estimate REE and factors that may affect EE in critically ill children, whereas data on methods to measure EE and determine protein needs were limited. No indirect calorimeters have been validated in critically ill children undergoing ventilation. Research in this area is urgently needed, but there are many challenges, including which reference method to use. Predictive equations frequently underestimate and/or overestimate REE. The Schofield equation was the least inaccurate of the traditional equations, and the metabolic equation, which used a fixed RQ and measured VCO_2, performed better. Apart from weight and age, no clinical factors were clearly correlated with EE and should be included in the new predictive equations without further investigation.

AUTHOR CONTRIBUTIONS

Corinne Jotterand Chaparro, Clémence Moullet, Frédéric V. Valla, Nilesh M. Mehta, and Lyvonne Tume designed the study and wrote the protocol; Corinne Jotterand Chaparro, Clémence Moullet, and Céline Pabion reviewed the study abstracts and full texts and extracted the data; Corinne Jotterand Chaparro, Clémence Moullet, Lyvonne Tume, Nilesh M. Mehta, Céline Pabion, and Frédric V. Valla analyzed and interpreted the data; Corinne Jotterand Chaparro wrote the draftprotocol and the draft manuscript, which was reviewed and approved by all authors; and Lyvonne Tume and Nilesh M. Mehta English-edited the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Corinne Jotterand Chaparro http://orcid.org/0000-0002-1538-7127
Lyvonne Tume https://orcid.org/0000-0002-2547-8209
Nilesh M. Mehta http://orcid.org/0000-0001-8146-2407
Frédéric V. Valla https://orcid.org/0000-0001-5285-1104
Clémence Moullet https://orcid.org/0000-0003-1056-9869

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APPENDIX A: SEARCH STRATEGY

Name of database: MEDLINE PubMed and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 30, 2023>.

The full-search strategy was developed by combining population, intervention, and comparison terms and excluded animal studies, reviews, and editorials. The search was conducted on January 30, 2023.

#	Searches	Results
1	(preterm* OR neonatology OR neonate* OR Child or Infant or Infant, Newborn or Adolescent or Pediatrics or child* or infant* or newborn* or pediatr* or paediatr*)	5,251,666
2	(Intensive Care Units or Critical Care or Critical Illness or Critical Care Nursing or Intensive Care Units, Pediatric or Intensive Care, Neonatal or ICU* or PICU* or NICU*)	522,674
3	1 AND 2	148,673
4	Proteins or Amino Acids or protein* or amino acid or amino acids	8,813,237
5	Energy Metabolism OR Basal Metabolism OR energy expenditure OR Energy OR calori*	1,529,262
6	4 OR 5	9,774,246
7	Calorimetry OR Calorimetry, Indirect OR indirect calorimetry OR calorimeter OR equation OR doubly labelled water OR nitrogen OR urinary loss* OR chemoluminescence OR Kjeldahl)	598,101
8	3 AND 6 AND 7	623
9	Humans	543
10	NOT (review[Publication Type])	477
	NOT (editorial[Publication Type])	512
11	Final equation: (preterm* OR neonatology OR neonate* OR Child or Infant or Infant, Newborn or Adolescent or Pediatrics or child* or infant* or newborn* or pediatr* or paediatr*) AND (Intensive Care Units or Critical Care or Critical Illness or Critical Care Nursing or Intensive Care Units, Pediatric or Intensive Care, Neonatal or ICU* or PICU* or NICU*) AND ((Proteins or Amino Acids or protein* or amino acid or amino acids) OR (Energy Metabolism OR Basal Metabolism OR energy expenditure OR Energy OR calori*)) AND (calorimetry OR Calorimetry, Indirect OR Calorimetry, methods* OR indirect calorimetry OR calorimeter OR equation OR doubly labelled water OR nitrogen OR urinary loss* OR chemoluminescence OR Kjeldahl OR isotope OR isotop*) NOT (review[Publication Type]) NOT (editorial[Publication Type]) Limit: Last 15 years (1 January 2008 to 30 January 2023)	398