Is Energy Delivery Guided by Indirect Calorimetry Associated With Improved Clinical Outcomes in Critically Ill Patients? A Systematic Review and Meta-analysis

Nutrition and Metabolic Insights
Volume 13: 1–10

DOI: 10.1177/1178638820903295

Oana A Tatucu-Babet[1], Kate Fetterplace[2,3], Kate Lambell[1], Eliza Miller[1], Adam M Deane[3] and Emma J Ridley[1,4]

[1]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia. [2]Allied Health (Clinical Nutrition), The Royal Melbourne Hospital, Parkville, VIC, Australia. [3]Department of Medicine, The Royal Melbourne Hospital, The University of Melbourne, Parkville, VIC, Australia. [4]Nutrition Department, The Alfred Hospital, Melbourne, VIC, Australia.

ABSTRACT

BACKGROUND: Indirect calorimetry (IC) is recommended to guide energy delivery over predictive equations in critical illness due to its precision. However, the impact of using IC to measure energy expenditure on clinical outcomes is uncertain.

OBJECTIVE: To evaluate whether using IC to measure energy expenditure to inform energy delivery reduced hospital mortality and improved other important outcomes compared to using predictive equations in critically ill adults.

METHODS: A systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline. Medline, Embase, CINAHL, and the Cochrane Library were searched for studies using IC to guide energy delivery compared to a predictive equation in adult critically ill patients with the primary outcome (hospital mortality) or any of the secondary outcomes reported (including but not limited to hospital and intensive care unit (ICU) length of stay (LOS) and duration mechanical ventilation (MV). Risk of bias within studies was assessed using the Cochrane "Risk of Bias" 1 tool. Random-effect meta-analyses were used when heterogeneity between studies existed ($I^2 > 50\%$). Data are reported as median (interquartile range [IQR]), binomial outcomes as odds ratio (OR), 95% confidence interval (CI), and continuous outcomes as mean difference (MD).

RESULTS: Of 4060 articles, 4 randomized controlled trials were identified with 396 patients included in analysis. Three studies were considered low risk of bias and 1 as high risk. Two studies reported hospital mortality (n = 130 and 40 participants, respectively). When combined, no association between IC-guided energy delivery and hospital mortality was found (OR = 0.81, 95% CI = [0.25, 2.67], $P = 0.73$, $I^2 = 52$). No differences were reported with ICU mortality and hospital LOS between groups, but ICU LOS and duration of MV varied across all studies. According to the meta-analysis, no differences were observed in ICU LOS (MD = 1.39, 95% CI = [−5.01, 7.79], $P = 0.67$, $I^2 = 81\%$), although the duration of MV was increased when energy delivery was guided by IC (MD = 2.01, 95% CI = [0.45, 3.57], $P = 0.01$, $I^2 = 26\%$). In all 4 studies, prescribed energy targets were more closely met when energy delivery was informed by IC compared to a predictive equation. Three studies reported the percentage delivered versus the prescribed energy target, with the median (IQR) delta between the IC and predictive equation arms 19% (10%-32%).

CONCLUSION: Limited data exist to assess the impact of using IC to inform energy delivery in comparison to predictive equations on hospital mortality. The association of IC use with other important outcomes, including duration of MV, needs to be further explored before definitive conclusions can be made.

KEYWORDS: Critical illness, indirect calorimetry, energy expenditure, predictive equations, systematic literature review, meta-analysis

RECEIVED: November 28, 2019. **ACCEPTED:** January 3, 2020.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Emma J Ridley, Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Level 3, 553 St Kilda Road, Melbourne, VIC 3004, Australia. Email: Emma.ridley@monash.edu

Introduction

Predictive equations are the most commonly used method for estimating energy expenditure in critical care. Various equations exist, mainly derived using data from healthy subjects, and commonly adjusted for hyper-metabolism associated with critical illness by adding a stress factor.[1] Although predictive equations are efficient and inexpensive, resulting energy estimations have repeatedly shown to be inaccurate when compared to measured energy expenditure with indirect calorimetry (IC).[2-4] IC provides a more accurate alternative to predictive equations by quantifying oxygen consumption and carbon dioxide production to approximate energy expenditure. It is therefore considered the gold standard method for determining energy expenditure in critically ill patients and is recommended by

2 recent critical care guidelines as the preferred method to guide energy delivery in critical illness.[5-8]

The amount of energy to deliver during critical illness is unknown, regardless of whether energy delivery approximates a measured or estimated expenditure. A recent large (n = 3957) multicenter randomized controlled trial (RCT) investigating augmented energy delivery compared to standard care found no benefit in the primary outcome of 90-day mortality.[9] One possible explanation is that energy delivery was guided by a predictive equation rather than guided by an expenditure measured with IC. However, it is currently unclear if using a measured energy expenditure determined with IC to guide energy provision is superior to predictive equations in relation to clinical outcomes. The aim of this systematic review was to evaluate whether using IC to measure energy expenditure to inform energy delivery reduced hospital mortality and improved other important outcomes compared to using predictive equations in critically ill adults.

Method

A systematic review was conducted using methods outlined in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, the Cochrane Handbook for Systematic Reviews of Interventions, and the Center for Research and Dissemination (CRD's) guidance.[10-12] A protocol was developed a priori and registered on PROSPERO, the international register of systematic reviews, on January 11, 2019 (CRD42019117921).[13]

Population

Randomized and nonrandomized studies were included if they investigated adult (as per definition used in the paper of interest) critically ill patients who had a minimum of 1 IC measurement completed and a predictive equation estimate(s) was used as a comparator. Patients were defined as "critically ill" based on previously published criteria.[14,15]

Intervention and comparator

The intervention group included participants where IC was used to guide energy delivery in critical illness and the comparator included participants where a predictive equation was used.

Outcomes measures

Primary

- Hospital mortality.

Secondary

- Intensive care unit (ICU) mortality.
- Duration of mechanical ventilation (MV) (days).
- Ventilator-free days.
- ICU and hospital length of stay (LOS).
- Measure(s) of muscle strength (using the definition in the primary paper).
- Measure(s) of muscle mass (using the definition in the primary paper).

Eligibility criteria

Studies were screened based on the following eligibility criteria:

Inclusion criteria

- Conducted in adult critically ill patients.
- Used IC to guide nutrition therapy in the intervention.
- Used predictive equations to guide nutrition delivery as comparator.
- Original articles.
- Reported the primary outcome measure or one of the secondary clinical outcomes.

Exclusion criteria

- Study abstracts where the primary publication could not be located.
- Review articles.
- Case studies.
- Case series.
- Cluster-randomized trials.
- Non-English studies.

Both randomized and nonrandomized study designs were considered for inclusion in the review.

Search strategy

The following databases were searched on November 6, 2018: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (Medline) including published electronically ahead of print (Ovid SP, from 1948), Excerpta Medica Database (Embase) (Ovid SP, from 1974), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost, from 1948). This was prior to registration of the review on PROSPERO; however, no study processes were commenced until after submission of the protocol for registration (which was registered without changes).[13]

The Medline strategy was adapted for other databases with advice from a senior librarian. Publication restrictions for English language and studies containing humans were used pending the accuracy of the indexing for each search engine and at the advice of the senior librarian (see Appendix 1 for the Ovid Medline search strategy).

Study selection

Following the removal of duplicates, 2 investigators (O.A.T.-B. and E.M.) independently screened study titles and abstracts for inclusion in the review. Discrepancies were resolved by

consensus with a third investigator (E.J.R.). Processes were refined to ensure consistent methodology during the early stage of the screening process and prior to formal processes beginning. Articles deemed eligible for full-text review were assessed according to previously described inclusion and exclusion criteria by the same 2 investigators independently, with discrepancies resolved by the same third reviewer and group consensus. Once a final list of relevant articles was established, reference lists of included studies, relevant review papers, and clinical practice guidelines were hand searched for any additional eligible articles.

Data extraction and management

Data were independently extracted by 2 investigators (O.A.T.-B. and K.F.) and any discrepancies resolved with a third reviewer (E.J.R.). Prespecified data points for extraction included study methodology, sample size, patient characteristics, clinical characteristics, measured and estimated energy expenditure, method of estimated energy expenditure, and IC details including device used and if a steady state was reached, type of nutrition provided, energy delivered, percentage energy delivered versus measured or predicted requirements, and clinical outcome data. Authors were not contacted where data were unavailable in the primary publication.

Assessment of risk of bias in included studies

The Cochrane Risk of Bias Tool was used to assess the risk of bias of included randomized studies.[12] Two investigators (O.A.T.-B. and K.F.) independently assessed the risk of bias in included articles, with discrepancies resolved by a third reviewer (E.J.R.).

Study selection and management of review processes

EndNote reference manager software program (version X8.2, New York City: Thomas Reuters) and the online systematic review management program, Covidence 2013 (www.covidence.org) were used to coordinate the screening and data collection process.

Statistical reporting

Data from included studies is reported as "intention to treat" (ITT) where available or otherwise as "per-protocol." For continuous variables, mean and standard deviations (SDs) were directly recorded. To allow for comparison, where median with interquartile range (IQR) were reported, the data were converted to mean (SD) data as described by Wan et al.[16] Mortality is presented as odds ratio (OR) with 95% confidence interval (CI) and the duration of MV and ICU LOS as mean difference (MD) with 95% CI. Where meta-analysis has been conducted, the presence of statistical heterogeneity between studies was assessed using the chi-square statistic, with ≤ 0.10 indicating significant statistical heterogeneity and the I^2 indicating the magnitude of the heterogeneity. An I^2 of $\geq 50\%$ was considered problematic heterogeneity and a random-effects meta-analysis performed. Where I^2 was $<50\%$, a fixed-effects meta-analysis is presented.

Results

Study selection

The literature search identified 4060 articles following the removal of duplicates (Figure 1), with 203 articles retrieved for full-text screening and 5 RCTs included.[17-21] One study was excluded following initial inclusion, as it did not meet the review definition of being conducted in a critically ill population,[17] leaving 4 studies that analyzed 396 participants.[18-21] No nonrandomized studies met the eligibility criteria.

Study characteristics

Study characteristics are summarized in Table 1. All 4 of the included studies were single-center parallel RCTs and participant numbers ranged from 27 to 203 patients.[18-21] Three studies (Singer et al,[18] Allingstrup et al,[20] and Gonzalez-Granda et al[21]) comprised of predominantly medical ICU patients and the remaining study (Landes et al[19]) included patients admitted to a long-term acute-care hospital for failure to wean from MV.

Risk of bias

The risk of bias assessment can be seen in Figures 2 and 3. Overall, 3 studies (Singer et al, Landes et al, and Allingstrup et al) were considered low risk of bias and 1 as high risk of bias.

Allocation concealment was unclear in one study (Singer et al[18]) and inadequately described in another study (Gonzalez-Granda et al[21]). The remaining 2 studies were considered low risk of bias.[19,20]

Study personnel were blinded in one study by having alternate study members estimate and measure energy expenditure (although details of blinded outcome assessors were lacking)[19] and outcome assessors were blind to group allocation in another.[20] The remaining 2 studies were considered at high risk of bias as participants and study personnel were not blinded.[18,21]

One study (Gonzalez-Granda et al[21]) was deemed at high risk of attrition bias due to incomplete outcome data (informed consent was withdrawn from just under 50% of the initially recruited patients). The remaining 3 studies were considered low risk of bias.[18-20]

All studies were considered to have a low risk of bias for the "selective outcome reporting" and "other" sources of bias.

Nutrition characteristics and delivery

Studies reported that IC measurements repeated at frequent intervals were used to guide nutrition therapy in the

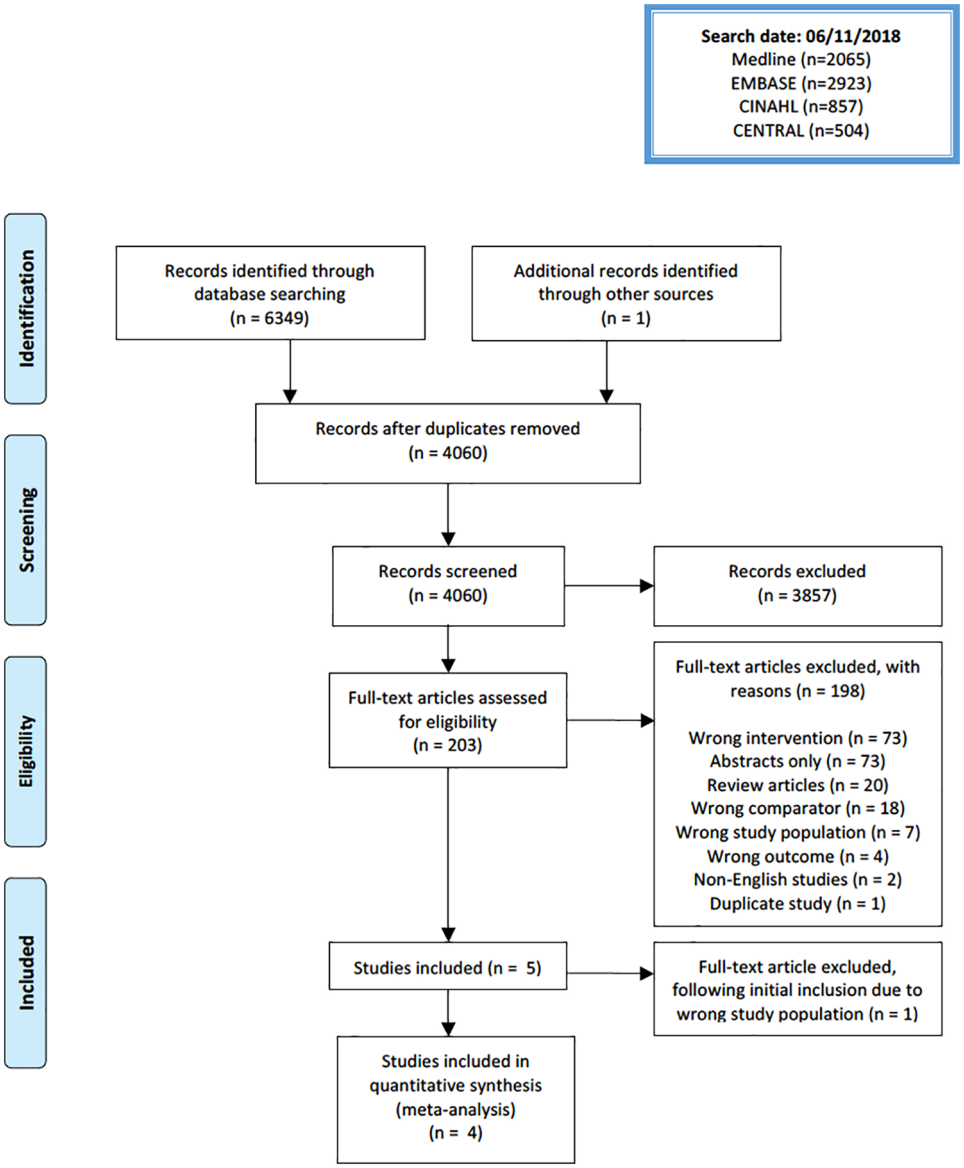

Figure 1. PRISMA flow diagram.
PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-analyses.

intervention arm, but the total number of IC measurements completed was not specified in all studies. Enteral nutrition (EN) was used preferentially to meet energy targets, with supplemental parenteral nutrition (PN) used as required in 3 studies (Singer et al, Allingstrup et al, and Gonzalez-Granda et al). Details of nutrition protocols between study arms are detailed in Table 1. All 4 studies reported higher receipt of energy close to the measured energy expenditure by IC compared to the predictive equation arm, although only 3 studies[19-21] reported a percentage delivered versus prescribed energy target. In these 3 studies, the mean range of energy delivery reported in the primary articles was 62% to 79% and 87% to 98% in the predictive equation and IC arms, respectively. When the data were transposed for comparison, the median (IQR) delta between the IC and predictive equation arms was 19% (10%-32%).

Hospital mortality

Hospital mortality was reported in 2 studies (Singer et al[18] and Gonzalez-Granda et al[21]). One study (Singer et al[18]) reported a nonsignificant reduction in hospital mortality with IC and the other (Gonzalez-Granda et al[21]) reported a nonsignificant increase. When combining these studies, hospital mortality was not associated with the use of IC to inform energy delivery (2 studies, 170 participants, random-effects analysis; OR = 0.81, 95% CI = [0.25, 2.67], $P = 0.73$, $I^2 = 52$, Figure 4A). One study (Allingstrup et al[20]) included data on 28-day, 90–day, and 6-month mortality with no differences reported between the IC and predictive equation arms (Table 2). Including 28-day mortality in a meta-analysis with the 2 studies that reported hospital mortality did not alter the association between mortality and IC (3 studies, 369 participants, fixed-effects analysis;

Table 1. Study interventions.

AUTHOR, YEAR, COUNTRY (REF)	TRIAL DETAILS			INTERVENTION ARM: IC				CONTROL ARM: PREDICTIVE EQUATIONS	
	ICU POPULATION	DURATION OF INTERVENTION	SUMMARY	IC DEVICE	TIMING/ NUMBER OF IC MEASUREMENTS	DURATION OF IC TESTS/ STEADY STATE	% ENERGY DELIVERY OF TARGET (MEAN ± SD)	CONTROL ARM: ENERGY ESTIMATION METHOD	ENERGY ADEQUACY, % TARGET
Singer et al, 2011, Israel[18]	Medical (36 [55%] in both arms), all requiring MV	2 weeks	Aim of reaching energy goal within 24 h of study inclusion. IC: Dietitian responsible for meeting energy goal. Control: Ward staff responsible for meeting energy goal using routine nutrition protocol	Deltatrac II	Randomized within 48 h of ICU admission. IC measurements were repeated every 48 h	30-60 minutes steady state recorded	~106*†	25 kcal/kg/day	~81*†
Landes et al, 2016, United States[19]	Long-term acute-care hospital for failure to wean from MV	3 weeks	EN was guided by IC + 10% in the IC group and physician estimates in the control arm. Detailed nutrition protocol information not provided	Colorado Med Tech Metascope	At the time of study entry. Weekly for 3 weeks to completion of study	NR	87 ± 12‡	Estimated by physicians using clinical equation of choice (Harris-Benedict or 25 kcal/kg/ day)	77 ± 18
Allingstrup et al, 2017, Denmark[20]	Medical (43 [43%] PE and 52 [52%] IC), all requiring MV	ICU discharge or Day 90	EN initiated with 24 h of randomization. IC: Aim to meet 100% EE from the first full study day (EN ± PN). Control: Gradual increase in EN, supplemental PN used if EE not met by study Day 7	COSMED Quark RMR	As soon as possible after inclusion. Every other day until extubation/ICU discharge	NR	97 (91-100)# 96 ± 7^	25 kcal/kg/day	64 (40-84)# 62 ± 33^
Gonzalez-Granda et al, 2018, Germany[21]	Medical ICU patients, all requiring MV	Until ICU discharge	Fed preferentially by EN, supplemental or sole PN as required. Gradual increase in feeds from Day 1 to Day 4 (25%, 50%, 75%, 100%). Control: Nutrition therapy as per standard care by ward staff. IC: Nutrition therapy adapted/ controlled by study personnel + ward staff	COSMED Quark RMR 2.0	Within 24-72 h after intubation. Repeated if changes in metabolism were anticipated, ~weekly tests	30-40 minutes, steady state not discussed	98 ± 8	25 kcal/kg/day	79 ± 29

Abbreviations: EE, energy expenditure; EN, enteral nutrition; IC, indirect calorimetry; MV, mechanical ventilation; NR, not reported; PE, predictive equation; PN, parenteral nutrition; RMR, resting metabolic rate.
*% energy adequacy not reported in paper, calculated by review authors using mean energy prescribed/delivered; †Per protocol analysis (56 patients per group); ‡Value reported in the primary paper rounded to the nearest whole number; #Data are median (IQR) as reported in the paper; ^These data have been transposed as per the method outlined in the methods and as per Wan et al.[16]

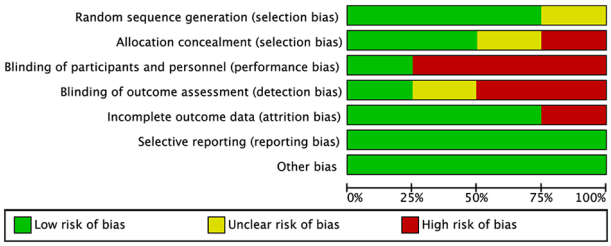

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

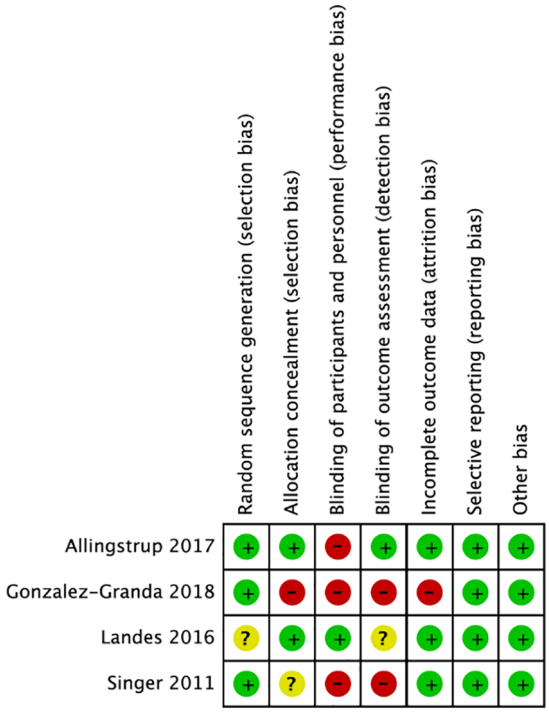

Figure 3. Risk of bias graph summary: review authors' judgments about each risk of bias item for each included study.

OR = 0.77, 95% CI = [0.48, 1.23], $P = 0.28$, $I^2 = 25$, Figure 4B). The remaining study did not report hospital mortality.[19]

Secondary outcomes

Secondary outcomes defined for this review and reported in included studies are displayed in Table 2. No differences in ICU mortality and hospital LOS were reported between study arms in any study.[18,20,21] One study (Singer et al[18]) reported an increase in the mean duration of MV in the IC versus the predictive equation groups, while no differences were reported in 3 studies (Landes et al,[19] Allingstrup et al,[20] and Gonzalez-Granda et al.[21]). When combined, the use of IC was associated with a significantly longer mean duration of MV (4 studies, 396 participants, fixed-effect analysis; MD = 2.01, 95% CI = [0.45, 3.57], $P = 0.01$, $I^2 = 26\%$, Figure 4C). No studies reported ventilator-free days. Mixed findings were reported for ICU LOS; one study (Gonzalez-Granda et al[21]) reported a significant reduction, and 2 studies a significant increase (Singer et al[18] and Allingstrup et al[20]). When combined, ICU LOS was not associated with the use of IC (3 studies, 369 participants, random-effects analysis; MD = 1.39, 95% CI = [–5.03, 7.79], $P = 0.67$, $I^2 = 81\%$, Figure 4D). The remaining study (Landes et al[19]) did not report ICU LOS. Only 1 study investigated outcomes related to muscle mass.[21] Although the authors did not report on changes in muscle mass (secondary outcomes of this review), a decreasing trend in phase angle (a marker of cell health and reported to relate to nutrition status and muscularity) from baseline to discharge was noted in the predictive equation arm with no change in the IC arm.[21] No studies reported on muscle strength measures.

Discussion

This is the first systematic review to explore whether using IC to inform energy delivery impacts patient outcomes compared to using a predictive equation. Few studies were identified, and this limits definitive conclusions; no benefit was observed in hospital mortality with using IC over predictive equations and the results of secondary outcomes were conflicting; 1 study reporting a longer duration of MV when IC informed energy delivery, 2 studies an increased ICU LOS, 1 study reporting a reduced ICU LOS, and the remaining studies reporting no differences in secondary outcomes. When combined in a meta-analysis, IC informed energy delivery was associated with a longer duration of MV but there were no differences in ICU LOS. No differences were observed for ICU mortality and hospital LOS in any of the included studies, and there were limited studies that reported outcomes relating to muscle mass and/or strength. Higher energy adequacy was achieved across all studies in the IC arm, using predominantly EN, supplemented with PN. The quality of studies varied, with the main limitation relating to the lack of blinding of study personnel and patients to group allocation.

A clear finding of this review is that energy delivery that approximates measured energy expenditure can be achieved when IC is used, although there was variation in the amount of additional energy achieved in the intervention arms, likely due to variations in study protocols. The variation in study protocols included different approaches to ensure energy targets in the IC groups were met soon after study inclusion (eg, using EN supplemented with PN), and the monitoring provided by study personnel or dietitians, which differed from usual care adopted in the predictive equation control arm.[18,20,21] This hindered comparison between studies. In one study, energy delivery was above 100% of measured targets on some days in comparison to approximately 80% in the predictive equation control arm.[18] The higher energy delivery in the IC arm across included studies may have impacted the duration of MV, which was significantly greater in the IC arm in the meta-analysis. This finding is hypothesis generating, with data from adequately powered studies required before this can be confirmed.

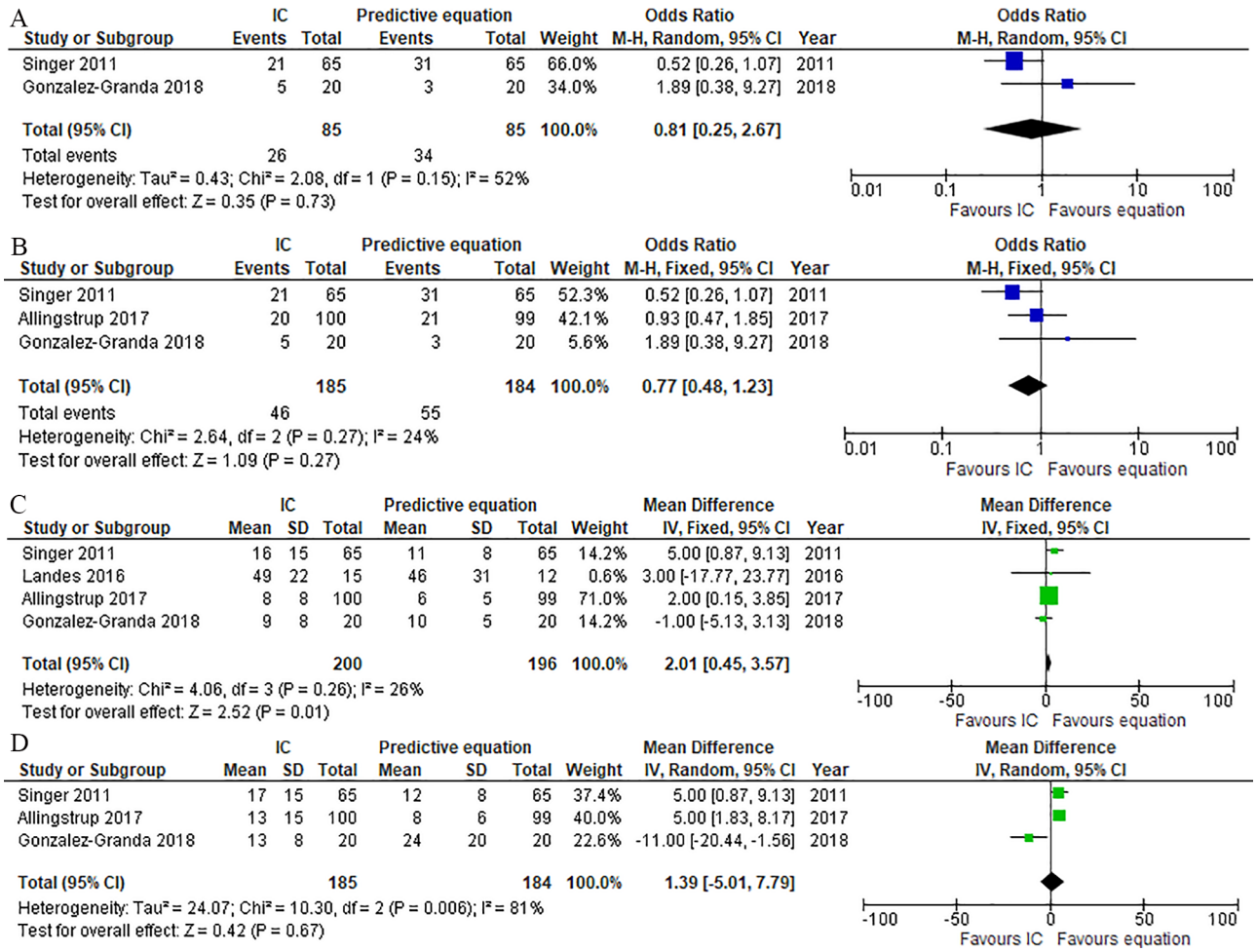

Figure 4. (A) Forest plot comparing indirect calorimetry to predictive equations on primary outcome of hospital mortality. (B) Forest plot comparing indirect calorimetry to predictive equations on primary outcome of hospital mortality (using 28-day mortality data from Allingstrup et al). (C) Forest plot comparing indirect calorimetry to predictive equations on length of mechanical ventilation. (D) Forest plot comparing indirect calorimetry to predictive equations on Intensive Care Unit length of stay.

Reductions in mortality or improvements in other clinical outcomes have not been observed in recent RCTs investigating differing energy targets (hypocaloric, trophic, or augmented) in critical illness, when energy delivery was guided by predictive equations.[9,22,23] Moreover, recently conducted meta-analyses have not demonstrated a benefit with greater energy delivery, although such analyses are subject to the limitations of the trials included.[24-29] The rationale underlying the use of IC is that an accurate measure of energy expenditure should facilitate greater precision in the delivery of energy when compared to the use of a predictive equation, thereby, minimizing the risk of inadequate or excessive energy delivery. This imprecision with predictive equations is a possible explanation for the no-effect findings from recent RCTs.[9,22,23] This concept of precision to avoid under or excessive feeding is supported by an observational study of 1171 patients from a single center in Israel investigating the routine use of IC in critical illness. Study findings indicated a u-shaped relationship between energy delivery and mortality, such that delivery of 70% of a measured expenditure was associated with the lowest mortality risk.[30] An alternative hypothesis is that the phase of illness is of greater importance, with less energy during the acute phase and more energy during the later phase of critical illness being of greater consequence than the method used to direct the amount at any time.[5] This has also not been addressed in the aforementioned trials, with 2 of the 4 studies aiming to meet 100% of IC energy targets soon after study inclusion.[20] The use of IC to improve precision of nutrition delivery across the different phases of illness and the impact on outcomes requires evaluation in adequately powered RCTs.

Implications for practice and research

Although recommended in clinical guidelines, this review highlights that there is a lack of definitive data to prove that using IC to guide energy delivery influences clinical outcomes compared to predictive equations. Furthermore, the review findings suggest that the use of IC may be associated with a longer duration of MV, although this may be a reflection of the small sample size and increased energy delivery in the IC arm of included studies rather than an indication of the usefulness

Table 2. Baseline characteristics and outcomes in included studies.

AUTHOR, YEAR, COUNTRY (REF)	NO. INCLUDED IN ANALYSIS		AGE, YEARS (MEAN ± SD)		BMI, KG/M² (MEAN ± SD)		SEX, N % MALE		APACHE/SOFA SCORE (MEAN ± SD)		HOSPITAL MORTALITY, N (%)		ICU MORTALITY, N (%)		DURATION OF MV, DAYS (MEAN ± SD)		ICU LOS, DAYS (MEAN ± SD)		HOSPITAL LOS, DAYS	
	IC	PE	IC	PE	IC	PE	IC	PE	IC	PE	IC	PE	IC	PE	IC	PE	IC	PE	IC	PE
Singer et al, 2011, Israel[18]	65	65	59 ± 18	62 ± 17	27.8 ± 6.3	27.4 ± 7.3	35 (54)	41 (63)	22.1 ± 7.4/ 6.4 ± 2.9	22.4 ± 6.8/ 6.6 ± 3.5	21 (32)‡	31 (48)‡	16 (25)‡¶	17 (26)‡¶	16 ± 15‡	11 ± 8*‡	17 ± 15*‡	12 ± 8*‡	34 ± 23‡	32 ± 27‡
Landes et al, 2016, United States[19]	15	12	72 ± 7‡	74 ± 10‡	25.3 ± 6.4	25.7 ± 7.5	9 (60)	10 (83)	34.7 ± 12.0/ NR	38.7 ± 13.4/ NR					49 ± 22‡	46 ± 31‡				
Allingstrup et al, 2017, Denmark[20]	100†	99†	63 (51–72)#^ 62 ± 16^	68 (52–75)#^ 65 ± 17^	22 (20–26)#^ 22.7 ± 4.5^	22 (20–25)#^ 22 ± 3.8^	65 (65)	59 (60)	NR/ 8 (6-11)#	NR/ 8 (5-10)#					6 (4-15)#§ 8 ± 8^	5 (3-10)#§ 6 ± 5^	8 (5-25)*#§ 13 ± 15^	7 (4-12)*#§ 8 ± 6^	30 (12–53)#| 32 ± 31^	34 (14–53)#| 34 ± 29^
Gonzalez-Granda et al, 2018, Germany[21]	20	20	57 ± 16	56 ± 14	27.8 ± 6.2	25.0 ± 4.3	13 (65)	11 (55)	28.7 ± 7.0/ 12.1 ± 3.3	28.9 ± 8.3/ 11.4 ± 3.0	5 (25)	3 (15)	3 (15)	3 (15)	9 ± 8	10 ± 5	13 ± 8*	24 ± 20*	31 ± 24	40 ± 23

Abbreviations: APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; BMI, body mass index; IC, indirect calorimetry (intervention arm); ITT, intention to treat; NR, not reported; PE, predictive equation (standard care arm); SOFA: Sequential Organ Failure Assessment.
*Difference is statistically different between groups; †203 patients randomized, 199 included in the ITT analysis; ‡Value reported in the primary paper rounded to the nearest whole number; §Results of post hoc analyses; ¶No. (n) calculated from reported mortality percentage in paper. #Data are median (IQR) as reported in paper; ^These data have been transposed as per the method outlined in the methods and as per Wan et al;[16] |Length of stay among 6-month survivors.

of IC. Considering the cost of the device, salary for staff time and consumable expenses involved with IC and technical limitations prohibiting use in all patients, widespread implementation in clinical practice is not justified until further data from adequately powered trials is available to support or discount current guideline recommendations.[1] Where IC is available, it is the opinion of the authors that IC should be reserved for patients in whom clinicians feel individualized nutrition may be an advantage and in whom are likely to stay for extended periods in ICU.

Strengths and limitations

This is the first dedicated systematic review that addresses the impact of IC on clinical outcomes in critical illness. The methodology adopted represents the strength of the present review, with processes aligned to the PRISMA guideline. This ensures that the review processes were conducted in a way that minimizes bias and that findings are reported in an objective manner. The major limitation is the small number of papers eligible for inclusion. The decision to omit studies that used IC to guide nutrition therapy without a comparator arm related to the clinical question being addressed in the review; however, the approach to exclude observational data does reduce the number of patients included in the review. It is also likely that the effects of energy and protein are synergistic; however, we did not focus on protein in this review. There is increasing interest in the influence of protein adequacy on outcomes in ICU patients.[31-33] Ideally, future studies of energy should ensure that protein delivery remains constant between study arms to minimize the influence of protein adequacy as a confounder.

There are also limitations within the studies included. Specifically, the studies were (1) underpowered to detect differences in outcomes; (2) the duration of intervention ranged from 2 weeks to ICU discharge; (3) there was unclear reporting of the quality of IC measurements and how many repeat tests were conducted per patient (meaning even using IC, nutrition can be misguided if measurements are not repeated); (4) energy delivery was not tailored according to the metabolic phase of illness in all studies and energy targets were more closely met in the acute early phase in IC versus the predictive equation study arms and; (5) the outcome measures used may not be intuitive to a nutrition intervention and were reported inconsistently. These inconsistencies may explain the conflicting secondary outcomes observed within included studies and need to be addressed in any future trials.

Conclusion

Limited data exist to evaluate the impact of using IC to measure energy expenditure to inform energy delivery in comparison to predictive equations on patient-centered outcomes during critical illness. Whether the use of IC is associated with other important outcomes, including duration of MV, needs to

be further explored with adequately powered, multicenter RCTs that attend to the limitations of previous studies.

Acknowledgements

The authors thank Lorena Romero, Senior Medical Librarian, The Ian Potter Library, and Alfred Health for advice during the review.

Author Contribution

All authors made a substantial contribution to the concept and design of the work. OAT-B, KF, KL and EJR contributed equally to the acquisition, analysis and interpretation of data. OAT-B and EJR drafted the article. All authors revised it critically for important intellectual content and approved the version to be published. All authors participated sufficiently in the work to take public responsibility for appropriate portions of the content.

ORCID iD

Emma J Ridley https://orcid.org/0000-0002-7922-5717

REFERENCES

1. Walker RN, Heuberger RA. Predictive equations for energy needs for the critically ill. *Respir Care*. 2009;54:509-521.
2. Tatucu-Babet OA, Ridley EJ, Tierney AC. Prevalence of underprescription or overprescription of energy needs in critically ill mechanically ventilated adults as determined by indirect calorimetry: a systematic literature review. *JPEN J Parenter Enteral Nutr*. 2016;40:212-225.
3. Kross EK, Sena M, Schmidt K, Stapleton RD. A comparison of predictive equations of energy expenditure and measured energy expenditure in critically ill patients. *J Crit Care*. 2012;27:321.e5-321.e12.
4. Zusman O, Kagan I, Bendavid I, Theilla M, Cohen J, Singer P. Predictive equations versus measured energy expenditure by indirect calorimetry: a retrospective validation. *Clin Nutr*. 2019;38:1206-1210.
5. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019;38:48-79.
6. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40:159-211.
7. Rattanachaiwong S, Singer P. Should we calculate or measure energy expenditure? Practical aspects in the ICU. *Nutrition*. 2018;55-56:71-75.
8. De Waele E, Honore PM, Malbrain MLNG. Does the use of indirect calorimetry change outcome in the ICU? Yes it does. *Curr Opin Clin Nutr Metab Care*. 2018;21:126-129.
9. Chapman M, Peake SL, Bellomo R, et al. Energy-dense versus routine enteral nutrition in the critically ill. *N Engl J Med*. 2018;379:1823-1834.
10. University of York, Centre for Reviews and Dissemination. *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care*. 3rd ed. York, UK: Centre for Reviews and Dissemination, University of York; 2009:x, 281.
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
12. Higgins JPT, Green S; Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK; Hoboken, NJ: Wiley-Blackwell; 2008:xxi, 649.
13. Tatucu O, Lambell K, Deane A, Fetterplace K, Ridley E. Is the use of indirect calorimetry associated with improvements in clinical outcomes in critically ill patients? A systematic literature review. http://www.crd.york.ac.uk/PROSPERO/display_record. php?ID=CRD42019117921. Updated 2019. Accessed September 10, 2019.
14. Ridley EJ, Davies AR, Hodgson C, Deane A, Bailey M, Cooper DJ. Full predicted energy from nutrition and the effect on mortality and infectious complications in critically ill adults: a protocol for a systematic review and meta-analysis of parallel randomised controlled trials. *Syst Rev*. 2015;4:179.
15. Simpson F, Doig GS, Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. *Intensive Care Med*. 2005;31:12-23.
16. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
17. Saffle JR, Larson CM, Sullivan J. A randomized trial of indirect calorimetry-based feedings in thermal injury. *J Trauma*. 1990;30:776-782; discussion 782-783.
18. Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med*. 2011;37:601-609.
19. Landes S, McClave SA, Frazier TH, Lowen CC. Indirect calorimetry: is it required to maximize patient outcome from nutrition therapy? *Curr Nutr Rep*. 2016;5:233-239.
20. Allingstrup MJ, Kondrup J, Wiis J, et al. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. *Intensive Care Med*. 2017;43:1637-1647.
21. Gonzalez-Granda A, Schollenberger A, Haap M, Riessen R, Bischoff SC. Optimization of nutrition therapy with the use of calorimetry to determine and control energy needs in mechanically ventilated critically ill patients: the ONCA study, a randomized, prospective pilot study. *JPEN J Parenter Enteral Nutr*. 2019;43:481-489.
22. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;307:795-803.
23. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med*. 2015;372:2398-2408.
24. Tian F, Wang X, Gao X, et al. Effect of initial calorie intake via enteral nutrition in critical illness: a meta-analysis of randomised controlled trials. *Crit Care*. 2015;19:180.
25. Ridley EJ, Davies AR, Hodgson CL, Deane A, Bailey M, Cooper DJ. Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: a systematic review and meta-analysis of randomised controlled trials. *Clin Nutr*. 2018;37:1913-1925.
26. Parikh HG, Miller A, Chapman M, Moran JL, Peake SL. Calorie delivery and clinical outcomes in the critically ill: a systematic review and meta-analysis. *Crit Care Resusc*. 2016;18:17-24.
27. Marik PE, Hooper MH. Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis. *Intensive Care Med*. 2016;42:316-323.
28. Choi EY, Park DA, Park J. Calorie intake of enteral nutrition and clinical outcomes in acutely critically ill patients: a meta-analysis of randomized controlled trials. *JPEN J Parenter Enteral Nutr*. 2015;39:291-300.
29. Al-Dorzi HM, Albarrak A, Ferwana M, Murad MH, Arabi YM. Lower versus higher dose of enteral caloric intake in adult critically ill patients: a systematic review and meta-analysis. *Crit Care*. 2016;20:358.
30. Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. *Crit Care*. 2016;20:367.
31. Hurt RT, McClave SA, Martindale RG, et al. Summary points and consensus recommendations from the international protein summit. *Nutr Clin Pract*. 2017;32:142S-151S.
32. Heyland DK, Stapleton R, Compher C. Should we prescribe more protein to critically ill patients? *Nutrients*. 2018;10:462.
33. Fetterplace K, Deane AM, Tierney A, et al. Targeted full energy and protein delivery in critically ill patients: a pilot randomized controlled trial (FEED Trial). *JPEN J Parenter Enteral Nutr*. 2018;42:1252-1262.

Appendix 1. Ovid Medline search strategy.

#	OVID MEDLINE(R) AND EPUB AHEAD OF PRINT, IN-PROCESS & OTHER NON-INDEXED CITATIONS, DAILY AND VERSIONS(R) 1946 TO NOVEMBER 06, 2018
1	Calorimetry/or Calorimetry, Indirect/or Energy Metabolism/or Basal Metabolism/
2	(indirect calorimet* or metabolic cart* or metabolic monitor* or COSMED or Deltatrac* or Quark RMR or respirat* calorimet*).mp.
3	(resting metabolic rate* or energy expenditure* or energy metabolism*).mp.
4	1 or 2 or 3
5	Critical Illness/or Critical Care/or Intensive Care Units/or Burn Units/or Coronary Care Units/or Respiration, Artificial/or Ventilators, Mechanical/or Pulmonary Ventilation/or Respiratory Insufficiency/or Multiple Organ Failure/or Systemic Inflammatory Response Syndrome/or Respiratory Distress Syndrome, Adult/or Sepsis/or Shock, Septic/
6	(critical care or critical* ill* or intensive care or intensive treatment unit* or intensive therapy unit* or high dependency unit* or burn unit* or coronary care unit* or respiratory care unit*).mp.
7	((mechanical* or artificial* or noninvasive or noninvasive or positive-pressure) adj3 (ventilat* or respirat*)).mp.
8	(sepsis or septic shock or septic?emi* or septic syndrome*).mp.
9	(multiple organ dysfunction* or multiple organ failure*).mp.
10	Systemic inflammatory response.mp.
11	Respiratory distress syndrome*.mp.
12	5 or 6 or 7 or 8 or 9 or 10 or 11
13	4 and 12
14	exp animals/not humans.sh.
15	13 not 14
16	Limit 15 to English language