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

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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 (I² > 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, I² = 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, I² = 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, I² = 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

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. 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). 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

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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).

**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. 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. 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 \( \leq 0.10 \) 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. One study was excluded following initial inclusion, as it did not meet the review definition of being conducted in a critically ill population, leaving 4 studies that analyzed 396 participants. 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. Three studies (Singer et al, Allingstrup et al, and Gonzalez-Granda et al) comprised of predominantly medical ICU patients and the remaining study (Landes et al) 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) and inadequately described in another study (Gonzalez-Granda et al). The remaining 2 studies were considered low risk of bias.

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) and outcome assessors were blind to group allocation in another. The remaining 2 studies were considered at high risk of bias as participants and study personnel were not blinded.

One study (Gonzalez-Granda et al) 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.

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
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 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 and Gonzalez-Granda et al). One study (Singer et al) reported a nonsignificant reduction in hospital mortality with IC and the other (Gonzalez-Granda et al) 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) 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;
| AUTHOR, YEAR, COUNTRY (REF) | 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, Israel18 | 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 | Deltrac 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 States19 | 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, Denmark20 | 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)* 98 ± 7™ | 25 kcal/kg/day | 64 (40-84)* 62 ± 33® |
| Gonzalez-Granda et al, 2018, Germany21 | 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 (58 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
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.\textsuperscript{18,20,21} One study (Singer et al\textsuperscript{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,\textsuperscript{19} Allingstrup et al,\textsuperscript{20} and Gonzalez-Granda et al.\textsuperscript{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\textsuperscript{2} = 26%, Figure 4C). No studies reported ventilator-free days. Mixed findings were reported for ICU LOS; one study (Gonzalez-Granda et al\textsuperscript{21}) reported a significant reduction, and 2 studies a significant increase (Singer et al\textsuperscript{18} and Allingstrup et al\textsuperscript{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\textsuperscript{2} = 81%, Figure 4D). The remaining study (Landes et al\textsuperscript{19}) did not report ICU LOS. Only 1 study investigated outcomes related to muscle mass.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.
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. 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. 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. 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.

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, HOSPITAL, COUNTRY, REF | NO.INCLUDED IN ANALYSIS | AGED (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 (MEAN ± SD) |
|-------------------------------|-------------------------|-----------------|------------------------|---------------|-----------------------------|--------------------------|------------------------|-------------------------------|--------------------------|-------------------------------|
| Singer et al, 2011, Israel²⁶   | 65                      | 59 ± 18         | 27.8 ± 6.3             | 35 (54)       | 22.1 ± 7.4/6.4 ± 2.9        | 21 (32)                  | 5 (25)                 | 16 ± 15*‡                    | 11 ± 8*‡                  | 17 ± 15*‡                     |
| Landes et al, 2016, United States⁶  | 17 (26)                 | 72 ± 71         | 25.3 ± 6.4             | 9 (60)        | 34.7 ± 12.0/12.4 ± 7.4      | 38.7 ± 13.4/12.7 NR     | 49 ± 22*‡               | 46 ± 31*‡                    | 6 (4-15)*‡                 | 6 (4-15)*‡                    |
| Allingstrup et al, 2017, Denmark⁶ | 101                      | 63 (5-7)-3 62 ± 16 | 22.0-20-26 22.7 ± 4.5 | 65 (85)       | 6 (8-9)                     | 6 (8-9)                  | 6 (8-9)                | 6 (8-9)                       | 8 (6-8)                  | 6 (8-8)                       |
| Gonzalez-Granda et al, 2018, Germany¹ | 8 (25)                 | 57 ± 16         | 27.8 ± 6.2             | 13 (65)       | 28.7 ± 7.0/12.1 ± 3.3       | 28.9 ± 8.3/114 ± 3.0    | 3 (15)                 | 5 (25)                       | 13 ± 15*‡                 | 13 ± 15*‡                    |
| 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. Length of stay among 6-month survivors.

**Conclusion**

Limited data exist to evaluate the impact of using IC to measure energy expenditure to inform energy delivery outcomes in patients during critical illness. Whether the use of IC is associated with other important outcomes, including duration of MV, needs to be addressed in any future trials.

**Strengths and limitations**

The first dedicated systematic review that addresses the impact of IC on clinical outcomes in critical illness. The methodology employed presents the strength of the present review, with process aligned to the PRISMA guideline. This ensures that the review processes are conducted in an objective manner. The major limitation is the small number of patients included, and the approach to exclude observational data and consumable expenses involved with IC and technical limitations are available to support or discount current guideline recommendations. Where IC is available, it is the opinion of the authors that IC should be reserved for individualized nutrition, which is likely to stay for extended periods in ICU.
be further explored with adequately powered, multicenter RCTs that attend to the limitations of previous studies.

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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.

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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 |
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