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EDITORIAL

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Be early for enteral, no rush for calories!

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The recent systematic review and meta-analysis by Marik and Hooper [1] challenges the long-held belief that more calories are better, one of the most controversial areas of discussion in the field of metabolic and nutritional support of the critically ill [2]. This classical statement has been mainly based on observational studies reporting an association between low caloric intakes and higher rate of complications [3, 4], while other retrospective studies have suggested a better outcome with hypocaloric than with normocaloric feeding [5, 6]. Importantly, the thorough and rigorous review of the recent randomized controlled trials [1] revealed no significant outcome difference between groups randomized to "hypocaloric" or "trophic" over "normocaloric" feeding, defined as the provision of energy designed to match the energy expenditure early during the course of critical illness (Fig. 1).

In all retrieved studies, enteral feeding was initiated at an early stage in critical illness, although the studies had several differences in the amount of proteins between the "normocaloric" and the "hypocaloric" or "trophic" groups [6–9], in the management on enteral feeding and in the calculation of caloric intakes. In addition, the degree and duration of caloric restriction differed, by design, between trophic and permissive underfeeding studies (Fig. 1). Nevertheless, the absence of difference in outcome is definitely relevant to contemporary ICUs, as the individual studies were all performed after 2010, the caloric intakes were well separated between groups, and the study populations are reasonably representative of mixed ICUs of the Western world, except for the young age [8–10].

Are these findings surprising? Probably not, when nuancing the potential benefit of early caloric intake with the high risk of inadvertent overfeeding, when the endogenous production of glucose cannot be inhibited by exogenous substrates [11, 12], and considering the non-nutritional calories provided when glucose or lipids are used as maintenance solutions or solvents, which are not always accounted for. As a result, during the early days of critical illness, the excess calories can be stored as adipose tissue within muscles [13] instead of being used to provide energy or to increase muscle mass. Other potential explanations for the lack of benefits or the potential toxicity of normocaloric feeding include the inhibition of autophagy [14]. From a teleological standpoint, the anorexia occurring during the early phase of critical illness could be adaptive to prevent the toxicity of overfeeding, while prioritizing vital functions. This hypothesis is supported by the tight regulation process of appetite by enterohormones released from the gastrointestinal tract.

In contrast to the risk associated with a high caloric intake early during the course of critical illness, the use of the enteral route as early as possible is desirable. Several

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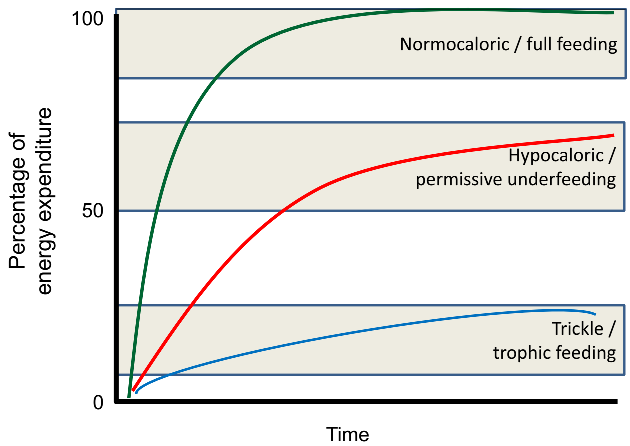

Fig. 1 Schematic representation of 3 feeding strategies: normocaloric or full feeding (*green line*) aims to match energy expenditure (EE) as early as possible; hypocaloric or permissive underfeeding aims to match 50–70 % of EE according to individual tolerance; trickle or trophic feeding aims to provide a minimal amount of enteral feeds, resulting in the provision of 10–20 % of EE

lines of evidence support the preferential use of the gastrointestinal tract over the intravenous route for nutrition, even though the final proof of prevention of translocation by enteral nutrition is still lacking in humans. The proponents of trickle or trophic feeds suggest the infusion of a minimal amount of enteral nutrition, irrespective of the amount of calories infused [9]. Interestingly, the absorption of nutrients itself can be delayed during the acute phase [15], consistent with adaptive changes in digestive physiology to prevent overfeeding.

Several additional issues are raised and left unanswered by the studies analyzed by Marik and Hooper [1], including the selection of the best end-point to assess the efficacy of nutrition. The authors of the meta-analysis reported only the available variables, mortality, length of stay and infectious complications, which could reflect the safety of nutritional interventions, rather than their actual efficacy. Likewise, a global strategy of nutrition associated with physical activity is more likely to preserve muscular function and autonomy, but this assumption needs to be assessed prospectively and rigorously. The frequency of refeeding syndrome, a major safety outcome, could be overlooked in the absence of stratification based on the prior nutrition status, or could also be relevant in patients starving for a few days.

Compliance with ethical standards

Conflicts of interest None.

References

1. Marik PE, Hooper MH (2015) Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis. Intensive Care Med. doi: 10.1007/s00134-015-4131-4
2. Preiser JC, van Zanten ARH, Berger MM, Biolo G, Casaer MP, Doig GS et al (2015) Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care 19:35
3. Villet S, Chiolero RL, Bollmann MD, Revelly J-P, Cayeux RNM-C, Delarue J et al (2005) Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr 24:502–509
4. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R et al (2009) The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 35:1728–1737
5. Crosara ICR, Mélot C, Preiser JC (2015) A J-shaped relationship between caloric intake and survival in critically ill patients. Ann Intensive Care 5:37
6. Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA (2004) Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. Crit Care Med 32:350–357
7. Petros S, Horbach M, Seidel F, Weidhase L (2014) Hypocaloric vs normocaloric nutrition in critically ill patients: a prospective randomized pilot trial. J Parenter Enteral Nutr. doi: 10.1177/0148607114528980
8. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP (2011) Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med 39:967–974
9. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M et al (2012) Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA 307:795–803
10. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G et al (2015) Permissive underfeeding or standard enteral feeding in critically ill adults. N Engl J Med 372:2398–2408
11. Preiser JC, Ichai C, Orban J-C, Groeneveld ABJ (2014) Metabolic response to the stress of critical illness. Br J Anaesth 2014(113):945–954
12. Fraipont V, Preiser JC (2013) Energy estimation and measurement in critically ill patients. J Parenter Enteral Nutr 37:705–713
13. Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Güiza FG et al (2013) Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med 41:2298–2309
14. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S et al (2013) Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 1:621–629
15. Deane AM, Rayner CK, Keeshan A, Cvijanovic N, Marino Z, Nguyen NQ et al (2014) The effects of critical illness on intestinal glucose sensing, transporters, and absorption. Crit Care Med 42:57–65

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SYSTEMATIC REVIEW

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Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis

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Take-home message: In this meta-analysis of 6 studies with 2517 ICU patients, which compared trophic feeding and permissive underfeeding with normocaloric nutritional goals, there was no difference in the risk of acquired infections, hospital mortality, ICU length of stay or ventilator-free days stay between the two groups.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-015-4131-4) contains supplementary material, which is available to authorized users.

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Abstract *Introduction:* Current clinical practice guidelines recommend providing ICU patients a daily caloric intake estimated to match 80–100 % of energy expenditure (normocaloric goals). However, recent clinical trials of intentional hypocaloric feeding question this approach. *Methods:* We performed a systematic review and meta-analysis to compare the outcomes of ICU patients randomized to intentional hypocaloric or normocaloric goals. We included randomized controlled trials that enrolled ICU patients and compared intentional hypocaloric with normocaloric nutritional goals. We included studies that evaluated both trophic feeding as well as permissive underfeeding. Data sources included MEDLINE, Cochrane Register of Controlled Trials and citation review of relevant primary and review articles. The outcomes of interest included hospital acquired infection, hospital mortality, ICU length of stay (LOS) and ventilator-free days (VFDs). *Results:* Six studies which enrolled 2517 patients met our inclusion criteria. The mean age and body mass index (BMI) across the studies were 53 ± 5 years and 29.1 ± 1.5 kg/m^2, respectively. Two studies compared normocaloric feeding (77 % of goal) with trophic feeding (20 % of goal), while four studies compared normocaloric feeding (72 % of goal) with permissive underfeeding (49 % of goal). Overall, there was no significant difference in the risk of infectious complications (OR 1.03; 95 % CI 0.84–1.27, $I^2 = 16$ %), hospital mortality (OR 0.91; 95 % CI 0.75–1.11, $I^2 = 8$ %) or ICU LOS (mean difference 0.05 days; 95 % CI 1.33–1.44 days; $I^2 = 37$ %) between groups. VFDs were reported in three studies with no significant difference between the normocaloric and intentional hypocaloric groups (data not pooled). *Conclusion:* This meta-analysis demonstrated no difference in the risk of acquired infections, hospital mortality, ICU length of stay or ventilator-free days between patients receiving intentional hypocaloric as compared to normocaloric nutritional goals.

Keywords Enteral nutrition · Permissive underfeeding · Trophic feeding · Caloric goals

Introduction

Nutritional support is considered an essential component of the management of critically ill patients [1], with Clinical Practice Guidelines (CPG) emphasizing early (within 24–48 h of ICU admission) normocaloric enteral nutrition (daily caloric intake estimated to match 80–100 % of energy expenditure) [2–5]. It is generally

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believed that early normocaloric enteral nutrition attenuates the catabolic response of acute illness, reduces disease severity, attenuates the pro-inflammatory and anti-inflammatory immune response, diminishes complications, decreases ICU and hospital length of stay (LOS) and favorably impacts patient outcome [2–5]. Observational cohort studies suggest that underfeeding critically ill patients with the accrual of a large caloric deficit (difference between required and delivered calories) is associated with worse patient outcomes [6–11]. However, a number of recent randomized controlled trials (RCTs) have failed to demonstrate an improvement in the outcomes of critically ill patients receiving a normocaloric feeding protocol as opposed to a strategy of intentional hypocaloric feeding. The objective of this systematic review and meta-analysis was to determine whether nutritional support targeting recommended caloric goals improves the outcomes of ICU patients as compared to an intentional hypocaloric approach.

Methods

Identification of trials and outcome variables

Our aim was to identify all relevant RCTs that compared a normocaloric (targeting 80–100 % of daily energy expenditure) with an intentional hypocaloric feeding strategy. We included studies that compared normocaloric feeding with a protocol that used "tropic feeding" as well as studies that compared normocaloric feeding versus permissive underfeeding (<70 % of daily energy expenditure). We excluded studies in which parenteral nutrition was the main source of nutrition. We limited the search strategy to adult ICU patients. There was no restriction on language, publication year or setting. Both authors independently searched the National Library of Medicine's MEDLINE database for relevant studies in any language published from 1966 to July 2015. The MEDLINE (OVID) search strategy is depicted in Fig. S1. In addition, we searched the Cochrane Register of Controlled Trials (CENTRAL) and the bibliographies of all selected articles and review articles for other relevant articles. This search strategy was done iteratively, until no new potential citations were found. We performed and reported this meta-analysis according to the guidelines proposed by the PRISMA group [12, 13]. The outcome measures of interest were infectious complications, hospital mortality, ICU LOS and ventilator-free days (VFDs).

Data extraction and quality assessment

Both reviewers independently assessed eligibility of articles identified in the initial search strategy for inclusion in the review. They discussed those papers deemed potentially eligible, independently extracted data using a standardized data abstraction form, and assessed studies' methodological quality using the risk of bias assessment tool from the Cochrane handbook for randomized trials [14]. Disagreements between the reviewers were resolved by consensus. Missing data were kindly provided by the primary investigator when available [15, 16].

Data analysis

Summary data is presented as sample size, time to enrollment in study, patient characteristics, caloric goals, the average amount of calories and protein delivered and the outcomes of interest in each group of patients. Studies were grouped according to whether a trophic feeding or permissive underfeeding strategy was used. When sufficient data elements were available and, when appropriate, meta-analytic techniques were used to summarize the data. We used the random-effects model (more conservative) using Review Manager 5.3.4 (Cochrane Collaboration, Oxford, UK) and considered $p \leq 0.05$ (two-sided) as significant. We report binary outcomes as odds ratios (OR) and continuous outcomes as weighted mean differences (WMD). Summary effects estimates are presented with 95 % confidence intervals (CI). We assessed heterogeneity between studies for each outcome using the Cochran Q statistic [17], with $p \leq 0.10$ indicating significant heterogeneity [18], and I^2 with suggested thresholds for low (25–49 %) moderate (50–74 %) and high (>75 %) values. We performed a Funnel plot to determine publication and study bias [19, 20].

Results

Our initial search strategy identified 191 possible studies for inclusion in this analysis. A total of 133 studies were excluded after screening and, of the 58 full text articles assessed for eligibility, 54 were excluded. In addition to the four studies identified by our primary search, two additional studies were identified from the bibliographies of the primary articles identified and review articles. The results of the search strategy are depicted in Fig. S2. The six studies included in the systematic review and meta-analysis are summarized in Table 1. In all, 2517 patients were enrolled in these six studies. The average sample size was 420 (83–1000) patients. Two studies evaluated trophic feeds ($n = 1200$) [15, 16], while four studies evaluated permissive underfeeding ($n = 1317$) [21–24]. The risk of bias assessment of the included studies in depicted in Fig. S3. None of the studies blinded patients or their healthcare providers. Blinding of outcome assessment was not reported in any of the studies included.

Table 1 Characteristics and nutrition data of studies included in meta-analysis

Author	Year	Setting	Patients[a]	*n*	Time[b]	Age		BMI (kg/m^2)		APACHE II		Caloric goal	
						St	Hypo	St	Hypo	St	Hypo	St	Hypo
Trophic													
Rice	2011	Single center	MV >3 days	200	<24	54	53	28.2	29.2	27	27	25–30 kcal/kg/day	300 cals/day
Rice	2012	Multicenter	Acute lung injury	1000	<48	52	52	30.4	29.9	–	–	25–30 kcal/kg/day	300 cals/day
Permisssive underfeeding													
Arabi	2011	Single center	ICU >2 days; 99 % MV	240	<24	52	50	28.5	28.5	25	25	90–100 % goal	60–70 % goal
Charles	2014	Single center	SICU >2 days	83	–	53	50	28.1	32.9	17	17	25 kcal/kg/d	12.5–15 kcal/kg/day
Petros	2014	Single center	ICU >3 days	100	<24	64	67	27.1	28.6	27	30	100 % goal[c]	50 % goal
Arabi	2015	Multicenter	ICU >3 days; 97 % MV	894	<24	51	50	29.7	29.0	21	21	70–100 % goal	40–60 % goal

MV mechanical ventilation, *SICU* surgical ICU, *St* standard feed, *hypo* hypocaloric

[a] Studies enrolled patients expected to require mechanical ventilation >3 days or ICU stay in excess of 2 (or 3 days)

[b] Time to randomization (h)

[c] Determined by indirect calorimetry

The demographics of the patients were similar across studies with a mean age of 53 ± 5 years and a mean BMI of 29.1 ± 1.5 kg/m^2. The APACHE II score was reported in five studies with a mean of 24 ± 5. The nutrition provided and outcomes data are listed in Table 2. In the trophic studies, 1359 ± 83 Kcal (77 % of goal) was provided in the normocaloric group as compared to 350 ± 70 Kcal (20 % of goal) in the trophic group during the first week of hospitalization. Patients in the trophic group did not receive supplemental protein, receiving 54 and 11 g, respectively. In the permissive underfeeding studies, patients in the normocaloric group received 1246 ± 126 kilocalories (72 % goal) as compared to 910 ± 73 kilocalories (49 % of goal) in the permissive underfeeding group (see Table 2). Three of the permissive underfeeding studies provided additional protein in the hypocaloric group to achieve similar protein intake [21–23]. In the trophic studies, patients in the intentional hypocaloric arm were underfed for 6 days (at which point they were transitioned to target nutritional goals if they remained in the ICU) [15, 16]. In the permissive underfeeding studies, the intentional hypocaloric group were underfed for the duration of the patients ICU stay or until day 14 [22].

Infectious complications were reported in all six studies; summary data demonstrated no difference in the risk of infectious complications (OR 1.03; 95 % CI 0.84–1.27) with minimal heterogeneity between studies ($I^2 = 16$ %) (see Fig. 1). The funnel plot revealed no evidence of publication bias (Fig. S4). Hospital mortality was reported in all six studies; overall, there was no difference in the risk of death between the intentional

Table 2 Nutrition received and outcome data of studies included in meta-analysis

Author	Kilocalories/goal (%)		Protein (g)		VFD		ICU LOS		Hospital mortality (%)	
	St	Hypo	St	Hypo	St	Hypo	St	Hypo	St	Hypo
Trophic										
Rice	1418/75	300/16	54	11	18	18	7.6 ± 5.9	8.1 ± 6.1	19.6	22.4
Rice	1300/80	400/25	–	–	15	15	11.0 ± 9.8	11.3 ± 10.6	22.2	23.2[d]
Permissive underfeeding										
Arabi	1102/71	915/59	43	47	–	–	14.5 ± 15.5	5 11.7 ± 8.1	42.5	30
Charles	1338/–	982/–	83	86	–	–	13.5 ± 7.1	16.7 ± 17.2	9.5	7.3
Petros	19.7[c]/75	11.3[c]/42	–	–	–	–	–	–	22.2	21.7
Arabi	1299/71	835/46	59	57	75[a,b]	77	13[a]	13	27.6	24.2

VFD ventilator-free days (28 day), *St* standard feed, *Hypo* hypocaloric feed

[a] Median

[b] VFD to 90 days

[c] Kcal/kg/day

[d] Hospital mortality was censored at 60 days

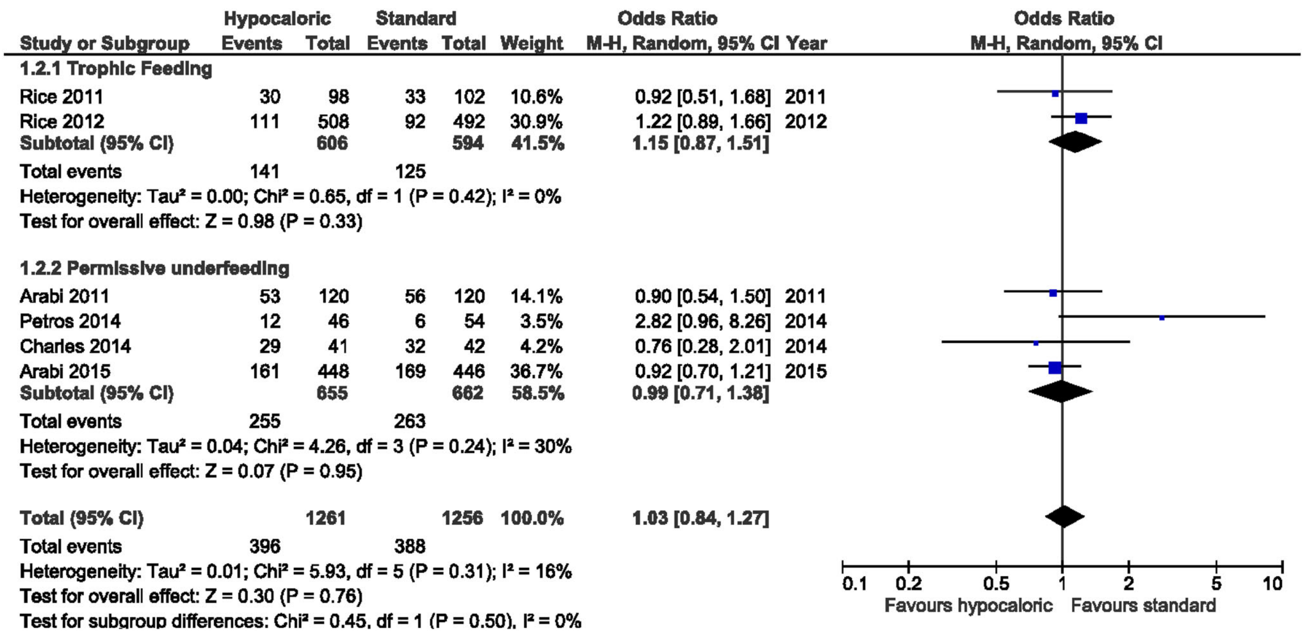

Fig. 1 Comparison of the risk of hospital acquired infections/sepsis for patients receiving standard feeds as compared to hypocaloric feeds grouped by tropic feeds and underfeeding. Weight is the relative contribution of each study to the overall treatment effect (odds risk ratio and 95 % confidence interval) on a log scale assuming a random effects model

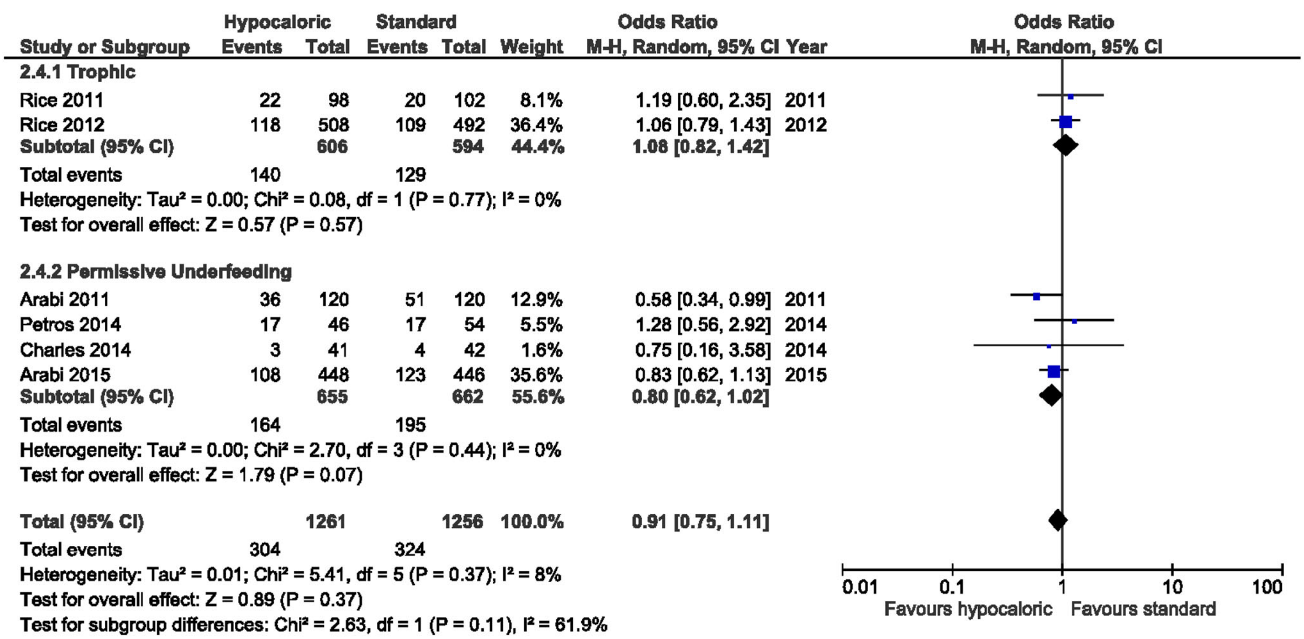

Fig. 2 Comparison of the risk of hospital mortality during study period for patients receiving standard feeds as compared to hypocaloric feeds grouped by tropic feeds and underfeeding. Weight is the relative contribution of each study to the overall treatment effect (odds risk ratio and 95 % confidence interval) on a log scale assuming a random effects model

hypocaloric and normocaloric group (OR 0.91; 95 % CI 0.75–1.11, $I^2 = 8$ %) (see Fig. 2); however, there was a trend towards a lower mortality favoring hypocaloric feeding in the permissive underfeeding subgroup (OR 0.80; 95 % CI 0.62–1.02, $p = 0.07$, $I^2 = 0$ %). ICU length of stay was reported in four studies, with no overall difference between the intentional hypocaloric and normocaloric groups (mean difference 0.05 days; 95 % CI

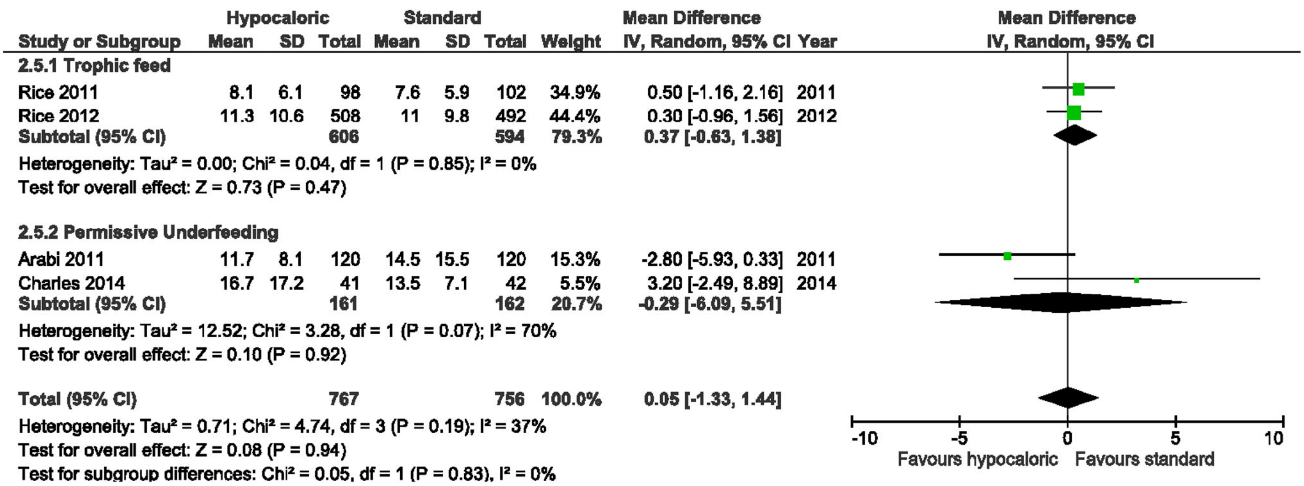

Fig. 3 Comparison of length of hospital stay (LOS) for patients receiving standard as compared to hypocaloric feeds grouped by tropic feeds and underfeeding. Weight is the relative contribution of each study to the overall treatment effect (weighted mean difference with 95 % confidence interval)

1.33–1.44 days; $I^2 = 37$ %) (see Fig. 3). VFDs were reported in three studies, and in each of these there was no significant difference in VFDs between the intentional hypocaloric and normocaloric group (see Table 2). VFDs to study day 28 was reported in two studies [15, 16], while VFD to study day 90 was reported in one study [22]. Due to the characteristics of the data, it was not possible to pool these end-points to determine the summary statistics.

Discussion

The results of our meta-analysis demonstrated no benefit of targeting estimated caloric requirements (80–100 % of daily energy expenditure) as compared to intentional hypocaloric enteral nutrition in the acute phase of critical illness. Furthermore, the studies by Rice et al. [15, 16] suggest that trophic nutrition combined with limited protein intake does not adversely affect patient outcomes. These findings challenge conventional wisdom and current Clinical Practice Guidelines [3–5]. It is noteworthy that intentional hypocaloric nutrition did not increase hospital mortality and infectious complications nor decrease VFDs. It has been suggested that hypocaloric nutrition may impair immune responsiveness and increase infectious complications. However, limiting nutritional intake stimulates autophagy which is an important host defense mechanism against intracellular pathogens [25–27]. Critical illness is characterized by stress hyperglycemia which appears to be an evolutionary preserved response to provide energy at a time of crises [28]. "Occult overfeeding", when exogenous calories are delivered on top of the non-inhibitable endogenous production of glucose by gluconeogenic organs [29], may result in metabolic dysequilibrium with adverse effects. Critical illness is associated with the rapid loss of skeletal and diaphragmatic muscle mass, and this hampers attempts at weaning patients from mechanical ventilation and is associated with muscle weakness up to 5 years post-ICU discharge [30, 31]. Aggressive nutritional support with increased provision of protein has been postulated to limit this catabolic response and therefore preserve muscle mass [32]. The finding that VFDs were not decreased with hypocaloric feeding suggests that underfeeding does not accelerate loss of muscle mass. This finding is further supported by the studies of Needham et al., who followed the patients enrolled in the EDEN study for up to a year post-hospital discharge [33, 34]. Muscle strength, muscle mass and 6 min walk distance did not differ between the trophic and full feeding groups at 6 and 12 months [33]. Furthermore, the age and sex adjusted physical function domain of the SF-36 instrument at 12 months did not differ between the two groups [34].

The results of our meta-analysis are consistent with two additional randomized controlled trials that did not meet the inclusion criteria for our meta-analysis [35, 36]. These studies tested the hypothesis that a "volume-based" feeding strategy that enhanced the delivery of calories and protein would improve patient outcomes. Heyland et al. performed a prospective, cluster randomized controlled trial to determine the effect of the PEP uP protocol combined with a nursing educational intervention on the outcomes of 1059 critically ill mechanically ventilated patients in 18 ICUs [35]. Although the proportion of prescribed protein and energy delivered by enteral nutrition was significantly greater ($p = 0.004$) in the intervention ICUs compared to the control ICUs, none of the outcome measures investigated differed significantly between the control and intervention ICUs. Braunschweig et al. randomized 78 patients with acute lung injury to a volume based or standard nutritional protocol [36]. The percent of energy needs received per day averaged 85 % in the volume-based group as compared to 55 % in the control group. The trial was terminated prematurely by the Data Safety Monitoring Board due to a significantly higher risk of hospital death in the volume-based group (40 vs. 16 %, $p = 0.02$).

The reasons for the lack of benefit of normocaloric over hypocaloric feeding in ICU patients are not entirely clear. It is possible that normocaloric enteral nutrition does not alter the catabolic process or immune response associated with acute critical illness. Anorexia is an evolutionary preserved response during acute illness which may be protective [37, 38]. Nutrient deprivation promotes autophagy and this may play a key role in promoting host defences and the immune response to intracellular pathogens [27, 39]. In all the studies included in this meta-analysis, patients received continuous rather than intermittent enteral nutrition. Intermittent enteral nutrition is more physiologic than continuous feeding and could possibly explain the lack of benefit of normocaloric nutrition provided as a continuous infusion [40–43]. Finally, it is possible that the combined trials do not have the power to rule out the presence of a clinically meaningful effect.

The meta-analysis reported here combines data across studies in order to estimate treatment effects with more precision than is possible in a single study [12]. The main limitation of this meta-analysis is that the patient population and feeding protocols were not the same across studies. It should be recognized that, while all the studies enrolled "typical" ICU patients and did not exclude patients based on age or BMI, the mean age of the patients' was 55 years and their BMI was 29.1 kg/m^2. Furthermore, the duration of hypocaloric nutrition was limited to either 7 days, 14 days or the duration of ICU stay; it is likely that prolonged intentional hypocaloric nutrition (once the acute critical illness has resolved) is neither safe nor desirable. It has been suggested that "trophic feeds and permissive underfeeding cannot be considered safe or indicated in older, higher risk ICU patients as it appears to increase mortality and impair long-term quality of life" [44]. There are, however, no prospective studies that support this contention. Additional prospective studies targeting this patient population would be required to resolve this issue. It is important to emphasize that this meta-analysis compared the provision of different levels of energy and not protein. It may be that the quantity, quality and mode of delivery of protein may be more relevant for outcome than the level of energy supplied.

Conclusions

This meta-analysis failed to demonstrate an outcomes benefit from normocaloric as opposed to intentional hypocaloric nutrition in heterogenous ICU patients during the acute phase of their illness. The optimal strategy for providing calories and protein in critically ill patients has yet to be determined.

Compliance with ethical standards

Conflicts of interests None.

References

1. Casaer MP, van den Berghe G (2014) Nutrition in the acute phase of critical illness. N Engl J Med 370:1227–1236
2. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P (2003) Canadian Clinical Practice Guidelines for nutrition support in mechanically ventilated, critically ill adult patients. J Parenter Enteral Nutr 27:355–373
3. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G (2009) 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.). J Parenter Enteral Nutr 33:277–316
4. Heyland DK, Dhaliwal R, Lemieux M, Drover J, Jurewitsch B, Greenwood J, Kutsogiannis J, McCall M, Pagliarello G, Wynn C, Garrel D, Gramlich L, Rahman A, Jeejeebhoy K, Macdonald G, Muscedere J (2015) Canadian clinical practice guidelines. http://www.criticalcarenutrition.com/2015. Accessed 9 Sep 2015
5. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J, Ebner C, Hartl W, Heymann C, Spies C, DGEM (German Society for Nutritional Medicine) (2006) ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr 25:210–223
6. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, Heyland DK (2009) The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an International Multicenter Observational Study. Intensive Care Med 35:1728–1737
7. Elke G, Wang M, Weiler N, Day AG, Heyland DK (2014) Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large International Nutrition Databse. Crit Care 18:R29
8. Artinian V, Krayem H, DiGiovine B (2006) Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest 129:960–967

9. Weijs PJ, Stapel SN, de Groot SD, Driessen RH, de Jong E, Girbes AR, van Strack Schijndel RJ, Beishuizen A (2012) Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. J Parenter Enteral Nutr 36:60–68
10. Faisy C, Lerolle N, Dachraoui F, Savard JF, Abboud I, Tadie JM, Fagon JY (2009) Impact of energy deficit calculated by a predictive method on outcome in medical patients requiring prolonged acute mechanical ventilation. Br J Nutr 101:1079–1087
11. Singer P, Pichard C, Heidegger CP, Wernerman J (2010) Considering energy deficit in the intensive care unit. Curr Opin Clin Nutr Metab Care 13:170–176
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339:b2700
13. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339:b2535
14. Higgins JP and Green S (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0. www.cochrane-handbook.org. Accessed 15 July 2015
15. Rice TW, Morgan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP (2011) A randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med 39:967–974
16. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, Morris A, Dong N, Rock P (2012) Initial trophic vs full enteral feeding in patients with acute lung injury. The EDEN randomized trial. JAMA 307:795–803
17. Cochran W (1954) The combination of estimates from different experiments. Biometrics 10:101–129
18. Berlin JA, Laird NM, Sacks HS, Chalmers TC (1989) A comparison of statistical methods for combining event rates from clinical trials. Stat Med 8:141–151
19. Egger M, Smith GD (1998) Bias in location and selection of studies. Br Med J 316:61–66
20. Biljana M, Jelena M, Branislav J, Milorad R, Biljana M, Jelena M, Branislav J, Milorad R (1999) Bias in meta-analysis and funnel plot asymmetry. Stud Health Technol Informat 68:323–328
21. Arabi YM, Tamim HM, Dhar GS, Al-Dawood A, Al-Sultan M, Sakkijha MH, Kahoul SH, Brits R (2011) Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr 93:569–577
22. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, Mehta S, McIntyre L (2015) Permissive underfeeding or standard enteral feeding in critically ill adults. N Engl J Med 372:2398–2408
23. Charles EJ, Petroze RT, Metzger R, Hranjec T, Rosenberger LH, Riccio LM, McLeod MD, Guidry CA, Stukenborg GJ, Swenson BR, Willcutts KF, O'Donnell KB, Sawyer RG (2014) Hypocaloric compared with eucaloric nutritionaql support and its effect on infection rates in a surgical intensive care unit: a randomized controlled trial. Am J Clin Nutr 100:1337–1343
24. Petros S, Horbach M, Seidel F, Weidhase L (2015) Hypocaloric vs normocaloric nutrition in critically ill patients: a prospective randomized trial. J Parenter Enteral Nutr . doi: 10.1177/0148607114528980
25. Xu Y, Eissa NT (2010) Autophagy in innate and adaptive immunity. Proc Am Thorac Soc 7:22–28
26. Rich KA, Burkett C, Webster P (2003) Cytoplasmic bacteria can be targets for autophagy. Cell Microbiol 5:455–468
27. Levine B, Mizushima N, Virgin HN (2011) Autophagy immun inflamm. Nature 469:323–335
28. Marik PE, Bellomo R (2013) Stress hyperglycemia: an essential survival response! Crit Care 17:305
29. Tappy L, Schwarz JM, Schneiter P, Cayeux C, Revelly JP, Fagerquist C, Jequier E, Chiolero R (1998) Effects of isoenergetic glucose-based or lipid-based parenteral nutrition on glucose metabolism, de novo lipogenesis, and respiratory gas exchanges in critically ill patients. Crit Care Med 26:860–867
30. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CM (2003) One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 348:683–693
31. Herridge MS, Tansey CM, Matte A, Tomlionson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta A (2011) Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 364:1293–1304
32. Hoffer LJ, Bistrian BR (2013) Why critically ill patients are protein deprived. J Parenter Enteral Nutr 37:300–309
33. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, Wozniak AW, Colantuoni E, Ely EW, Rice TW, Hopkins RO (2013) Physical and cognitive performance of acute lung injury patients one year after initial trophic vs full enteral feeding: EDEN trial follow-up. Am J Respir Crit Care Med 188:567–576
34. Needham DM, Dinglas VD, Bienvenu OJ, Colantuoni E, Wozniak AW, Rice TW, Hopkins RO (2013) One-year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. BMJ 346:f1532
35. Heyland DK, Murch L, Cahill N, McCall M, Muscedere J, Stelfox HT, Bray T, Tanguay T, Jiang X, Day AG (2013) Enhanced protein-energy provision via the enteral route feeding protocol in critically ill patients: results of a cluster randomized trial. Crit Care Med 41:2743–2753
36. Braunschweig CA, Sheean PM, Peterson SJ, Perez SG, Freels S, Lateef O, Gurka D, Fantuzzi G (2015) Intensive nutrition in acute lung injury: a clinical trial (INTACT). J Parenter Enteral Nutr 39:13–20
37. Asarian L, Langhans W (2010) A new look on brain mechanisms of acute illness anorexia. Physiol Behav 100:464–471
38. Langhans W (2007) Signals generating anorexia during acute illness. Proc Nutr Soc 66:321–330
39. Choi AM, Ryter SW, Levine B (2013) Autophagy in human health and disease. N Engl J Med 368:651–662
40. Gazzaneo MC, Suryawan A, Orellana RA, Torrazza RM, El-Kadi SW, Wilson FA, Kimball SR, Srivastava N, Nguyen HV, Fiorotto ML, Davis TA (2011) Intermittent bolus feeding has a greater stimulatory effect on protein synthesis in skeletal muscle than continuous feeding in neonatal pigs. J Nutr 141:2152–2158
41. Stoll B, Puiman PJ, Cui L, Chang X, Benight NM, Bauchart-Thevret C, Hartmann B, Holst JJ, Burrin DG (2012) Continuous parenteral and enteral nutrition induces metabolic dysfunction in neonatal pigs. J Parenter Enteral Nutr 36:538–550

42. Chowdhury AH, Murray K, Hoad CL, Costigan C, Marciani L, MacDonald IA, Bowling TE, Lobo DN (2015) Effects of bolus and continuous nasogastric feeding on gastric emptying, small bowel water content, superior mesenteric artery blood flow, and plasma hormone concentrations in heathy adults. A randomized crossover study, Ann Surg (in press)
43. Marik PE (2015) Feeding critically ill patients the right "whey":thinking outside the box. Ann Intensive Care 5:11
44. Wischmeyer PE (2015) Ensuring optimal survival and post-ICU qulaity of life in high-risk ICU patients: permissive underfeeding is not safe! Crit Care Med 43:1769–1772