Clinical sequelae from overfeeding in enterally fed critically ill adults: Where is the evidence?

Manuscript

Authors

Chapple LS^{1,2}, Weinel L^{1,2}, Ridley EJ^{3,4}, Jones D^{5,6}, Chapman MJ^{1,2}, Peake S^{2,7}

Affiliations

¹Intensive Care Research, Royal Adelaide Hospital, Adelaide 5000, Australia

²Discipline of Acute Care Medicine, School of Medicine, University of Adelaide, Adelaide 5000, Australia

³Australasian and New Zealand Intensive Care Research Centre, School of Public Health and Preventative Medicine, Monash University Melbourne 3004, Australia

⁴Nutrition Department, Alfred Health, Melbourne 3004, Australia

⁵Intensive Care Unit, Austin Health, Melbourne 3084, Australia

⁶School of Public Health and Preventive Medicine, Monash University Melbourne 3004, Australia

⁷Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Adelaide 5011, Australia

Corresponding author

Dr Lee-anne Chapple

Email: lee-anne.chapple@adelaide.edu.au

Phone: +61 8 7074 1763

Postal address: ICU Research, Desk 40, 4G751, Royal Adelaide Hospital, Port Road, Adelaide 5000, Australia

Contact details:

Dr Lee-anne Chapple

PhD MNutDiet BMedSc

Intensive Care Research

Royal Adelaide Hospital, Port Road, Adelaide

Email: lee-anne.chapple@adelaide.edu.au

Mr Luke Weinel

Research Scientist

Intensive Care Research

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Royal Adelaide Hospital, Port Road, Adelaide

Email: luke.weinel@sa.gov.au

Dr Emma Ridley

Senior Research Fellow & Lead, Nutrition Program, ANZIC-RC

Senior Dietitian, Intensive Care, The Alfred Hospital, Melbourne

Email: emma.ridley@monash.edu

Associate Professor Daryl Jones

BSc(Hons) MBBS FRACP FCICM MD PhD

A/Prof ANZIC-RC, Monash University

ICU Consultant, Austin Health

Email: daryl.jones@austin.org.au

Professor Marianne Chapman

MBBS, PhD, FJFICM, FANZCA

Director of Research, Intensive Care Unit

Royal Adelaide Hospital, Port Road, Adelaide

Email: marianne.chapman@sa.gov.au

Professor Sandra Peake

BM BS, BSc(Hons) FCICM, PhD

Director, Intensive Care Unit

The Queen Elizabeth Hospital, Woodville Road, Woodville, Adelaide

Email: sandra.peake@sa.gov.au

ABSTRACT

Enteral calorie delivery in excess of requirements (overfeeding) is believed to cause adverse effects during critical illness, but the literature supporting this is limited. We aimed to quantify the reported frequency and clinical sequelae of calorie overfeeding with enterally-delivered nutrition in critically ill adult patients. A systematic search of MEDLINE, EMBASE, and CINAHL from conception to November 28, 2018 was conducted to identify clinical studies of nutrition interventions in enterally-fed critically ill adults that reported overfeeding in one or more study arms. Overfeeding was defined as calorie delivery >2000 kcal per day, >25 kcal/kg per day, or $\geq 110\%$ of calorie prescription. Data were extracted on methodology, demographics, prescribed and delivered nutrition, clinical variables and pre-defined outcomes. Cochrane 'Risk of Bias' tool was used to assess the quality of RCTs. Eighteen studies were included; of which 10 were randomized (n=4386 patients) and 8 were non-randomized (n=223). Only 4 studies reported a separation in calorie delivery between treatment groups whereby one arm met the definition of overfeeding, for which no between-group differences in mortality, infectious complications or ventilatory support were reported. Overfeeding was associated with increased insulin administration (median 3 [IQR: 0-41.8] vs 0 [0-30.6] units/day) and upper gastrointestinal intolerance in one large RCT, and duration of antimicrobial therapy in a small RCT. There is limited high quality data to determine the impact of calorie overfeeding of critically ill patients by the enteral route; however, based on available evidence, does not appear to increase mortality or affect other important clinical outcomes.

Keywords

Overfeeding, critical care, enteral nutrition, calories

INTRODUCTION

Overfeeding, the provision of calories and protein in excess of metabolic requirements to critically ill patients, is thought to be associated with adverse clinical sequelae, including hyperglycemia, liver dysfunction, increased risk of infection, prolonged weaning from ventilatory support and increased mortality.¹ However, despite reported concerns, there is no universally agreed definition as to what constitutes calorie overfeeding or the clinical consequences. Moreover, the literature on overfeeding has predominantly been limited to calorie delivery via the parenteral, rather than enteral, route.² In contrast to parenterally delivered nutrients, innate enteral control mechanisms may prevent or reduce the risk of overfeeding in the critically ill. Nutrient delivery to the small intestine initiates important feedback mechanisms that control gastric emptying.³ In health, nutrient emptying into the intestine occurs at a rate of 1-4 kcal/minute.⁴ In critical illness, the feedback mechanism is exaggerated and nutrient delivery to the small intestine can be markedly slowed. Gastrointestinal dysfunction is common and typically characterized by reduced gastric motility,⁵ and decreased absorption of both lipids and glucose.^{6, 7} Enteral provision of nutrients during critical illness is preferred over the

parenteral route, yet the frequency of enteral calorie overfeeding and how it may contribute to adverse outcomes in the critically ill is uncertain.

International critical care nutrition guidelines currently recommend a calorie goal of 20-25⁸ (European Society of Parenteral and Enteral Nutrition (ESPEN)) or 25-30⁹ (American Society of Parenteral and Enteral Nutrition (ASPEN)) kcal/kg body weight/day. The avoidance of calorie overfeeding is also suggested, despite limited and low quality evidence to support this recommendation.^{8, 9} Further, a consensus of what defines overfeeding is not available, and there is no distinction between overfeeding via the parenteral or enteral route. However, the ASPEN guidelines state that when enteral nutrition is adequate, the provision of supplemental parenteral nutrition should be reduced to avoid the complications associated with overfeeding.⁹

Given the lack of agreed definition for overfeeding associated with calorie delivery in the critically ill and the potential adverse outcomes, a systematic literature review was conducted to identify and quantify the frequency and clinical sequelae of documented enteral calorie overfeeding in critically ill adult patients.

MATERIALS AND METHODS

A systematic review of the literature was conducted in accordance with the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement¹⁰ and the protocol was prospectively registered with PROSPERO (CRD42018091648).

Search strategy

An electronic search to identify randomized and non-randomized studies using the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE via OVID and CINAHL via EBSCOhost published from database inception to November 28, 2018. These databases were searched for studies using variations on the key words “intensive care” together with “enteral nutrition” and limited to human and adult studies. Only studies published in English were identified. The search strategies and MeSH headings are shown in **Supplementary Tables S1-4**.

Study selection

Duplicates were removed and titles and abstracts screened for eligibility (LW). Where relevance of the article was unclear from the abstract, the full text was obtained. Full texts were assessed against pre-specified inclusion and exclusion criteria by two independent reviewers (LC and LW).

Studies conducted in adult critically ill patients (≥ 18 years for all patients or where the mean or median age was ≥ 18 years in all groups) were included. Critically ill patients were defined as patients

recruited whilst present in an intensive care unit (ICU) and requiring invasive ventilation or where >50% of the trial population required invasive mechanical ventilation.¹¹

Studies were included if: 1) calorie delivery was via the enteral route (supplemental parenteral calories were permitted but were not a defined study intervention); 2) calorie prescription and delivery (in kcal per day or kcal/kg per day) or the percent of calories above prescription were reported or could be calculated from published data; 3) documented or calculated calorie delivery from one or more patient cohorts met one or more of our study definitions for overfeeding and; 4) at least one pre-defined clinical outcome including mortality, ventilator-free days, or infectious complications was reported (for a list of the pre-defined clinical outcomes see **Supplementary Table S5**). Only data published in the primary manuscript and supplementary materials were included.

For the purposes of this review, overfeeding was defined *apriori* as delivery of >25 kcal/kg per day or >2000 kcal per day or $\geq 110\%$ of calorie prescription. This definition was irrespective of the method (e.g. indirect calorimetry, fixed equation) or body weight (e.g. actual, ideal) used to determine calorie prescription and delivery. Calorie prescription >25 kcal/kg per day exceeds the ESPEN recommendations of 20-25 kcal/kg per day and equates to >2000 kcal per day assuming an actual body weight of 80 kg; the average weight of a critically ill patient receiving invasive mechanical ventilation.^{8, 9, 12} ~~A sensitivity analysis was conducted including only those~~ Data were also reported separately for studies where >30 kcal/kg per day was received, as this is the upper calorie recommendation according to the ASPEN guidelines.⁹ Finally, calorie administration of $\geq 110\%$ above the defined target is consistent with the definition provided in the ESPEN guidelines for overfeeding.⁸

Studies were excluded if: 1) data on calorie delivery was not provided; 2) oral nutrition, animals or children were included; 3) no pre-defined clinical outcomes were reported; or 4) they were case reports, editorials, or reviews.

Data extraction and quality assessment

Data were independently extracted in duplicate (LW and also by LC or ER or DJ) using pre-defined data extraction forms. Discrepancies in data extraction were resolved by consensus.

Extracted data were: 1) study methodology i.e. study design, aim, intervention, population; 2) patient characteristics i.e. age, sex, injury severity of illness, weight, body mass index (BMI); 3) nutrition therapy prescribed and delivered; 4) patient outcomes i.e. mortality, duration of stay, organ support, respiratory parameters, infectious complications, blood glucose control, and other clinical complications (**Supplementary Table S5**).

Data presented in median and range/interquartile range were converted to mean (standard deviation) as per methodology by Wan and colleagues.¹³ Only papers in which relevant data were reported under each heading were presented in the tables.

Statistical analyses:

'A sensitivity analysis was conducted for the four studies that reported differences in calorie delivery, where only one group met a criterium for overfeeding. The two types of studies, observational and randomised controlled trial, were combined using the principled method of Bayesian evidence synthesis¹⁴ via the "bayesmeta" package (<https://cran.r-project.org/web/packages/bayesmeta/index.html>) in the R statistical environment. Estimates were reported as (median) odds ratio and 95% credible intervals (CrI).'

Risk of bias

Risk of bias of individual studies was only assessed for randomized trials and completed in duplicate (LW and also by LC or ER or DJ) using the Cochrane 'Risk of Bias' tool which classifies risk as 'low', 'some concerns', or 'high'. Disagreements in risk of bias were resolved by discussion.

Assessment of publication bias using a funnel plot created in Review Manager 5 (RevMan5)¹⁵ was planned if more than 10 papers were identified that reported mortality as a dichotomous outcome.¹⁶

RESULTS

The database search identified a total of 5373 articles. After removing duplicates, 4481 unique articles remained. Title and abstract screening led to the retrieval of 140 full text articles for potential inclusion. Of these, 122 articles were excluded, with 18 studies eligible for inclusion in the final review (**Figure 1**).

Only four of the included studies (two randomized^{12, 17} and two non-randomized^{18, 19}) reported a separation in calorie delivery between treatment groups in which one arm, and not the other, met the definition of overfeeding. In all of these trials, the definition of overfeeding met was >25 kcal/kg per day. In only two of these studies were patients fed >27 kcal/kg per day^{12, 17}.

The included studies consisted of 10 randomized parallel-arm trials (4386 patients),^{12, 17, 20-27} and eight non-randomized studies (223 patients) of which three were before-after studies,^{19, 28-30} three prospective observational studies,³¹⁻³³ one prospective cross-over trial,³⁰ and one retrospective observational study¹⁸ (**Table 1**). In three of the non-randomized studies, there was no comparator group.³¹⁻³³ The total number of patients included was 4609 and ranged from 5 to 3957.

Trial characteristics

The interventions evaluated were immuno-nutrition (n=7),^{19, 21, 23-26, 29} calorie provision (n=5),^{12, 17, 18, 30, 32} macronutrient composition (n=3),^{20, 22, 28} timing of enteral feeding (n=1),³¹ micronutrient provision (n=1)²⁷ and insulin therapy (n=1, a post-hoc analysis of a previously reported trial).³³ One immuno-

nutrition study reported burns and trauma sub-groups separately. Only the burns sub-group met an overfeeding criterium and was included in this review.¹⁹

Patient characteristics

Overall, the patient populations were young and the majority of studies included more males than females (**Table 1**). Body mass index (BMI) was only reported in three randomized trials^{12, 17, 26} and two non-randomized studies.^{18, 19} Only one randomized trial reported a BMI in the healthy weight range²⁶ according to the World Health Organization classification.³⁴

Calorie prescription

A fixed, weight-based equation was used to determine the feeding rate in 11 of the 18 included studies (61%), of which seven were randomized trials^{12, 17, 21, 23, 24, 26, 27} and four were non-randomized studies^{18, 19, 28, 29} (**Table 2**). Calorie prescription was 25-35 kcal/kg per day in six of these studies (four randomized, two non-randomized)^{21, 23, 24, 27, 28, 29} and 1 ml/kg/hour in two randomized studies.^{12, 17} The fixed, weight-based equation used to determine calorie prescription was not reported in the remaining three studies.^{26, 18, 19}

A predictive equation was applied in another five of the 18 included studies (28%), including two randomized and three non-randomized studies.^{22, 25, 31-33} (Harris-Benedict, n=2;^{31, 32} Scholfield, n=1;²² Curreri, n=1;²⁵ Carlson and Milner, n=1³³). Three studies reported using a combination of fixed weight-based or predictive equation with indirect calorimetry^{25, 27, 33} and one of the 18 included studies reported using indirect calorimetry alone to determine calorie prescription.³⁰ Finally, one non-randomized study did not report the method for determining calorie prescription.²⁰

Calorie delivery

Five randomized studies^{12, 17, 21, 23, 24} and five non-randomized studies^{18, 19, 28, 31, 33} reported calorie delivery >25 kcal/kg per day (**Table 2**). Of these, four reported delivery >30 kcal/kg per day.^{12, 28, 31, 33} Calorie delivery >2000 kcal per day was reported in seven randomized^{12, 20, 22, 24-27} and five non-randomized^{19, 29, 30, 32, 33} studies. Four of the included studies met both the overfeeding criteria for both total calories and >25 kcal/kg per day.^{12, 19, 24, 33} The mean duration of feeding ranged from 4 to 13 days in six randomized trials^{12, 17, 21, 22, 24, 26}, and 8 to 31 days in four non-randomized trials.^{18, 28, 29, 31} Four randomized^{20, 23, 25, 27} and four non-randomized^{19, 30, 32, 33} studies did not report the duration of enteral feeding.

Outcomes

Mortality at one or more time-points was reported in 12 of the 18 included studies (67%), of which six were randomized trials^{12, 17, 21, 24-26} and six were non-randomized studies^{18, 19, 29, 31-33} (**Table 3**). In four of the 12 studies, the time-point at which mortality was recorded was not reported or was unclear.^{18, 24, 25, 29} Calorie delivery that met an overfeeding inclusion criterium was not found to be associated with increased mortality when compared to lower calorie delivery in the four studies (two randomized;^{12, 17}

two non-randomized^{18, 19}) that reported a significant difference in calorie delivery between treatment groups.

In a sensitivity analysis based on the Bayesian approach for the four studies that reported differences in calorie delivery, where only one group met a criterium for overfeeding, there was no demonstrable treatment effect of overfeeding on trial reported mortality: median OR: 0.983 (95% CrI: 0.517 - 1.832).

Outcomes related to organ support and respiratory parameters are reported in **Table 4**. Data relating to mechanical ventilation were reported in seven randomized trials^{12, 17, 21-23, 25, 26} and six non-randomized studies.^{18, 19, 28-30, 32} Seven studies reported the number of mechanically ventilated patients with over 85% of included patients in those studies receiving invasive ventilation.^{12, 17, 22, 25, 28, 30, 32} There were no between-group differences in rates of ventilation in studies that reported differences in calorie delivery between the two arms. Five randomized trials^{12, 17, 21, 25, 26} and four non-randomized studies^{18, 19, 29, 30} reported either the duration of mechanical ventilation^{18, 19, 21, 25, 26, 29, 30} or the number of ventilator-free days to day 28.^{12, 17} The two randomized trials reporting a difference in calorie delivery between groups did not find an association between calorie overfeeding and ventilator-free days. No studies reported the development of new onset respiratory failure. Only one randomized study¹² reported the percentage of patients receiving vasopressor support and acute renal replacement and the number of organ-free days. Calorie overfeeding was not associated with an increase in the number of patients requiring vasopressors or acute renal replacement therapy or the duration of support.

Five randomized trials^{12, 21, 24-26} and three non-randomized studies^{18, 19, 29} reported one or more infectious complications (44% of included studies) (**Table 5**). Calorie overfeeding was not found to be associated with increased rates of bacteremia or antimicrobial administration in the one randomized trial that reported a significant difference in calorie delivery between treatment groups,¹² while one non-randomized trial reported an increased duration of antibiotic therapy with overfeeding (27.4 (17.3) vs 16.6 (11.7) days).¹⁸

Calorie overfeeding was associated with hyperglycemia and increased insulin administration in one randomized trial reporting a significant difference in calorie delivery between treatment groups.¹² A smaller non-randomized trial also reported a significant increase in total insulin administration with overfeeding in a sub-group of burns patients¹⁹ (**Table 6**), while a small randomized trial reported no difference in mean concentrations of glucose and insulin or glucose turnover during the study.²⁷ One large randomized trial reported increased gastric residual volumes and promotility administration with overfeeding.¹² One randomized trial reported a similar frequency of diarrhoea between study arms, both of which were overfed.²⁰ No studies reported new-onset fever or pancreatitis.

Risk of bias

The risk of bias for the randomized controlled trials is shown in the supplemental files; Figure S1. According to the Cochrane 'Risk of Bias' tool classifications three studies were considered to have low risk of bias^{12, 17, 27}, six studies had met the criteria of 'some concerns'^{20, 22-26} and one study had a high risk of bias²¹.

A funnel plot for publication bias for the outcome of mortality was not constructed as less than 10 randomized papers were available.

DISCUSSION

Overview of results

This systematic review evaluating the effects of enteral calorie overfeeding in critically ill adults did not find an association with mortality or key clinical outcomes including duration of mechanical ventilation and infectious complications. However, only 18 studies fulfilled the pre-defined criteria for calorie overfeeding in one or more patient cohorts, of which only half were randomized trials and only four reported a separation in calorie delivery between treatment arms in which only one arm met the pre-defined criterium for overfeeding. The paucity of high-quality evidence precludes any meaningful conclusions regarding the potential for harm associated with enteral calorie overfeeding. Our findings do not provide evidence to support the stated risks of overfeeding in international guidelines⁸ and opinion pieces.^{1, 35, 36}

Relationship to other literature

The major clinical concerns of overfeeding are increased CO₂ production, and hence prolonged ventilatory dependence, and glycemic control. The literature suggesting any adverse effects of calorie overfeeding on respiratory outcomes primarily relates to parenterally fed patients.³⁷⁻³⁹ Our review did not find that enteral calorie overfeeding was associated with worse outcomes. Moreover, an observational study of long-term mechanically ventilated patients, in which overfeeding was defined as >110% of estimated caloric goals using indirect calorimetry, reported lower minute ventilation with greater calorie delivery.⁴⁰ A post-hoc analysis of an international database also reported more ventilator-free days with increased calorie delivery.⁴¹ While few studies reported glycaemia outcomes our review only found one study, albeit a large randomised trial, demonstrating inferior glycemic control with overfeeding with an increase in the number of patients receiving insulin and the daily insulin dose. However, interpretation of these results should consider macronutrient composition as the group receiving greater calories received a higher carbohydrate dose (180 g vs 125 g per liter enteral nutrition formulation).¹² Furthermore, as insulin resistance and stress-induced hyperglycemia are common in critical illness it is likely that blood glucose concentrations are directly related to the

amount of carbohydrate delivered, even when enteral calorie delivery does not meet the definition of overfeeding.

Strengths/weaknesses

This systematic review provides the first comprehensive analysis of studies reporting enteral calorie overfeeding (as defined in our review) to critically ill patients and associated clinical outcomes. Strengths of this review include a comprehensive literature search, adherence to a pre-registered protocol, limiting the search to only include studies of enteral calorie delivery, the recommended route for nutrition in the critically ill,^{8,9} and the inclusion of a large, recent, multi-centre, randomized, double-blind enteral nutrition trial evaluating increased calorie delivery in mechanically ventilated patients.¹² While several definitions of overfeeding were included in order to capture the breadth of research in this area, these definitions are not standardized. This lack of uniformity may have limited the number of identified publications and under- or over- estimated the effect of overfeeding on clinical outcomes. Further, only four studies that met our definition of calorie overfeeding included only one arm that was overfed. Of these, only two were randomized (and one of these was the pilot trial for the larger randomized study). The third study was non-randomized and patients were only overfed at particular time-points rather than the entire study duration, and the fourth, in a sub-set of burns patients, overfed for the kcal/kg per day criterium only and not total kcal per day. In addition, the mean calorie intake at a group level only was considered, and hence it should be recognised that inter-patient variation means it is likely not all patients within the overfed group were overfed.

The small number of studies identified, combined with heterogeneity in calculating calorie goals and outcome reporting precluded the synthesis of results. Only four studies used indirect calorimetry, the recommended technique for estimating metabolic rate.⁸ For those studies that used a fixed weight or predictive equation to prescribe calories, the determination of calorie overfeeding will differ according to the use of actual, ideal or adjusted weight to calculate calorie delivery. The lack of a uniform approach as to which weight to use highlights the need to standardize weight, not only for critical care nutrition research but also for calculating calorie requirements at the patient's bedside.

Implications for clinicians:

This review demonstrates a lack of high-quality evidence supporting the view that enteral calorie delivery to a level that meets our pre-defined criteria of overfeeding in critical illness is harmful, with the exception of upper gastrointestinal intolerance and poorer glycemic control. Clinicians should however remain cautious about overfeeding via intravenous routes.

Implications for further research:

Prior to implementing changes in practice, further research should assess the effects of calorie overfeeding via the enteral route on physiologically-plausible clinical outcomes such as respiratory outcomes and glycemic control. In particular, differentiation as to the effect of specific macronutrient overfeeding from total calorie overfeeding via the enteral route is required. High protein intake is

recommended in current nutrition guidelines^{8, 9} and yet the safety and benefits of this remain uncertain. In addition, it is recommended that a consensus statement for standardized reporting of demographics, caloric goals, calorie and macronutrient delivery, and outcome measures be developed in order to allow synthesis of trials in the field of critical care nutrition. A systematic review on the quality of reporting of nutrition variables in critical care nutrition trials is currently underway (<https://www.crd.york.ac.uk/prospero/>; CRD42019127194).

Conclusion:

The literature on overfeeding of enteral calories is sparse. Limited high quality data of the impact of calorie overfeeding on outcomes exists; however documented adverse effects from calorie overfeeding by the enteral route in critical illness are minor and concerns of overfeeding in enterally fed critically ill patients are not supported by the current literature, other than increased gastrointestinal intolerance and a greater need for insulin to manage blood glucose levels. This evidence should be carefully considered by trialists in the design of future studies aimed to deliver full calorie targets.

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Statement of Authorship:

LSC, DJ, EJR, MJC, and SP contributed to the conceptualization and research design. LSC and LW performed the literature review. LSC, LW, EJR, and DJ collected and analyzed the data. All authors provided crucial intellectual input to the analysis and interpretation of the results and drafting of the manuscript. All authors read and approved the final manuscript.

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Table 1. Study and patient characteristics

Author, Year	Study design	N°. arms	Intervention	Population	N	Age, years		Sex Male, n (%)		Weight, kg ^a		BMI, kg/m ²		Severity illness	
						Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Randomized trials															
Diboune 1992 ²⁰	RCT	3	EN with 3 different FA composition	Head-injury, cerebral stroke	32	57.7 (26.2)	49.1 (24.9)	6 (55)	6 (55)	60.7 (14.9)	60.0 (10.2)	NR	NR	NR	NR
Van den Berg 1994 ²²	RCT	2	High fat/low carb vs standard EN	COPD, trauma, neurological illness, pneumonia	32	NR	NR	13 (76)	10 (67)	1.15 (0.27) % IBW	0.94 (0.24) % IBW	NR	NR	AP II: 14 (4)	AP II: 15 (4)
Moore 1994 ²¹	RCT	2	Immunoenhancing vs standard 'stress' EN	Major torso trauma	98	30.1 (1.3) ^c	30.7 (1.5) ^c	36 (71)	33 (70)	76.5 (2.0) ^c IBW for non-obese , moderate obesity adj	77.9 (2.7) ^c IBW for non-obese , moderate obesity adj	NR	NR	ISS: 20.6 (1.2) ^c GCS: 13.7 (0.3) ^c	ISS: 21.8 (1.2) ^c GCS: 13.7 (0.4) ^c
Long 1995 ²³	RCT	2	Glutamine-enriched vs standard EN	Trauma	30	35.1 (3.2) ^c	29.4 (3.5) ^c	6 (43)	10 (63)	72.9 (3.6) ^c	73.8 (3.8) ^c	NR	NR	ISS: 33.8 (2.1) ^c	ISS: 30.0 (1.5) ^c
Mendez 1997 ²⁴	RCT	2	Immunoenhancing vs standard EN	Obese trauma	43	25.5 (1.2) ^c	35.3 (2.7) ^c	14 (64)	15 (71)	NR	NR	NR	NR	AP: 15.05 (1.38) ^c ISS: 28.2 (2.1) ^c	AP: 15.67 (1.05) ^c ISS: 32.2 (2.3) ^c
Garrel 2003 ²⁵	RCT	2	Glutamine vs placebo	Severe burns (≥20% TBSA)	41	38 (8)	39 (7)	21 (95)	16 (84)	92 (13)	86 (29)	NR	NR	NR	NR
Falcão de Arruda 2004 ²⁶	RCT	2	Glutamine/probiotic-enriched vs standard EN	TBI	20	30 (9.7) ^d	30 (8.7) ^d	9 (90)	10 (100)	NR, mean IBW	NR, mean IBW	22.5 (1.0) ^d	22.5 (1.0) ^d	GCS: 7 (1.3) ^d TISS: 32 (5)	GCS: 7.5 (1.3) ^d TISS: 34 (8)
Berger 2007 ²⁷	RCT	2	IV copper, selenium + zinc vs placebo	Burns	21	38 (16)	46 (15)	6 (60)	9 (82)	NR	NR	NR	NR	NR	NR
Peake 2014 ¹⁷	RCT pilot	2	1 vs 1.5 kcal/ml EN	General ICU, MV	112	56.4 (16.8)	56.5 (16.1)	42 (74)	41 (75)	83 (23.2) ABW 67 (9.2) IBW	77 (16.4) ABW 67 (9.1) IBW	27.8 (7.9)	26.2 (6.4)	AP II: 23 (9.1)	AP II: 22 (8.9)
TARGET	RCT	2	1 vs 1.5	General	395	57.2	57.5	1221	1272	84.6	84.9	29.2	29.3	AP II:	AP II:

Investigators 2018 ¹²			kcal/ml EN	ICU, MV	7	(16.6)	(16.5)	(62)	(64)	(23.3) ABW 64.4 (11.1) IBW	(23.6) ABW 64.7 (10.9) IBW	(7.7)	(7.9)	22.0 (8.3)	22.1 (8.5)
Non-randomized															
van den Berg 1988 ³⁰	Prospective cross-over	2 d cross-over	Moderate vs high caloric intake	MV	9	58 (13) (reported for whole group only)		6 (67) (reported for whole group only)		NR	NR	NR	NR	NR	NR
Buonpane 1989 ³¹	Prospective observational	1	Early aggressive EN	Trauma	12	28 (8)		11 (92)		70.1 (5.8)		NR		AP II: 20 (3.0) ISS: 29 (10)	
Cerra 1989 ²⁸	Prospective observational, retrospective cohort	3	EN: Stressin vs Reabilitation vs Vivonex	Metabolic, surgical, malnourished, post-operative, trauma	35	55.6 (19.9)	56 (15.0)	NR	NR	71.7 (3.5)	69.7 (20.5)	NR	NR	NR	NR
Dickerson 2002 ¹⁸	Retrospective cohort	2	Hypocaloric vs eucaloric EN	Obese trauma / surgical	40	43.3 (15.5)	45.0 (16.6)	4 (33)	10 (36)	102 (36) Adj weight	118 (41) Adj weight	36 (12.4)	41.3 (13.7)	AP II: 18.1 (5.1) ISS: 24.4 (4.9)	AP II: 17.2 (6.7) ISS: 22.2 (14.5)
Ravasco 2003 ³²	Prospective observational	1	Non-nutritive solutions and nutrient delivery	Respiratory	44	63 (12) [17-83], [range]		25 (57)		NR, Actual if not obese; adj if BMI > 30		NR		AP II: 24 (9)	
Farber 2005 ²⁹	Prospective observational, retrospective control	2	Immunomodulating vs standard EN	ISS≥25; GCS≤8; burns ≥30%; sepsis + MV; ARDS	17 + 21 historical cohort	39.1 (16.3)	39.8 (15.8)	10 (59)	17 (81)	NR	NR	NR	NR	ISS: 29.9 (9.9) GCS: 11.1 (4.8)	ISS: 31.2 (6.8) GCS: 9.2 (5.0)
Sogut 2008 ¹⁹	Prospective observational, retrospective cohort	2	Glutamine/AO-enriched vs standard EN	Burns/trauma: subgroups reported separately	20 + 20 historical cohort	44 (20)	45 (21)	15 (75)	15 (75)	73.5 (11.8)	77.5 (13.4)	24.1 (4.0)	28.9 (6.0)	SAPS II: 34 (9) [34] [Median]	SAPS II: 33 (12) [28.5] [Median]
Shields 2015 ³³	Prospective observational	1	High-dose insulin	Burns ≥20% TBSA	5	27.8		NR		80, pre-injury weight		NR		NR	

AO, antioxidants; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BSA, body surface area; COPD, chronic obstructive pulmonary disease; EN, enteral nutrition; EPA, eicosapentaenoic acid (omega 6); FA, fatty acids; Fn, fibronectin; GLA, gamma linolenic acid (omega 3); ICU, Intensive Care Unit; ISS, Injury Severity Score; IV, intravenous; MV, mechanical ventilation; RCT, Randomized controlled trial; Sm-C, somatomedin-C; Yrs, years; TBI, traumatic brain injury; TBSA, total body surface area; TE, trace elements; TISS, Trauma Injury severity score. Data are reported as mean (standard deviation) unless otherwise stated. Group 1 received the highest calorie delivery.

^a Weight assumed to be actual weight unless indicated

^b Patient population included both burns and trauma patients. Data presented on burns subgroup only.

^c Standard error of the mean

^d Median (range) converted to mean (SD)

Cerra 1989²⁸ also included a third arm for which the mean age was 54.6 (10.7) years.

Diboune 1992²⁰ also included a third arm for which the M,F was 4,6, mean age was 51.7 (15.1) years, and mean time-point of study conduct was 26.3 (18.1) days.

Table 2. Caloric prescription and delivery

Author	Calorie prescription methods	Calorie delivery, kcal/d			Definition of overfeeding met	Time from ICU admission to start study, days		Duration intervention, days	
		Group 1	Group 2	p-value for calorie delivery		Group 1	Group 2	Group 1	Group 2
Randomized trials									
Diboune 1992 ²⁰	NR	2950	2950	NR	>2000 kcal	27.9 (37)	26.5 (32.4)	NR	NR
Van den Berg 1994 ²²	Schofield 1.5 x BMR	2003 (277)	1943 (306)	NR	>2000 kcal	NR	NR	6	4
Moore 1994 ²¹	35 kcal/kg/d	d3 26.4 (1.4) kcal/kg/d ^a d7 29.2 (3.0) kcal/kg/d ^a	d3 24.1 (1.8) kcal/kg/d ^a d7 26.8 (2.3) kcal/kg/d ^a	NR	> 25 kcal/kg/d	NR	NR	7 (0.5)	8.2 (0.4)
Long 1995 ²³	30 kcal/kg/d	28.6 (1.2) kcal/kg/d	25.3 (1.2) kcal/kg/d	p 0.07	> 25 kcal/kg/d	28.9 hrs	27.7 hrs	NR	NR
Mendez 1997 ²⁴	30 kcal/kg/d	2200 (200) 29.5 (2.6) kcal/kg/d	2000 (185) 26.3 (3.2) kcal/kg/d	NR	>2000 kcal > 25 kcal/kg/d	2.5 (0.2)	2.6 (0.3)	9.1 (0.6)	9.8 (0.6)
Garrel 2003 ²⁵	IC and Curreri	2937 (1262)	2753 (1159)	NR	>2000 kcal	NR	NR	NR	NR
Falcao de Arruda 2004 ²⁶	Weight-based ^b	2400 (232)	2390 (206)	p=0.96	>2000 kcal	NR	NR	13 (5)	9 (4)
Berger 2007 ²⁷	30 kcal/kg/d to d3 then IC: 105-110% REE	2600 by day 5 2754 by day 10 2900 by day 20	2600 by day 5 2754 by day 10 2900 by day 20	NR	>2000 kcal	NR	NR	NR	NR
Peake 2014 ¹⁷	1 ml/kg IBW from height /hr	27.3 (7.4) kcal/kg/d	19 (6), kcal/kg/d	p<0.001	> 25 kcal/kg/d	23.3 (17.5) hrs ^c	25.0 (21.3) hrs ^c	6.7 (3.8) ^c	5.3 (4.6) ^c
TARGET Investigators 2018 ¹²	1 ml/kg IBW from height /hr	1863 (478) 29.1 (6.2) kcal/kg IBW/d	1262 (313) 19.6 (4.0) kcal/kg IBW/d	95% CI 576-626 kcal	> 25 kcal/kg/d	16.6 (13.8) hrs ^c	17.4 (15.1) hrs ^c	6.7 (5.9) ^c	6.7 (5.9) ^c
Non-randomized trials									
van den Berg 1988 ³⁰	IC: 1.5 or 2.0 x REE	3710 (600)	2555 (553)	NR	>2000 kcal	NR	NR	NR	NR
Buonpane 1989 ³¹	Harris Benedict x SF 1.5	33.2 (3.9) kcal/kg/d	-	N/A	> 25 kcal/kg/d	5.3 (3.8)	-	19.0 (7.0)	-
Cerra 1989 ²⁸	30-35 kcal/kg/d	33 (6) kcal/kg/d	29 (4) kcal/kg/d	NR	> 25 kcal/kg/d	NR	NR	8 (1)	8 (1)
Dickerson 2002 ¹⁸	Weight-based ^b	Wk 1: 18.5 (4.4) Wk 2: 25.6 (5.9) Wk 3: 25.9 (5.5) Wk 4: 24.7 (6.5)	Wk 1: 13.4 (4.1) Wk 2: 15.7 (5.1) Wk 3: 18.6 (3.2) Wk 4: 19.2 (4.6)	p≤0.05	> 25 kcal/kg/d	3.8 (1.5)	3.3 (1.4)	26.3 (14.8)	15.4 (10.8)
Ravasco 2003 ³²	Harris Benedict	2034 (432)	-	N/A	>2000 kcal	NR	-	NR	-
Farber 2005 ²⁹	25-35 kcal/kg/d	2700 (562)	2583 (441)	p=0.48	>2000 kcal	3.0 (1.3)	3.6 (2.2)	18 (11)	31 (22)
Soquel ^d 2008 ¹⁹	Weight-based ^b	1840 (840)	1675 (945)	p=0.012	> 25 kcal/kg/d	NR	NR	NR	NR

		26 (12) kcal/kg/d	23 (13), kcal/kg/d						
Shields 2015 ³³	Carlson, Milner and IC	3044 (1613) 39 (20) kcal/kg/d	-	N/A	>2000 kcal	NR	-	NR	-

ABW, Actual body weight; BMI, body mass index; BMR, Basal metabolic rate; d, day; IBW, Ideal body weight; IC, indirect calorimetry; REE, resting energy expenditure; NR, not stated. Data are reported as mean (SD) unless otherwise stated. Group 1 received the highest calorie delivery.

^a Mean (standard error of the mean)

^b Details of formula used not reported

^c Median (interquartile range)

^d Patient population included both burns and trauma patients. Data presented on burns subgroup only.

Cerra 1989²⁸ also included a third arm for which the mean weight was 84 (10.6) kg, mean calorie delivery was 28 (7) kcal/kg/d and duration of study intervention was 8 (1) days.

Dibourne, 1992²⁹ also included a third arm for which the mean weight was 66.4 (10.2) kg.

Table 3. Mortality

Author, year	ICU mortality, n (%)		Hospital mortality, n (%)		28 day mortality, n (%)		90 day mortality, n (%)		Other mortality time-points, n (%)	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Randomized trials										
Moore 1994 ²¹	NR	NR	1 (2)	2 (4)	NR	NR	NR	NR	NR	NR
Mendez 1997 ²⁴	NR	NR	NR	NR	NR	NR	NR	NR	1 (4.5) ^a	1 (5) ^a
Garrel 2003 ²⁵	NR	NR	NR	NR	NR	NR	NR	NR	12 (63) ^a	2 (13) ^a
Falcao de Arruda 2004 ²⁶	NR	NR	0 (0)	0 (0)	NR	NR	NR	NR	NR	NR
Peake 2014 ¹⁷	6 (11)	9 (16)	10 (19)	14 (27)	11 (20)	18 (33)	11 (20)	20 (37)	77 (4.5) ^b	68 (5.6) ^b
TARGET Investigators 2018 ¹²	NR	NR	468 (23.8)	470 (23.7)	450 (22.9)	455 (23.0)	523 (26.8)	505 (25.7)	NR	NR
Non-randomized trials										
Buonpane 1989 ³¹	0 (0)		0 (0)		NR		NR		NR	
Dickerson 2002 ²⁸	NR	NR	NR	NR	NR	NR	NR	NR	1 (8) ^a	0 (0) ^a
Ravasco 2003 ³²	NR		24 (55)		NR		NR		NR	
Farber 2005 ²⁹	NR	NR	NR	NR	NR	NR	NR	NR	1 (6) ^a	2 (10) ^a
Soguel ² 2008 ¹⁰	0 (0)	1 (5)	1 (5)	1 (5)	NR	NR	NR	NR	NR	NR
Shields 2015 ³³	5 (100)		NR		NR		NR		NR	

ICU, Intensive Care Unit; ITT, Intention to treat; NR, not reported. Data are reported as mean (SD) unless otherwise stated. Group 1 received the highest calorie delivery

^a Time point unclear

^b Mean (standard error) duration of survival, days

^c Patient population included both burns and trauma patients. Data presented on burns subgroup only.

Table 4. Mechanical ventilation

Author, year	Duration of MV, days		CO ₂ production, ml/min		O ₂ consumption, ml/min	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Randomized trials						
Van den Berg 1994 ²²	NR	NR	MV 0.225 (0.007) l/min ^a Weaning 0.231 (0.011) l/min ^a	MV 0.218 (0.013) l/min ^a Weaning 0.177 (0.010) l/min ^a	MV 0.225 (0.008) l/min ^a Weaning 0.271 (0.013) l/min ^a	MV 0.199 (0.011) l/min ^a Weaning 0.244 (0.010) l/min ^a
Moore 1994 ²¹	1.9 (0.4) ^a	5.3 (2.9) ^a	NR	NR	NR	NR
Long 1995 ²³	NR	NR	27.64 [3.76] % from glucose ^a	32.45 [3.36] % from glucose ^a	NR	NR
Garrel 2003 ²⁵	22 (10)	24 (11)	NR	NR	NR	NR

Falcao de Arruda 2004 ²⁶	21 (16.2) ^b	7.5 (4.5) ^b	NR	NR	NR	NR
Peake 2014 ¹⁷	16.5 (16.4) ^{c,d}	14.8 (19.5) ^{c,d}	NR	NR	NR	NR
TARGET Investigators 2018 ¹²	15 (18.5) ^{c,d}	15 (18.5) ^{c,d}	NR	NR	NR	NR
Non-randomized trials						
Van den Berg 1988 ³⁰	12-38 ^e	12-38 ^e	136 (28) ml/min/m ²	116 (16) ml/min/m ²	170 (32) ml/min/m ²	158 (27) ml/min/m ²
Cerra 1989 ²⁸	NR	NR	180 (25)	182 (25)	228 (30)	237 (27)
Dickerson 2002 ¹⁸	23.7 (16.6)	15.9 (10.8)	NR	NR	NR	NR
Farber 2005 ²⁹	24 (17)	27 (18)	NR	NR	NR	NR
Soguel ^f 2008 ¹⁹	7.2 (6.7)	6.1 (7.1)	NR	NR	NR	NR

IQR, interquartile range; NS, not specified; MV, mechanical ventilation; l/m, liters per minute; NR, not reported; temp, temperature; SEM, standard error of the mean; ml/min/m², milliliters per minute; VFD, ventilator free days. Data are reported as mean (SD) unless otherwise stated. Group 1 received the highest calorie delivery.

^a Mean (standard error of the mean)

^b Median (range) converted to mean (SD)

^c Ventilator free days to day 28

^d Median (interquartile range) converted to mean (SD)

^e Range

^f Patient population included both burns and trauma patients. Data presented on burns subgroup only.

Cerra 1989²⁸ also included a third arm for which the mean CO₂ production was 171 (22) ml/min and the mean O₂ consumption was 198 (28) ml/min.

Table 5. Infectious complications

Author, year	Total infections, n (%)		Pneumonia, n (%)		Bacteremia, n (%)	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Randomized trials						
Moore 1994 ²¹	NR	NR	4 (8)	4 (8)	2 (4)	4 (8)
Mendez 1997 ²⁴	19 (86)	12 (57)	16 (73)	11 (52)	6 (27)	7 (33)
Garrel 2003 ²⁵	NR	NR	NR	NR	10 (45)	7 (37)
Falcao de Arruda 2004 ²⁶	10 (100)	5 (50)	NR	NR	NR	NR
TARGET Investigators 2018 ¹²	NR	NR	NR	NR	228 (11.6)	221 (11.1)
Non-randomized trials						
Dickerson 2002 ¹⁸	NR	NR	8 (67)	12 (43)	NR	NR
Farber 2005 ²⁹	NR	NR	2 (12)	11 (52)	15 (88)	17 (81)
Soguel ^a 2008 ¹⁹	0.8 (0.5)	0.6 (0.6)	NR	NR	NR	NR

NR, Not reported. Data are reported as mean (standard deviation) unless otherwise stated. Group 1 received the highest calorie delivery

^a Patient population included both burns and trauma patients. Data presented on burns subgroup only.

Table 6. Blood glucose control

Author, year	Daily BGL, mmol/L		Hyperglycemia, n (%)		Total insulin dose, IU	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Randomized trials						
Garrel 2003 ²⁵	8.9 (1.8)	8.6 (1.4)	NR	NR	38 (24)	42 (29)
Peake 2014 ¹⁷	12.4 (3.9)	12.0 (3.9)	NR	NR	55 (22-131) ^a	43 (24-67) ^a
TARGET Investigators 2018 ¹²	NR	NR	Highest BGL: 12.5 (10.3-15.4) mg/dl ^a	Highest BGL: 11.8 (9.7-14.5) mg/dl ^a	3.0 (0-41.8) ^{ab}	0 (0-30.6) ^{ab}
Non-randomized trials						
Buonpane 1989 ³¹	NR	NR	3 (25)	NR	NR	NR
Soguel ^c 2008 ¹⁹	NR	NR	NR	NR	41 (34)	29 (48)

BGL, Blood glucose level; IU, International units. Data are reported as mean (SD) unless otherwise stated. Group 1 received the highest calorie delivery.

^a Median (interquartile range)

^b Daily insulin dose

^c Patient population included both burns and trauma patients. Data presented on burns subgroup only.

Figure Legend:

Figure 1. Consort diagram of included trials

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Author/s:

Chapple, L-AS;Weinel, L;Ridley, EJ;Jones, D;Chapman, MJ;Peake, SL

Title:

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