ARTÍCULO

Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial

Gordon S Doig Dr, Fiona Simpson PhD, Philippa T Heighes MNE, Rinaldo Bellomo Prof, Douglas Chesher PhD, Ian D Caterson Prof, Michael C Reade Prof y Peter W J Harrigan FCICM

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Summary

Background

Equipoise exists regarding the benefits of restricting caloric intake during electrolyte replacement for refeeding syndrome, with half of intensive care specialists choosing to continue normal caloric intake. We aimed to assess whether energy restriction affects the duration of critical illness, and other measures of morbidity, compared with standard care.

Methods

We did a randomised, multicentre, single-blind clinical trial in 13 hospital intensive care units (ICUs) in Australia (11 sites) and New Zealand (two sites). Adult critically ill patients who developed refeeding syndrome within 72 h of commencing nutritional support in the ICU were enrolled and allocated to receive continued standard nutritional support or protocolised caloric restriction. 1:1 computer-based randomisation was done in blocks of variable size, stratified by enrolment serum phosphate concentration (>0·32 mmol/L *vs* ≤0·32 mmol/L) and body-mass index (BMI; >18 kg/m ^{2} *vs* ≤18 kg/m ^{2}). The primary outcome was the number of days alive after ICU discharge, with 60 day follow-up, in a modified intention-to-treat population of all randomly allocated patients except those mistakenly enrolled. Days alive after ICU discharge was a composite outcome based on ICU length of stay, overall survival time, and mortality. The Refeeding Syndrome Trial was registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR number 12609001043224).

Findings

Between Dec 3, 2010, and Aug 13, 2014, we enrolled 339 adult critically ill patients: 170 were randomly allocated to continued standard nutritional support and 169 to protocolised caloric restriction. During the 60 day follow-up, the mean number of days alive after ICU discharge in 165 assessable patients in the standard care group was 39·9 (95% CI 36·4–43·7) compared with 44·8 (95% CI 40·9–49·1) in 166 assessable patients in the caloric restriction group (difference 4·9 days, 95% CI −2·3 to 13·6, p=0·19). Nevertheless, protocolised caloric restriction improved key

individual components of the primary outcome: more patients were alive at day 60 (128 [78%] of 163 *vs* 149 [91%] of 164, p=0·002) and overall survival time was increased (48·9 [SD 1·46] days *vs* 53·65 [0·97] days, log-rank p=0·002).

Interpretation

Protocolised caloric restriction is a suitable therapeutic option for critically ill adults who develop refeeding syndrome. We did not identify any safety concerns associated with the use of protocolised caloric restriction.

Funding

National Health and Medical Research Council of Australia.

Introduction

Unexpected deaths arising from the rapid reinstitution of nutritional support in people who were severely malnourished were first reported in medical literature during the mid-1940s. [1] Nowadays, the so-called refeeding syndrome is known to occur in patients who are apparently well nourished after only a short period of fasting. [2]

The “hallmark clinical sign” of refeeding syndrome is serum hypophosphataemia, [3] but patients often present with additional metabolic disturbances including hypokalaemia, fluid overload, and thiamine deficiency. [4] In patients who are accepted to have refeeding syndrome, the clinical sequelae of extreme metabolic disturbances might include respiratory failure, cardiac failure, delirium, rhabdomyolysis, haemolytic anaemia, seizures, coma, excess infections, and death. [4 5]

Correction of phosphate and other electrolyte imbalances, plus thiamine supplementation, are accepted as the first steps in the appropriate treatment for refeeding syndrome. [2 4 5 6] However, expert recommendations regarding other aspects of medical care for such patients differ. For example, healthy patients' serum phosphate concentrations can decrease after the ingestion or intravenous infusion of glucose. [7] Thus, some nutritional experts recommend that nutritional support should be stopped or restricted during phosphate and electrolyte replacement for refeeding syndrome. [2 5] With an absence of evidence from clinical trials [5] and outcome studies, [8] other experts recommend that “feeding can be continued” during electrolyte replacement. [5] This discordance in expert recommendations is mirrored by clinical practice. In a survey undertaken in 33 intensive care units (ICUs) throughout Australia and New Zealand, about half (52%) of the ICU clinicians interviewed reported that they restrict energy intake during the treatment of refeeding syndrome, whereas the other half reported that they continue feeding without energy restriction. [9]

PANEL

Evidence before this study

We searched MEDLINE and Embase, without language restrictions, between Jan 1, 1945, and Aug 20, 2015, to identify clinical trials that evaluated competing approaches for the treatment of refeeding syndrome in any population of patients. We used the search term "refeeding" in combination with "malnou*" or "starv*". Although case reports and case series were identified, we could not find any clinical trial that objectively evaluated the effects of competing approaches to the treatment of refeeding syndrome, in any patient population. All randomised and pseudo-randomised interventional studies done in any patient population with refeeding syndrome were eligible for inclusion. Observational studies, opinion papers, animal studies, and case reports were not eligible.

Added value of this study

The Refeeding Syndrome Trial is, to our knowledge, the first reported randomised clinical trial undertaken in any patient population with refeeding syndrome. Our results provide important evidence to guide treatment choices for the management of critically ill patients with this condition.

Implications of all the available evidence

Many health-care professionals, patients, and families might now judge caloric restriction during treatment for refeeding syndrome in critically ill adults preferable to continued standard caloric intake. Future research is needed to objectively assess the effects of caloric restriction in other patient populations and to investigate how appropriate the other aspects of care are for patients with refeeding syndrome (eg, thiamine dose, electrolyte replacement triggers, and doses).

Research in context

We aimed to address the equipoise surrounding the decision to restrict or continue the provision of nutritional support during electrolyte replacement in adult critically ill patients who developed refeeding syndrome; and assess whether energy restriction affects the duration of critical illness compared with standard care.

Methods

Study design and participants

We did a randomised, parallel-group, multicentre, single-blind clinical trial in 13 tertiary care and community hospitals across Australia (11 sites) and New Zealand (two sites). The Human Research Ethics Committee at each participating site reviewed and approved the study. The study protocol is available online (https://research.evidencebased.net/login/Refeeding/632615_Doig_Protocol_Ver2a.pdf) .

We screened critically ill adults (aged ≥18 years) for eligibility and enrolled them if their serum phosphate concentration decreased to below 0·65 mmol/L within 72 h after starting nutritional support in a participating ICU. To account for within-participant biological variation of serum phosphate concentrations, this change needed to be greater than a 0·16 mmol/L decrease from any concentration previously recorded during the patient's ICU stay. We excluded patients with

other major causes of hypophosphataemia—such as ongoing dialysis, recent parathyroidectomy, or treatment for hyperphosphataemia—from enrolment. The appendix (sec1) reports the complete eligibility and exclusion criteria.

Written informed consent was obtained from all patients or their legal representatives. Advance consent was obtained whenever possible; however, this study was approved to obtain delayed consent if advance consent was not practicable.

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to the restricted caloric management group (intervention) or no caloric restriction (control) group. Computerised random blocks of variable size were stratified within study site by enrolment serum phosphate concentration (>0·32 mmol/L *vs* ≤0·32 mmol/L) and body-mass index (BMI; >18 kg/m ^{2} *vs* ≤18 kg/m ^{2}). To further increase the difficulty of anticipating the allocation sequence, random seeds were generated between blocks and stratification thresholds were not disclosed to participating sites. [10]

Allocation concealment was maintained by use of a secure central randomisation web server. The allocation sequence was generated by the corresponding author using Statistical Analysis System (SAS; version 9.2). The corresponding author did not screen or enrol patients. The sequence was kept secure from all study personnel responsible for screening and recruiting patients.

Because the diagnosis of pneumonia can be subjective, written chest radiograph reports were obtained from radiologists who were unaware of the patient's assigned study treatment group.

Procedures

Participants randomly assigned to the intervention group received nutritional support directed by a study caloric management protocol, which reduced energy intake to 20 kcal/h for at least 2 days. After 2 days on the study caloric management protocol, if serum phosphate concentrations did not need to be supplemented as determined by the study phosphate replacement protocol, energy intake was returned to normal during 2–3 days by clinicians adhering to the study gradual return to normal intake protocol (appendix (sec1)). The study gradual return to normal intake protocol set energy goals to 40 kcal/h for 24 h, then increased goals to 60 kcal/h for 24 h, followed by 80% of calculated energy goals for another 24 h, with 100% of goals achieved by day 4. If a patient's serum phosphate concentrations dropped below 0·71 mmol/L at any time during management on the study gradual return to normal intake protocol, energy intake was reduced to 20 kcal/h and the patient was returned to day 2 of the study caloric management protocol.

Participants randomly assigned to the standard care group received nutritional support which was defined pragmatically and which consisted of continuing nutritional support as planned before study enrolment.

Phosphate monitoring, replacement, and thiamine supplementation were given as stated in a study phosphate replacement protocol [11] that was implemented in both standard care and caloric management protocol groups. Complete details of all study management protocols are in the appendix (sec1) . Follow-up assessments were done at days 60 and 90 after enrolment.

Zubrod/WHO performance status, [12] RAND-36 general health (version 1), and RAND-36 physical function scale (version 1) [13] were assessed at the day 90 interview. Vital status of patients was recorded at hospital discharge and at the day 90 interview.

Outcomes

The primary outcome was number of days alive after discharge from the ICU, at the 60 day follow-up. This outcome is a conceptual extension of the composite outcome measure of ventilator free days, [14] consisting of ICU stay, overall survival time, and mortality at the end of the follow-up (day 60).

Prespecified secondary outcomes were major infectious complications (defined as an attributable case-mortality rate >15%), [15] [16] receipt of systemic antibiotic treatment, insulin infusion requirements, daily blood glucose concentrations, daily dose of phosphate replacement, lowest daily serum potassium and phosphate concentrations, days of organ dysfunction by individual organ system, days of multiple organ dysfunction syndrome, [17] and other concomitant ICU treatments.

Investigators were required to attend a small group start-up meeting and complete a formal study run-in phase to become familiar with the application of eligibility criteria and the study intervention before they could recruit patients. [18]

Statistical analysis

A conservative estimate of the treatment effect attributable to reducing caloric intake was obtained from a database [19] [20] of 209 critically ill patients who developed refeeding-associated hypophosphataemia. 63 (30%) of the 209 patients in this database had their caloric intake reduced to below 500 kcal/day after the onset of hypophosphataemia, which was associated with a significant increase in the number of days alive after ICU discharge. On the basis of these data, a 336 patient clinical trial was calculated to have 90% power to detect a 6·4 day difference in the number of days alive after ICU discharge (SD 18·1 days). Complete details of the sample size calculation are presented elsewhere. [19]

Primary conclusions were based on a modified intention-to-treat analysis for efficacy. A detailed statistical analysis plan was published before completion of recruitment. [19] Unadjusted analysis of the primary outcome, and all outcomes based on count data (eg, length of stay or days of clinically significant organ failure), was done with Poisson regression. If the scaled deviance exceeded 1·4 units per degree of freedom, negative-binomial regression was used instead. Analyses of the composite primary outcome, and its major components, were controlled for the potential loss of independence due to stratified randomisation with completion of covariate adjusted analysis by including only terms for the main treatment effect and baseline stratification factors.

Dichotomous outcomes were assessed with an exact Pearson's χ^2 test, with 95% CIs calculated for the risk difference. A prespecified algorithm was used to identify baseline characteristics for inclusion in a covariate adjusted regression model to control for confounding. [19] Six a priori defined subgroup analyses were done on the following baseline criteria: severity of hypophosphataemia;

subjective global assessment [21] of muscle wasting and fat loss; energy intake; blood glucose; insulin dose rate; and timing of onset of hypophosphataemia (complete details are in the appendix (sec1)). If the two-sided p value for a formal test of the subgroup-treatment interaction was less than 0·10, differential treatment effects in subgroups were declared to be present. Missing data were deemed missing at random unless prespecified thresholds were exceeded. [19] A two-sided p value less than 0·05 was accepted to show significance. All analyses were done with SAS (version 9.2).

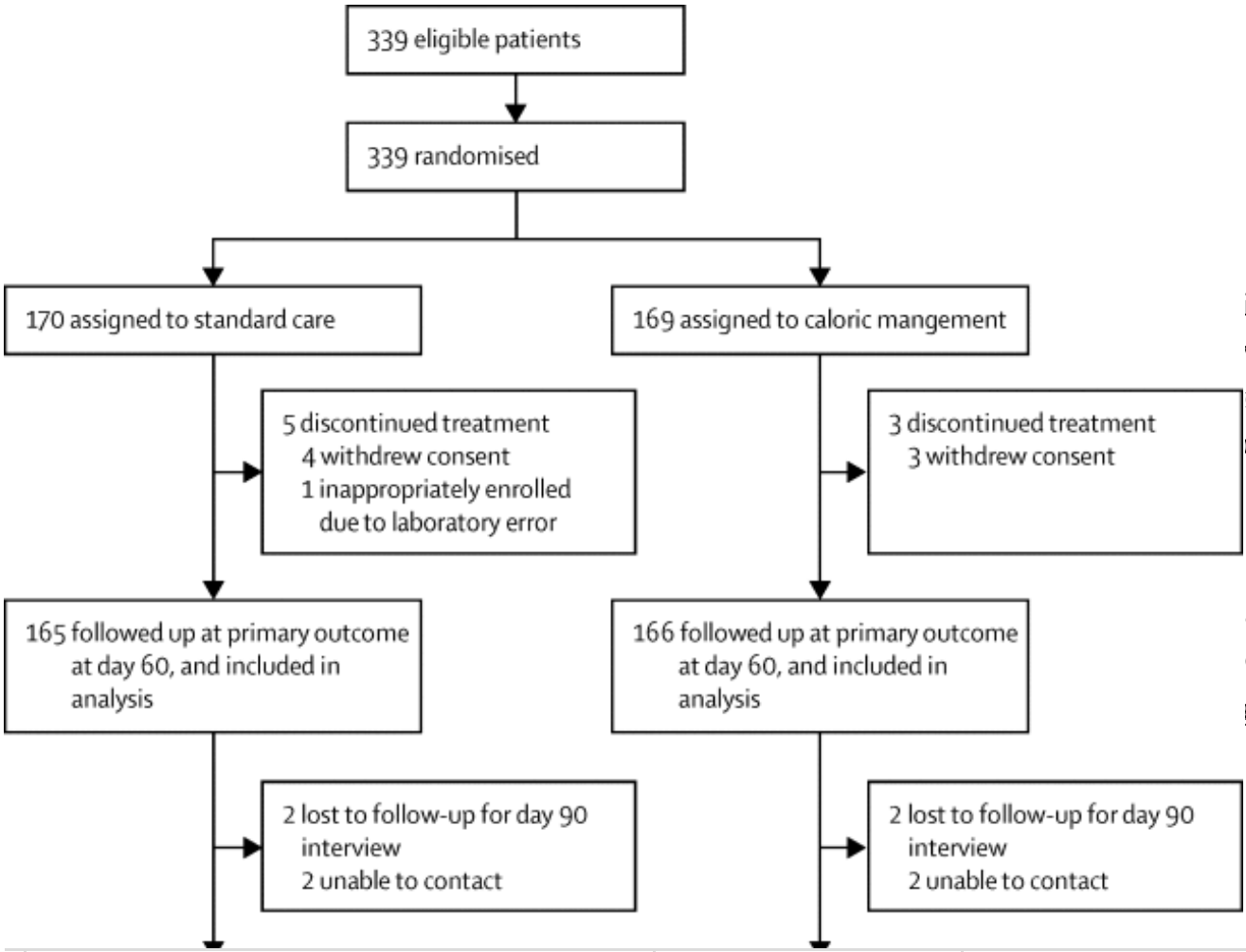
The independent Safety and Data Monitoring Committee was required to complete an interim analysis using Haybittle-Peto stopping rules if report of serious adverse events generated concerns for patient safety. [19] The Refeeding Syndrome Trial was registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR number 12609001043224).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 3, 2010, and Aug 13, 2014, we enrolled 339 adult critically ill patients from 13 participating hospitals in Australia and New Zealand: 170 patients were randomly allocated to standard care and 169 patients to protocolised caloric management (figure 1 (fig1)). Seven patients (four in standard care, three in caloric management) subsequently withdrew consent. Primary outcomes were available for all 332 consenting enrolled patients.



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	Standard care (n=165 patients)	Caloric management (n=166 patients)
Age (years)	61 (16)	59 (16)
Sex		
Female	61 (37%)	73 (44%)
Male	104 (63%)	93 (56%)
APACHE II score [22]	18 (6)	18 (6)
Mechanically ventilated	150 (91%)	152 (92%)
BMI (kg/m ^{2})		
Mean	28 (6·7)	28 (7·3)
<18 kg/m ^{2}	5 (3%)	6 (4%)
SGA		
Muscle wasting	1·3 (0·7)	1·4 (0·8)
Fat loss	1·4 (0·7)	1·5 (0·8)
Risk factors for refeeding-related hypophosphataemia		
Calories per h (EN, PN, and glucose) at time of enrolment (kcal/h)	69 (20)	68 (19)

Total caloric intake (EN, PN, and glucose) 24 h before enrolment (kcal)	1188 (533)	1180 (526)
Days since feeding started in ICU	1·4 (0·7)	1·3 (0·7)
Days in ICU before enrolment	2·4 (1·2)	2·3 (1·2)
Days in hospital before enrolment	4·0 (4·3)	4·0 (4·8)
Serum phosphate at study entry (mmol/L)	0·5 (0·1)	0·5 (0·1)
Serum potassium at study entry (mmol/L)	3·9 (0·5)	3·9 (0·5)
Lowest blood glucose in previous 24 h (mmol/L)	7·4 (1·7)	6·9 (1·5)
Highest blood glucose in previous 24 h (mmol/L)	10·7 (32·8)	10·6 (32·7)
Lowest serum albumin in previous 24 h (g/L)	25·4 (65·8)	25·0 (65·7)
Maximum insulin infusion rate (units per h)	5·6 (4·3) *(tbl1fn1)	5·0 (3·8) ‡(tbl1fn2)
Semipermanent (surgically placed) feeding tube	11 (7%)	19 (12%)
History of high alcohol intake ‡(tbl1fn3)	22 (13%)	18 (11%)
Distal loop diuretic (administered in previous 24 h)	57 (35%)	41 (25%)
Long term or high dose corticosteroids	8 (5%)	9 (5%)
Respiratory alkalosis §(tbl1fn4)	35 (21%)	33 (20%)
Creatinine (μmol/L)	84 (47)	84 (43)
Chronic health states		
Immunocompromised	11 (7%)	13 (8%)
Respiratory disease ¶(tbl1fn5)	10 (6%)	9 (5%)
Cardiovascular disease ¶(tbl1fn4)	5 (3%)	3 (2%)
Hepatic cirrhosis ¶(tbl1fn4)	3 (2%)	6 (4%)
Chronic dialysis ¶(tbl1fn4)	0	0
Insulin dependent diabetes	14 (8%)	7 (4%)
Source of admission to ICU		
Operating room	60 (36%)	57 (34%)
Emergency department	38 (23%)	50 (30%)
Hospital ward	21 (13%)	25 (15%)

Hospital ward	31 (19%)	25 (15%)
Other hospital	30 (18%)	30 (18%)
Transfer from ICU	4 (2%)	4 (2%)
ICU readmission	2 (1%)	0
Admission type		
Medical	105 (64%)	108 (65%)
Emergency surgery	42 (26%)	36 (22%)
Elective surgery	18 (11%)	22 (13)
APACHE III admission diagnosis [23]		
Respiratory	40 (24%)	51 (31%)
Gastrointestinal	24 (15%)	28 (17%)
Cardiovascular or vascular	29 (18%)	25 (15%)
Sepsis	7 (4%)	10 (6%)
Neurological	30 (18)	20 (12%)
Trauma	23 (14%)	27 (16%)
Metabolic	6 (4%)	2 (1%)
Haematological	0	0
Orthopaedic surgery	0	0
Renal	1 (0·6%)	0
Other	5 (3%)	3 (2%)

Data are n (%), or mean (SD). APACHE=acute physiology and chronic health evaluation; scores range from 0 to 71; APACHE scores have a significant non-linear relationship with the risk of death (higher scores suggest more severe disease, associated with a higher risk of death); scores greater than 37 have been associated with a greater than 99·9% risk of subsequent death in-hospital. BMI=body-mass index. SGA=subjective global assessment of nutritional status; grades muscle wasting and fat loss into four categories: no obvious loss, mild loss, moderate loss, and severe loss. EN=enteral nutrition. PN=parenteral nutrition. ICU=intensive care unit.

* Of 61 patients.

† Of 51 patients.

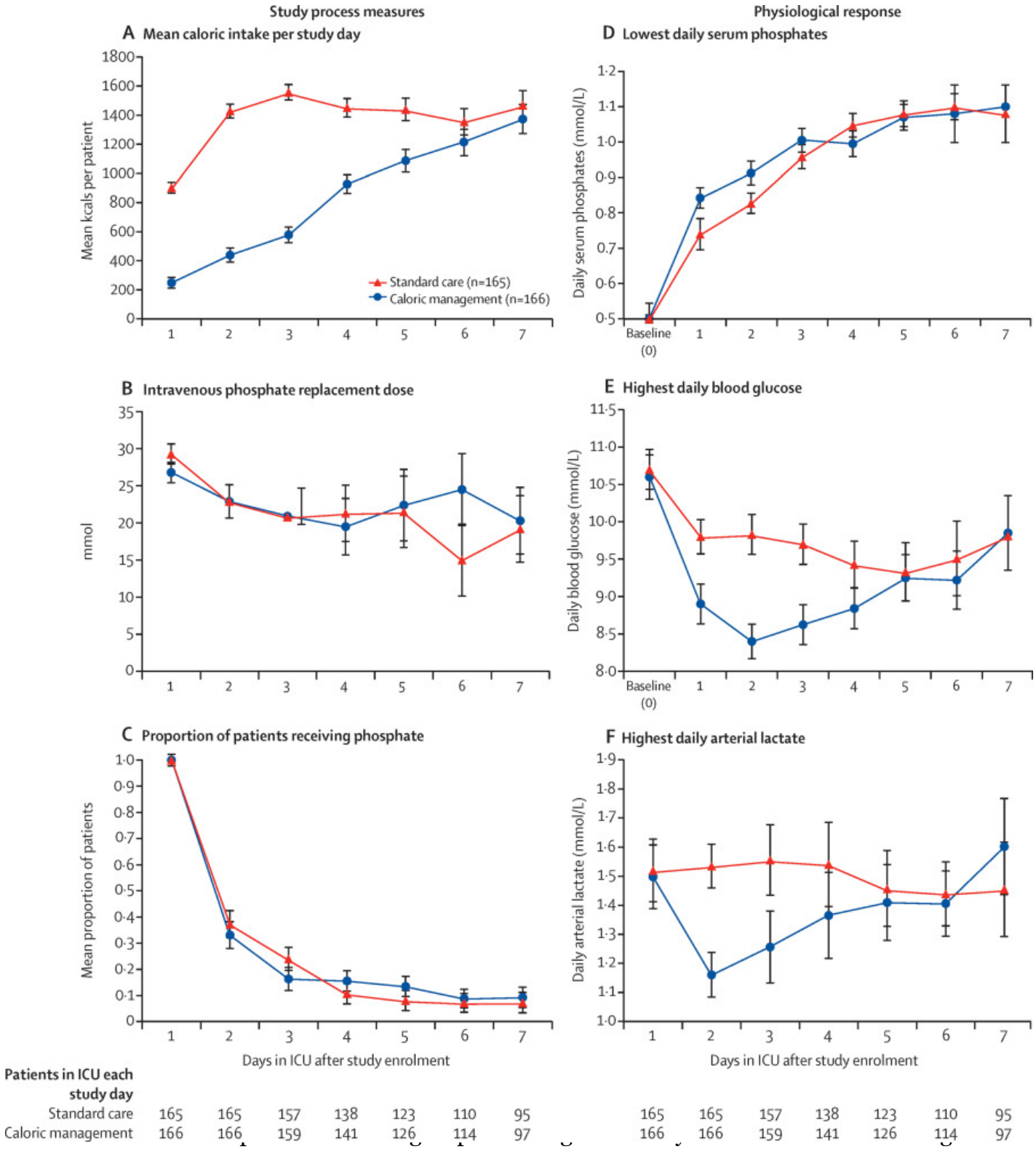
‡ Defined as five or more standard drinks a day at least three times per week for men, and four or more standard drinks a day at least two times a week for women.

§ Defined as arterial power of hydrogen (pH) greater than 7·45 and arterial partial pressure of carbon dioxide less than 38 mm of mercury.

¶ Defined by APACHE II criteria. [22]

Mean time from ICU admission to commencing nutritional support was 1·4 (SD 0·65) days. 172 (52%) of 331 enrolled patients developed hypophosphataemia within 24 h of starting nutritional support, 131 (40%) of 331 patients developed this condition within 48 h, and the remaining 28 (9%) of 331 patients developed hypophosphataemia within 72 h of starting nutritional support. Mean caloric intake at time of enrolment was 68·5 (SD 19·4) kcal/h. In addition to the onset of hypophosphataemia, at time of enrolment 319 (96%) of 331 patients had at least one other key sign consistent with refeeding syndrome: 88 (27%) had hypokalaemia, 171 (52%) had hyperglycaemia, 302 (91%) had respiratory failure, and 98 (30%) needed diuretics for the management of fluid balance.

After randomisation to the two groups, 159 (95·7%) of 166 patients assigned to the protocolised caloric management group had their energy intake appropriately reduced. Significant differences in total energy intake (sum of energy from carbohydrates, lipids, and protein) were achieved between the two study groups on each of the 5 days of management (for each day: p=0·0001) , guided by the study caloric management protocol and gradual return to normal intake protocol (figure 2 (fig2)).



(relative risk 1·12, 95% CI 0·93–1·35, p=0·22, negative-binomial regression).

With regards to the major components of the composite primary outcome, no significant differences were noted between groups for patient ICU stay or number of patients discharged alive from ICU (table 2 (tbl2)). However, significantly more patients were alive in the protocolised caloric management group at study day 60 than the standard care group (128 [78%] of 163 *vs* 149 [91%] of 164, p=0·002). This finding resulted in a significant increase in overall survival time when censored at day 60 (48·9 days [SD 1·46] *vs* 53·65 days [0·97] days, log-rank p=0·0020; figure 3 (fig3)). Analyses of the major components of the composite primary outcome were controlled for the effects of stratified randomisation.

Table 2

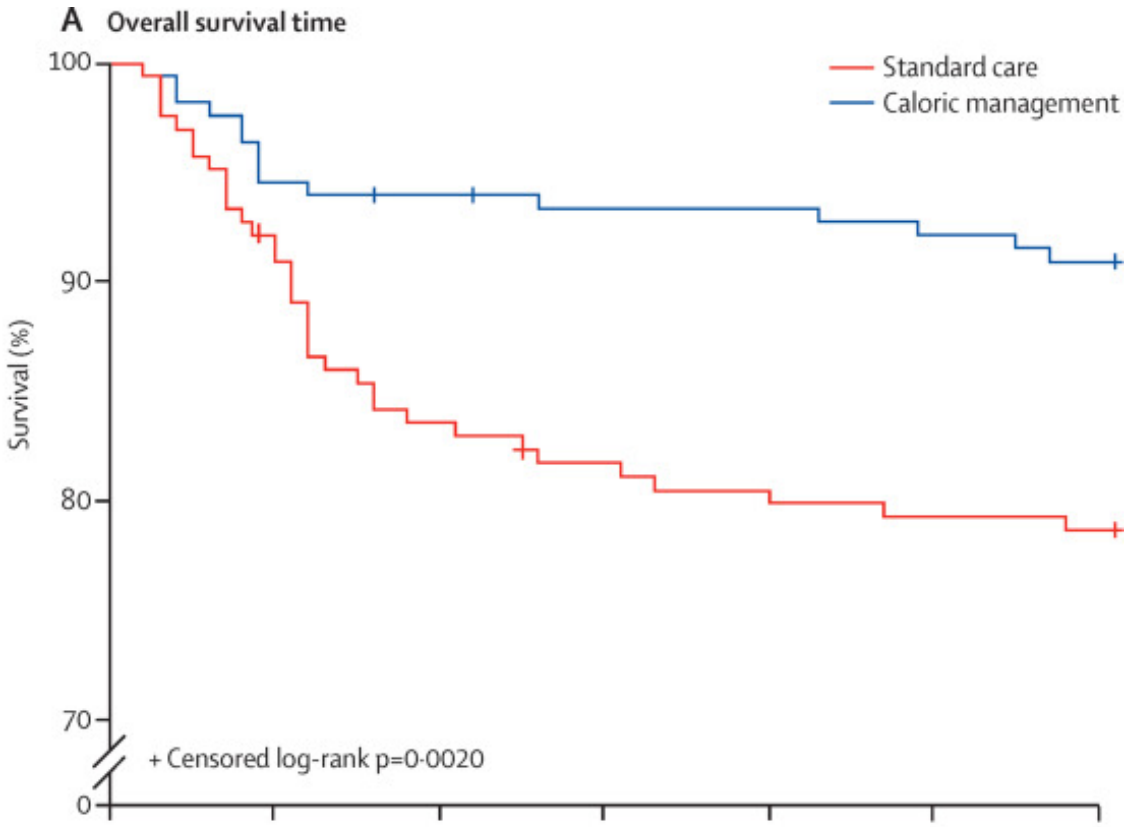
Vital status, length of stay, and quality of life interviews

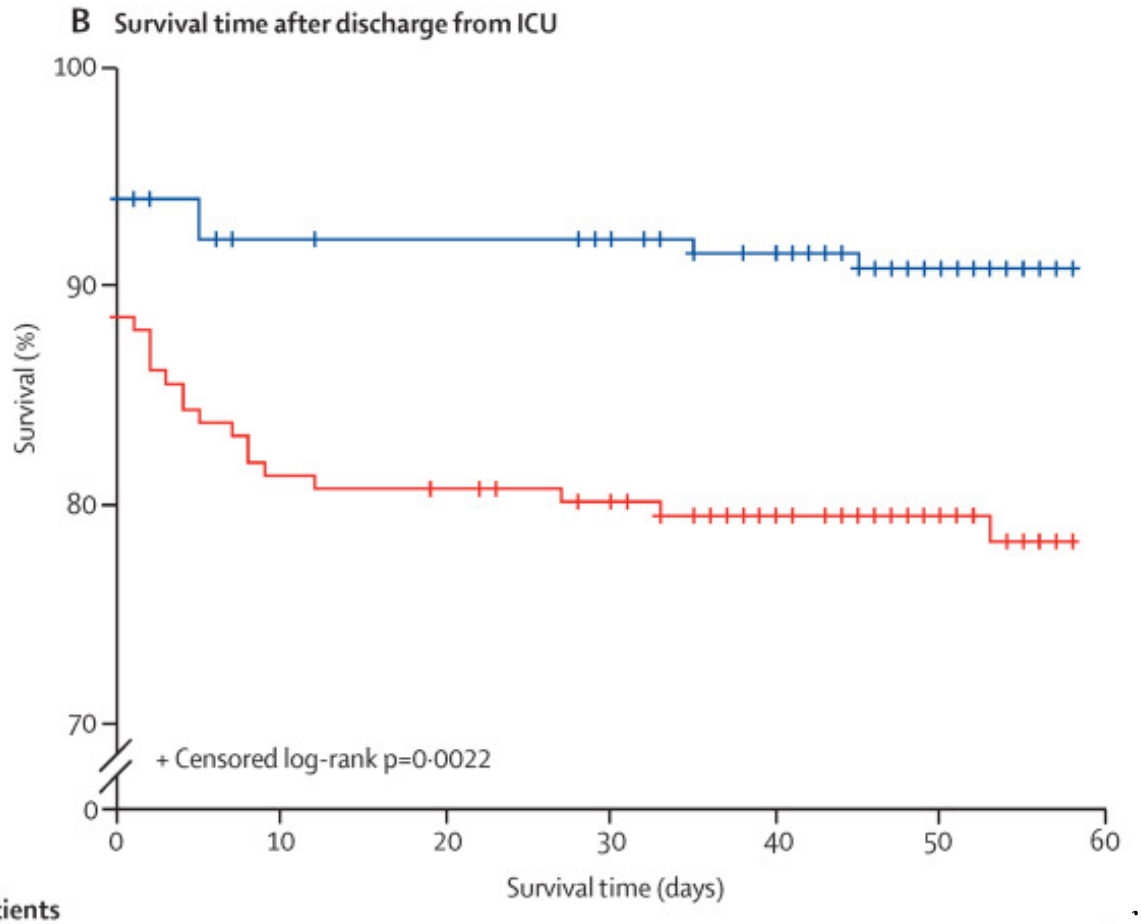
	Standard care (n=165 patients)	Caloric management (n=166 patients)	Risk difference (95% CI)	p value
Vital status (% alive)				
ICU discharge status	150/165 (91%)	157/166 (95%)	3·7% (−5·3 to 12·7)	0·20
Hospital discharge status	135/165 (82%)	151/166 (91%)	9·2% (0·7 to 17·7)	0·017
Day 60 status	128/163 (79%) * (tbl2fn1)	149/164 (91%) * (tbl2fn1)	12·3% (3·9 to 20·7)	0·002
Day 90 status	128/163 (79%) * (tbl2fn1)	143/164 (87%) * (tbl2fn1)	8·7% (0·04 to 17·0)	0·041
Length of stay (days)				
ICU	10·0 (9·2 to 10·9)	11·4 (10·5 to 12·4)	1·4 (−0·42 to 3·5)	0·14
Hospital	21·7 (20·0 to 23·5)	27·9 (25·7 to 30·3)	6·2 (2·0 to 11·2)	0·003
Quality of life and physical function scores † (tbl2fn2) (n responses available for analysis)				
RAND-36 general health	53·4 (22·6; n=124/128)	46·0 (26·0 n=136/143)	−7·5 (−13·4 to −1·5)	0·014
ECOG performance status	1·3 (1·0; n=125/128)	1·5 (1·1; n=135/143)	0·18 (−0·08 to 0·43)	0·18
RAND-36 physical function	47·3 (35·0; n=123/128)	40·9 (33·4; n=135/143)	−6·4 (−14·8 to 2·0)	0·13

Data are n/N (%), mean (95% CI), and mean (SD), unless otherwise stated. ICU=intensive care unit. RAND=the RAND Corporation. [13] ECOG=Eastern Collaborative Oncology Group.

* Four patients could not be contacted after hospital discharge (two in the standard care and two in the caloric management group).

† Reported by survivors at day 90 interview.





Number of patients

Day	1	5	10	15	20	25	30	35	40	45	50	55	60
Standard care	165	158	149	140	136	133	131	129	129	128	128	128	128
Caloric management	166	163	157	156	155	155	154	154	154	153	152	151	149

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other infections at different sites did not differ between groups (table 3 (tbl3)).

Table 3

New infections noted in patients after study enrolment

	Standard care (165 patients)	Caloric management (166 patients)	Risk difference (95% CI)	p value
Catheter [*](tbl3fn1)	4 (2%)	4 (2%)	0·0% (−10·7 to 10·7)	1·00
Catheter tip [*](tbl3fn1)	4 (2%)	4 (2%)	0·0% (−10·7 to 10·7)	1·00
Surgical wound	4 (2%)	1 (0·6%)	−1·8% (−12·5 to 8·9)	0·21
Bloodstream	8 (5%)	2 (1%)	−3·6% (−7·1 to 0·0)	0·06
Abdominal	1 (0·6%)	0	−0·61% (−1·8 to 0·6)	0·50
Clinically significant UTI	1 (0·6%)	0	−0·61% (−1·8 to 0·6)	0·50
Airway or lung [†](tbl3fn2)	52 (32%)	35 (21%)	−10·4% (−19·8 to −1·1)	0·0342
CPIS probable [‡](tbl3fn3) pneumonia	34 (21%)	25 (15%)	−5·5% (−13·8 to 2·7)	0·20
CPIS confirmed [§](tbl3fn4) pneumonia	22 (13%)	14 (8%)	−4·9% (−11·6 to 1·2)	0·16
Any major infection [¶](tbl3fn5)	27 (16%)	13 (8%)	−8·5% (−15·5 to −1·6)	0·0187

Data are n (%), unless otherwise stated. UTI=urinary tract infeciton. CPIS=clinical pulmonary infection score.

* Venous or arterial catheters.

† New or worsening infiltrates and consolidation plus positive respiratory tract culture of likely pathogen sampled on the day of, day before, or day after onset of new or worsening infiltrates and consolidation.

‡ CPIS ≥6 plus detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, endotracheal or bronchoscopic aspirate, or quantitatively cultured bronchoscopic bronchoalveolar lavage fluid or brush catheter specimen), or the presence of a negative lower respiratory tract culture if collected within 72 h after starting a new antibiotic regimen. [15]

§ CPIS ≥6 (using a Gram stain of a lower respiratory tract sample) plus a definite cause established by the recovery of a probable causing agent: from an uncontaminated specimen (ie, blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate); from respiratory secretions of a likely pathogen that does not colonise the upper airways (eg, *Mycobacterium tuberculosis,*

Legionella species, influenza virus, or *Pneumocystis jirovecii [carinii]*); of a possible respiratory pathogen in cultures of a lower respiratory tract sample (endotracheal aspirate, bronchoalveolar lavage, or protected specimen brush); or of a positive serology. [15]

¶ Attributable excess case mortality >15%. [16]

Patients in the caloric management group were more likely to be discharged from hospital alive and remain alive at day 90 than were standard care patients (table 2 (tbl2)). Compared with patients in the standard care group, those in the protocolised caloric management group's mean hospital stay was increased by about 6 days and survivors in the protocolised caloric management group reported significantly worse general health according to the RAND-36 questionnaire at the day 90 interview (table 2 (tbl2)). However, the extent of this difference in general health could not be declared to be clinically important because it did not reach the minimum threshold (half the SD of the pooled results of the scale, which equated to a difference between groups of 12·4 units) defined a priori in our statistical analysis plan. [19]

No significant differences were noted between groups of measures of organ dysfunction, duration of mechanical ventilation, other major concomitant treatments (table 4 (tbl4)), performance status, or physical function (table 2 (tbl2)).

Table 4

Clinically significant organ dysfunction and concomitant interventions, adjusted for time at risk (ICU stay)

	Standard care (165 patients)	**Caloric management (166 patients)**	**Mean difference (95% CI)**	**p value** * (tbl4fn1)
Organ system dysfunction (adjusted for time at risk of failure [ICU stay] days per 10 patient ICU days)				
Pulmonary dysfunction (ratio PaO_2:FiO_2 <301)	8·03 (7·68 to 8·41)	8·20 (7·84 to 8·57)	0·16 (−0·56 to 0·93)	0·67
Hepatic dysfunction (total bilirubin >32·5 μmol/L)	0·65 (0·49 to 0·86)	0·66 (0·50 to 0·89)	0·01 (−0·27 to 0·50)	0·98
Coagulation dysfunction (platelets <81×10^9/L)	0·32 (0·22 to 0·48)	0·36 (0·24 to 0·53)	0·03 (−0·16 to 0·47)	0·82
Cardiovascular dysfunction systolic blood pressure (<90 mm Hg, not fluid responsive)	0·60 (0·48 to 0·75)	0·63 (0·50 to 0·79)	0·03 (−0·20 to 0·39)	0·82
Renal dysfunction (creatinine >168 μmol/L)	0·28 (0·16 to 0·49)	0·48 (0·27 to 0·84)	0·19 (−0·13 to 1·20)	0·36
Multiple organ dysfunction syndrome ‡ (tbl4fn2)	1·12 (0·90 to 1·39)	1·21 (0·98 to 1·51)	0·10 (−0·33 to 0·76)	0·70

Number of dysfunctional organs per patient per ICU day	0·72 (0·67 to 0·78)	0·79 (0·73 to 0·84)	0·06 (−0·04 to 0·19)	0·25
Concomitant therapies (adjusted for time at risk [ICU stay] events per 10 patient ICU days)				
Days of mechanical ventilation	7·45 (7·16 to 7·65)	7·86 (7·54 to 8·18)	0·40 (−0·21 to 1·07)	0·21
Days of renal replacement therapy	0·06 (0·02 to 0·13)	0·23 (0·10 to 0·53)	0·17 (−0·02 to 1·17)	0·11
Pressure ulcer treatment days (treatment for stage ≥1)	0·77 (0·52 to 1·12)	0·63 (0·43 to 0·92)	−0·13 (−0·46 to 0·57)	0·61
Low serum albumin days (<25 g/L)	4·52 (4·00 to 5·12)	5·02 (4·44 to 5·69)	0·50 (0·61 to 1·91)	0·41
Systemic antibiotic days	7·06 (6·72 to 7·42)	7·32 (6·97 to 7·69)	0·26 (−0·42 to 1·02)	0·46
Witnessed aspiration (events per 1000 patient days)	2·5 (1·2 to 5·5)	2·0 (0·9 to 4·3)	−0·56 (−2·1 to 6·8)	0·75
Witnessed aspiration and new pulmonary infiltrates (events per 1000 patient days)	0 (−1·1 to 2·3)	1·6 (0·5 to 3·9)	−1·6 (−3·1 to 5·8)	0·97

Data are mean (95% CI), unless otherwise stated. ICU=intensive care unit. PN=parenteral nutrition.

* p values from negative binomial model, controlled for duration of risk (ICU stay).

† Defined as two or more organ system dysfunctions on the same day.

No differential treatment effects were noted across a-priori defined subgroups (appendix (sec1)).

In a post-hoc sensitivity analysis, we assessed outcomes in patients with two or more key signs of refeeding syndrome. At enrolment, 319 of 339 patients expressed two or more key signs consistent with refeeding syndrome: 161 patients were randomly allocated to standard care and 158 to protocolised caloric management.

In the 60-day follow-up, the mean number of days alive after discharge from the ICU was 39·5 days (95% CI 36·0–43·4) for standard care and 44·9 days (40·9–49·3) for protocolised caloric management patients, resulting in a mean difference of 5·4 days (95% CI −2·2 to 14·6, p=0·18).

No significant differences were recorded between groups with regards to ICU stay (mean difference 1·2 days, 95% CI −0·54 to 3·2, p=0·19) or number of patients discharged alive from ICU (standard: 146 [91%] of 161 *vs* caloric management: 149 [94%] of 158, p=0·28). However, significantly more patients in the protocolised caloric management group were alive at study day

60 than those receiving standard care (124 [78%] of 159 *vs* 142 [91%] of 156, p=0·002), resulting in a large increase in overall survival time, censored at day 60 (48·6 [SD 1·50] *vs* 53·79 [SD 0·98] days, log-rank p=0·001).

Discussion

Caloric restriction during treatment for refeeding syndrome did not increase the number of days alive after ICU discharge, although it did result in significant improvements in its two main components: overall survival time and mortality at day 60 follow-up. Moreover, caloric restriction significantly reduced incidence of major infections and incidence of airway or lung infections.

In view of our understanding of the physiology in refeeding syndrome and the association between caloric intake and subsequent hypophosphataemia, [7] experts in this area recommend nutritional support be stopped or restricted during phosphate and electrolyte replacement for patients with this syndrome. [2 5] Results of our Refeeding Syndrome trial provide objective clinical evidence to support these recommendations.

The onset of refeeding syndrome is associated with increased mortality in many patient groups, including elderly people, [24] patients with HIV, [25] and general ICU patients. [26] The hallmark clinical sign of refeeding syndrome, hypophosphataemia, is an independent risk factor for the subsequent development of sepsis [27] and septic shock. [28] Furthermore, a randomised clinical trial [29] reported a significant association between refeeding-associated hypophosphataemia and the onset of sepsis in infants with a very low birthweight. This increase in major infections, and attributable increase in mortality, might be mediated by a direct effect of serum phosphate on blood cell function. [30]

The metabolic rate of platelets, red blood cells (RBCs), and white blood cells (WBCs) is regulated by serum phosphate. Reduced serum phosphate concentrations result in reduced levels of high-energy phosphate compounds, such as ATP, in each blood cell type. [31 32 33] RBCs with reduced intracellular levels of ATP have low deformability and a striking increased affinity for oxygen, resulting in an impaired ability to offload oxygen at the target organ or microcapillary bed. [31] WBCs with reduced intracellular levels of ATP have substantially impaired chemotactic, phagocytic, and bactericidal ability. [32]

The acquired RBC and WBC dysfunction associated with decreased serum phosphate levels can be improved in vivo with phosphate replenishment. [31 32] Improvements in RBC and WBC function could account for the transient changes in arterial lactates and the decreased onset of major infections attributable to the caloric management protocol. Hypophosphataemia has been shown to greatly increase insulin resistance, [34] thus the reduction in hyperglycaemia associated with improved serum phosphate levels might also partly account for the reduction in infectious complications.

We used a simple and objective process to identify patients with refeeding syndrome: screening for the hallmark clinical sign of hypophosphataemia associated with the initiation of nutritional support followed by exclusion of patients with hypophosphataemia attributable to other major causes. With use of this process, 319 (96%) of 331 recruited patients in the modified intention-to-treat analysis

expressed at least two key diagnostic criteria for refeeding syndrome. Application of these objective criteria across 13 sites in Australia and New Zealand enhanced the generalisability of our trial to similar health-care settings.

Internal validity was enhanced by rigorous completion at each site, which minimised the risk of confounding by potential sources of bias. Adherence with the study caloric management protocol was high. Blinding of chest radiograph interpretation to diagnose pneumonia, and the application of robust and objective definitions to diagnose and grade the severity of all infectious complications across each site reduced the potential for ascertainment bias in this key outcome. [16] Furthermore, successful implementation of a best-practice protocol guiding phosphate replacement in both groups of the trial strengthened causal inferences attributable to the study intervention, caloric restriction. Additionally, the effects reported in this trial are internally clinically coherent and consistent with external evidence: a reduction in major infections translated into a reduction in mortality.

Survivors allocated to receive protocolised caloric management did report significantly worse general health at the day 90 interview. Our a priori reported statistical analysis plan stipulated threshold values for differences in quality of life measures that would allow us to define any improvements as clinically important to the patient; however, the self-reported difference in general health did not exceed our minimum threshold. [19] Therefore, this self-reported effect is statistically significant, but of questionable clinical importance. This effect on general health was not supported by differences in physical function or performance status. Larger studies with longer follow-up might be needed to fully explore these effects on quality of life.

The Refeeding Syndrome Trial did not show any clinically important harm associated with short-term caloric restriction in critically ill patients with refeeding syndrome. Major clinical trials have assessed the effects of medium-term caloric restriction in general critically ill patients, and also reported no measurable harm. [35] [36]

On the basis of these results, caloric restriction seems to be a suitable therapeutic option for adult critically ill patients with refeeding syndrome.

Contributors

All authors contributed to the writing of the manuscript through critical review, comments, and approval of early drafts of the manuscript, and all authors approved the final draft for publication. GSD, FS, and RB conceived the study. GSD did the data analysis and wrote the first draft of the manuscript. GSD, FS, PTH, RB, DC, IDC, MCR, and PWJH contributed to the design and interpretation of the study. GSD, FS, and PTH supervised the acquisition of data and all authors supervised the completion of the study.

Declaration of interests

GSD reports grants and personal fees from Fresenius Kabi Deutschland GmbH and Baxter Healthcare Australia Pty Ltd, and reports personal fees from Nestlé Healthcare, outside of the submitted work. FS reports grants and personal fees from Fresenius Kabi Deutschland GmbH and

Baxter Healthcare Australia Pty Ltd, outside of the submitted work. IDC reports grants and personal fees from NovoNordisk and Pfizer, reports grants from Bristol-Myers Squibb and Soho Flordis International, and reports personal fees from Servier Laboratories and Ache, outside of the submitted work. IDC is on the scientific advisory board of the Sansom Institute for Health Research, University of South Australia (Adelaide, Australia) and the Children's medical Research Institute, and chairs the executive management committee of the bariatric surgical register for the Obesity Surgery Society of Australia and New Zealand. PTH, RB, DC, MCR, and PWJH declare no competing interests.

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Supplementary Material

Supplementary appendix (/ui/service/content/url?section=static%2fimage&eid=1-s2.0-S221326001500418X&path=22132600%2FS2213260015X00129%2FS221326001500418X%2Fmmc1.pdf)

† see appendix (sec1) for the full list of investigators

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