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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Doig GS, Simpson F, Heighes PT, et al, for the Refeeding Syndrome Trial Investigators Group. 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. *Lancet Respir Med* 2015; published online Nov 17. http://dx.doi.org/10.1016/S2213-2600(15)00418-X.

Web extra material:

Restricted vs. continued normal caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, multicentre, single-blind, controlled trial.

Gordon S. Doig, Fiona Simpson, Philippa T. Heighes
for the Refeeding Syndrome Trial Investigators Group.

The Refeeding Syndrome Trial

www.EvidenceBased.net/Refeeding

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Note: Additional information can be found at the study web site: *www.EvidenceBased.net/Refeeding*

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1·0 BRIEF BACKGROUND

1·1 Overview:

Given equipoise established by a survey of current practice demonstrating that only 30 to 40% of critically ill patients with refeeding syndrome are managed with energy restriction by intensive care specialists in Australia and New Zealand, we initiated and conducted a multi-centre randomised controlled trial (RCT) to evaluate the efficacy and effectiveness of restricting energy intake during the management of refeeding related hypophosphatemia in critically ill patients.

1·2 Hypotheses to be tested:

In critically ill patients with refeeding related hypophosphatemia under the care of an ICU specialist who plans to continue or increase nutrition support, does energy restriction affect the duration of critical illness, and other measures of morbidity, compared to standard care plans?

1·3 Eligibility criteria:

See eAppendix S1 for the complete list of study eligibility criteria, to be applied within 72 h of commencing nutrition support after admission to a study ICU.

Note: Study Inclusion Criteria 3 and 4 required the calculation of the patient's energy intake:

3) Has the patient received at least 500 kcals energy from nutrition support over the previous 24 h?

4) Is the patient's current total energy intake from nutrition support at least 30 kcals per hour?
[*Nutrition support* was defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing ≥ 10% glucose/dextrose. Energy (calories) from propofol or boluses of glucose/dextrose solutions did not count towards energy intake from *nutrition support*.]

The study web site provided a tool to allow consistent calculation of current energy intake at all sites. The *study nrgCalc tool* (https://research.EvidenceBased.net/nrgCalc, See eAppendix S4 for Screen Capture) was not password protected, to allow site researchers and other healthcare staff to access the tool after hours and on weekends if required.

1·4 Randomisation:

Allocation concealment was maintained through the use of a central randomisation web site that was secure, encrypted, and password protected.

The study web site was accessible 24 hours a day, seven days a week. This academic web site (http://www.EvidenceBased.net/Refeeding) has been used to host numerous secure research projects.

The randomisation sequence was generated using SAS Version 9·2 with blocks of variable size and random seeds to ensure allocation concealment could not be violated by guessing the allocation sequence at the end of each block. Randomisation was stratified within study site by initial serum phosphate level and body mass index (BMI). Stratification variables and their thresholds were concealed from site investigators to further prevent anticipation of the allocation sequence.

1·5 Blinding:

Because certain ICU-based infections are notoriously subjective to diagnose, an objective grading scheme based on infecting organism, site of infection, and known impact on outcome, was used to identify clinically important major infectious complications, with key aspects of the diagnosis of certain infections (Ex. interpretation of chest x-rays for grading of the Clinical Pulmonary Infection Score) ascertained in a blinded fashion.

1·6 Study intervention:

If randomised to the intervention arm, the patient received nutrition support directed by the study Caloric Management Protocol (eAppendix S2).

The study Caloric Management Protocol required caloric intake to be decreased to 20 kcals/h for at least 2 days (48 h). If serum phosporous did not need to be replaced by the end of this 2 day period (defined by study protocol, eAppendix S1) caloric intake was gradually returned to normal by following the study Gradual Return to Normal Intake Protocol (eAppendix S2).

All study interventions and management protocols were discontinued when the patient was discharged from the study ICU.

1·7 Pragmatic Standard Care:
Standard care in the patients randomised to the control arm consisted of continuing or increasing nutrition support, as planned prior to study enrolment. The attending clinician selected the route, rate of increase, and metabolic targets based on their current standard practice.

1·8 Serum Phosphate Replacement Protocol (eAppendix 3):
Because different clinicians use different clinical triggers and prescribe different doses for phosphate replacement, potential confounding was reduced by the use of a protocol to guide phosphate replacement at all study sites in patients randomised to receive the study intervention (Caloric Management) *and* in patients randomised to receive Standard Care.

After a thorough review of all available evidence conducted independently by three members of the Management Committee, a previously published protocol known to be safe and efficacious was implemented in all study patients (eAppendix S3).

All study interventions and management protocols were discontinued when the patient was discharged from the study ICU.

1·9 Data collection and follow up:
Every randomised patient was followed up until hospital discharge or 90 days post-randomisation whichever was longer, unless death occurred first, as recommended by the UK Medical Research Council International Working Party for Clinical Trials in Patients with Sepsis and Septic Shock. If patients remained in hospital on study Day 180, follow-up was censored and outcomes were recorded as per status at Day 180.

1·10 Analysis
Complete details regarding the modified intention to treat analysis were published in the Statistical Analysis Plan, available on-line: http://dx.doi.org/10.4451/Refeeding_SAP

2·0 ADDITIONAL INFORMATION AND DATA

2.1 Patient f4f2d, excluded from modified intention to treat analysis.
Summary of information supplied to the Chair of the DSMC for blinded adjudication:

Patient f4f2d was appropriately enrolled into the trial at 8:16am on 20 Nov 2013. Their enrolment serum phosphorous level recorded in the study web site was 0·49 mMol/L.

f4f2d was a 50Kg, 85 year old male, admitted to ICU on 14 Nov 2013 after emergency surgery for a GI perforation. He had been in hospital since 7 Nov 2013. He was receiving EN at a rate of 45kcals/h. Although he was not ventilated at time of enrolment, there were 'new' 'patchy' infiltrates reported on x-ray within 24 h of enrolment. The patient was not expected to be discharged from ICU on the next day.

On 21 Nov 2013, the study management centre received this e-mail from the study site:

"<RCName> came back in the afternoon to fill out the CRF and write down the rest of the blood results to find the results had been taken off the computer and said sample mislabelled. Phosphate was replaced on this patient due to the morning blood result that was on the screen, and the blood was redone in the afternoon at 15:30 and the Phosphate was 1·27. We don't know if the blood was mislabelled or how they came to that conclusion, but we now do not have any blood results for that morning and not sure if the low Phosphate of 0·49 was really this patients? This had never happened to us before can you please advise. All study procedures have been done to this point."

Later, we learned the patient's Phos was actually 0·8, not 0·49· A phos of 0·8 does not qualify for enrolment.

All data was collected and all appropriate processes were followed at the site. This was a sample labelling/mishandling error, with results for another patient incorrectly entered into the laboratory computer database. Given this patient did not have hypophosphatemia, which is our primary and most important eligibility criteria, can we exclude this patient from our mITT?

The Chair responded:

"As chair of the SDMC, I have reviewed the information you have provided regarding the error in randomization of participant f4f2d due to actual ineligibly due to a laboratory error in reported serum phosphate.

I would agree and believe it is reasonable to exclude this patient from the primary modified ITT analysis for efficacy."

Additional information regarding patient f4f2d. This information was not provided to the Chair of the DSMC in order to allow for an independent blinded adjudication:

Patient f4f2d was randomized to Standard Care and was discharged from ICU on 27 Nov 2013. The patient died in hospital on 3 Jan 2014.

Inclusion of this patient's results in an ITT analysis does not alter the primary conclusions in any meaningful way.

2.1 Subgroup analyses

With regards to the primary outcome, number of days alive after ICU discharge, there were no differential treatment effects across *a priori* defined subgroups: 1) Severity of hypophosphatemia (≤50th vs . > 50th percentile, P=0·45); 2) Subjective Global Assessment of muscle and fat wasting (No evidence of wasting vs. Evidence of wasting, P=0·64); 3) Energy intake (≤ 50th vs. > 50th percentile, P=0·66); 4) Blood glucose (≤ 50th vs. > 50th percentile, P=0·86); 5) Insulin dose rate (≤ 50th vs. > 50th percentile, P=0·94); 6) Timing of onset of hypophosphatemia (≤ 50th vs . > 50th percentile for hours after initiation of Nutrition Support in ICU until study enrolment, P=0·70).

Table S1: Patients developing severe hyophosphataemia (< 0·32 mmol/L) on each of first 7 study days:

Severe Hypophosphataemia (<0·32 mmol/L)	Standard Care	Caloric Management	P-value
Study Day 1 (n/N)	1/165	0/166	0·49
Study Day 2 (n/N)	0/165	0/166	1·00
Study Day 3 (n/N)	0/157	0/159	1·00
Study Day 4 (n/N)	0/138	1/141	1·00
Study Day 5 (n/N)	0/123	0/126	1·00
Study Day 6 (n/N)	0/110	0/114	1·00
Study Day 7 (n/N)	0/95	0/97	1·00

There were no differences between groups with regards to severe hypophosphatemia over the first 7 days of the study (P=1·00 on each day). 1 Standard Care patient developed severe hypophosphatemia on Study Day 1 whilst 1 Caloric Management patient developed severe hypophosphatemia on Study Day 4. No other patients developed severe hypophosphatemia.

Table S2: Patients developing moderate hypophosphataemia (<0·65 mmol/L) on each of first 7 study days:

Moderate Hypophosphataemia (<0·65 mmol/L)	Standard Care	Caloric Management	P-value
Study Day 1 (n/N)	22/165	18/166	0·50
Study Day 2 (n/N)	41/165	23/166	0·0124
Study Day 3 (n/N)	17/157	11/159	0·24
Study Day 4 (n/N)	8/138	14/141	0·26
Study Day 5 (n/N)	5/123	7/126	0·77
Study Day 6 (n/N)	3/110	4/114	1·00
Study Day 7 (n/N)	3/95	1/97	0·37

Significantly more Standard Care patients developed moderate hypophosphatemia on Study Day 2 (41/165 vs 23/166, P=0·0124). There were no differences between groups on any of the other days.

Table S3: Patients developing hyperglycaemia (> 10 mmol/L) on each of first 7 study days:

Severe Hyperglycaemia (>10 mmol/L)	Standard Care	Caloric Management	P-value
Study Day 1 (n/N)	70/165	45/166	0·004
Study Day 2 (n/N)	62/165	30/166	<0·001
Study Day 3 (n/N)	64/157	31/159	<0·001
Study Day 4 (n/N)	47/138	33/141	0·06
Study Day 5 (n/N)	49/123	46/126	0·60
Study Day 6 (n/N)	49/110	38/114	0·10
Study Day 7 (n/N)	40/95	41/97	1·00

Significantly more Standard Care patients were hyperglycaemic on study days 1, 2, and 3.

Table S4: Patients receiving insulin infusion on each of first 7 study days:

Insulin infusion	Standard Care	Caloric Management	P-value
Study Day 1 (n/N)	64/165	50/166	0·11
Study Day 2 (n/N)	66/165	37/166	<0·001
Study Day 3 (n/N)	56/157	31/159	0·002
Study Day 4 (n/N)	49/138	24/141	<0·001
Study Day 5 (n/N)	41/123	24/126	0·01
Study Day 6 (n/N)	36/110	23/114	0·03
Study Day 7 (n/N)	30/95	23/97	0·26

Significantly more Standard Care patients required an insulin infusion on study day 2, 3, 4, 5, and 6.

Table S5: Patients developing hypoglycaemia (< 2·2 mmol/L) on each of first 7 study days:

Severe Hypoglycaemia (<2·2 mmol/L)	Standard Care	Caloric Management	P-value
Study Day 1 (n/N)	0/165	0/166	1·00
Study Day 2 (n/N)	0/165	0/166	1·00
Study Day 3 (n/N)	0/157	0/159	1·00
Study Day 4 (n/N)	0/138	1/141	1·00
Study Day 5 (n/N)	0/123	0/126	1·00
Study Day 6 (n/N)	0/110	0/114	1·00
Study Day 7 (n/N)	0/95	0/97	1·00

There were no differences between groups with regards to severe hypoglycemia over the first 7 days of the study (P=1·00 on each day). 1 Caloric Management patient developed hypoglycaemia on Study Day 4.

Table S6: Mean lowest daily serum potassium on each of first 7 study days:

Lowest Serum Potassium (mmol/L)	Standard Care	Caloric Management	P-value
Study Day 1, mean (SD)	3·79 (0·38)	3·73 (0·33)	0·26
Study Day 2, mean (SD)	3·81 (0·47)	3·86 (0·39)	0·24
Study Day 3, mean (SD)	3·84 (0·44)	3·80 (0·41)	0·39
Study Day 4, mean (SD)	3·86 (0·43)	3·78 (0·49)	0·18
Study Day 5, mean (SD)	3·84 (0·43)	3·80 (0·42)	0·49
Study Day 6, mean (SD)	3·83 (0·49)	3·80 (0·40)	0·63
Study Day 7, mean (SD)	3·84 (0·45)	3·85 (0·44)	0·85

There were no differences in mean lowest daily serum potassium on any of the first 7 days of study.

Table S7: CD4, CD8, and NK cell counts:

	Standard Care	Caloric Management	P-value
Baseline (pre-randomization)			
CD4 (x 10^6/L), mean (SD)	532 (351)	514 (384)	0·68
CD8 (x 10^6/L), mean (SD)	260 (176)	256 (199)	0·84
CD4:CD8 ratio, mean (SD)	2·9 (2·9)	3·0 (4·4)	0·87
NK (x 10^6/L), mean (SD)	123 (138)	105 (122)	0·25
Study Day 1			
CD4 (x 10^6/L), mean (SD)	505 (263)	537 (385)	0·45
CD8 (x 10^6/L), mean (SD)	249 (193)	249 (181)	0·98
CD4:CD8 ratio, mean (SD)	2·9 (2·3)	3·5 (7·0)	0·35
NK (x 10^6/L), mean (SD)	106 (157)	123 (368)	0·63
Study Day 3			
CD4 (x 10^6/L), mean (SD)	602 (390)	634 (474)	0·59
CD8 (x 10^6/L), mean (SD)	294 (231)	280 (217)	0·64
CD4:CD8 ratio, mean (SD)	3·0 (2·5)	3·2 (3·4)	0·56
NK (x 10^6/L), mean (SD)	99 (77)	112 (150)	0·44

There were no differences in white blood cells sub-typed by expression of the CD4 or CD8 marker, or sub-typed as Natural Killer (NK) cells.

Table S8: Location of patient at Day 90 follow-up:

Location	Standard Care (n = 128 survivors)	Caloric Management (n = 141 survivors)	P-value
1. Rehabilitation ward	17	14	
2. Acute care ward	4	12	
3· ICU/HDU	1	1	
4. Chronic care hospital	3	4	0·4272
5. Residential home	97	103	
6. Hostel	4	4	
7. Other	2	3	

*2 Caloric Management patients declined to provide a response to this question.

There were no significant differences between groups with regards to the location of patient at time the day 90 follow-up interview was conducted.

Table S9: Caloric targets by study group on each of the first 7 study days:

Caloric targets (kcals per hour)	Standard Care	Caloric Management
Study Day 1, mean (SD)	80·3 (17·9)	20·0 (0·1)
Study Day 2, mean (SD)	80·6 (13·1)	20·0 (0·1)
Study Day 3, mean (SD)	80·3 (12·7)	29·6 (10·2)
Study Day 4, mean (SD)	80·3 (14·1)	43·6 (15·7)
Study Day 5, mean (SD)	81·4 (13·4)	53·8 (19·4)
Study Day 6, mean (SD)	83·4 (13·9)	60·2 (22·5)
Study Day 7, mean (SD)	83·6 (14·2)	62·4 (23·2)

Targets for standard care patients were calculated by the clinical team using the technique usually used in their site. Targets for caloric management patients were set by the study protocol.

Table S10: Protein intake on each of first 7 study days:

Lowest Serum Potassium (g/day)	Standard Care	Caloric Management	P-value
Study Day 1, mean (SD)	39·5 (22·4)	10·8 (5·2)	<0·0001
Study Day 2, mean (SD)	63·1 (31·1)	18·6 (7·8)	<0·0001
Study Day 3, mean (SD)	60·9 (37·5)	23·4 (13·6)	<0·0001
Study Day 4, mean (SD)	57·6 (34·7)	34·7 (22·5)	<0·0001
Study Day 5, mean (SD)	55·9 (37·4)	41·6 (31·1)	0·0013
Study Day 6, mean (SD)	52·5 (36·0)	45·0 (36·6)	0·1243
Study Day 7, mean (SD)	53·89 (38·6)	51·5 (37·8)	0·6698

Note: Although it appears protein intake doubles from Day 1 to Day 2 in both groups, this is an artefact. Because Study Day 1 represents the first calendar day of enrolment, Study Day 1 is less than 24 h long.

Table S11: Thiamine dose and number of patients receiving thiamine on each of first 7 study days:

Thiamine dose (mg)	Standard Care	Caloric Management	P-value dose (P-value n)
Study Day 1, mean (SD) / n	130·9 (85) n = 13	123·4 (82) n = 13	0·8209 (1·0)
Study Day 2, mean (SD) / n	130·9 (62) n = 13	147·6 (130) n = 19	0·6731 (0·3525)
Study Day 3, mean (SD) / n	115·6 (51) n = 9	181·5 (186) n = 16	0·3143 (0·2105)
Study Day 4, mean (SD) / n	116·7 (40.8) n = 6	184·9 (203) n = 13	0·265 (0·1525)
Study Day 5, mean (SD) / n	120·0 (44) n = 5	108·0 (63) n = 13	0·7059 (0·0844)
Study Day 6, mean (SD) / n	125 (50) n = 4	120·0 (63.4) n = 10	0·8907 (0·1658)
Study Day 7, mean (SD) / n	100·0 (0) n = 5	133·3 (81) n = 6	0·3632 (1·0)

There were no significant differences in thiamine dose or number of patients receiving thiamine on each for the first 7 days of the study.

Table S12: Maximum insulin infusion rate on each of first 7 study days:

Maximum insulin infusion rate (Units per h)	Standard Care	Caloric Management	P-value dose (P-value n)
Study Day 1, mean (SD)	4·9 (3·5)	3·9 (2·5)	0·0638
Study Day 2, mean (SD)	5·0 (3·8)	3·1 (2·3)	0·0017
Study Day 3, mean (SD)	4·5 (3·4)	2·6 (1·5)	< 0·0001
Study Day 4, mean (SD)	4·7 (3·4)	3·9 (2·6)	0·3270
Study Day 5, mean (SD)	5·4 (3·6)	4·1 (3·3)	0·1326
Study Day 6, mean (SD)	5·5 (3·6)	4·3 (2·8)	0·1680
Study Day 7, mean (SD)	5·1 (3·2)	4·5 (2·3)	0·4586

As reported in the text of the manuscript, significantly more standard care patients had hyperglycaemia on the first three study days. These patients required a significantly higher maximum insulin infusion rate on each of these days.

Appendix S1: Detailed Study Inclusion and Exclusion Criteria

The onset of Refeeding Syndrome will be diagnosed according to the criteria of Marik and Bedigian: serum phosphorus drop of more than 0·16 mmol/L from a previous reading to below 0·65 mmol/L within 72 hours of the onset of nutritional support.

Inclusion Criteria

Patients will be considered *eligible* for the trial if *all* of the following *inclusion criteria* are met at the time of screening:

1) Within the past **72 hours**, has the patient commenced nutrition support for the first time during this current stay in the study ICU?
[Nutritional support is defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing ≥ 10% glucose/dextrose.]

2) Within the past **12 hours**, has the patient's serum phosphate dropped to below 0·65 mmol/L AND this drop was greater than a 0·16 mmol/L decrease from any previous phosphate value?
[Any previous phosphate value obtained within the past 72 hours that was collected during this current study ICU admission may be used.]

3) Has the patient received at least 500kcals energy from nutrition support over the previous 24 h?
*[Nutritional support is defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing≥ 10% glucose/dextrose· Energ y (calories) from propofol or boluses of glucose/dextrose solutions do **not** count towards energy intake.]*

4) Is the patient's current total energy intake from nutrition support *at least* 30 kcals per hour?
*[Nutritional support is defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing≥ 10% glucose/dextrose· Energy (calories) from propofol or boluses of glucose/dextrose solutions do **not** count towards energy intake.]*

5) Does the ICU specialist presently caring for the patient plan to continue, or increase, the current rate of nutrition support?
*[Specialist does **not** currently plan to reduce or stop energy intake as part of this patient's standard care plan.]*

6) Is the patient 18 years of age or older?

7) Does the patient have a working central venous access line through which an electrolyte infusion could be delivered?

See exclusion criteria, next page.

Exclusion Criteria

Patients will be considered *ineligible* for the trial if *any* of the following *exclusion criteria* are met at the time of screening:

(Answer **NO** to all questions)

1) Was the patient actively receiving enteral nutrition or parenteral nutrition at another location (outside of the study ICU) up to 6 hours prior to being admitted to the study ICU?
*[IV glucose/dextrose provided outside the ICU does **not** exclude the patient from enrolment.]*

2) Has the patient received an intravenous phosphate infusion during this current ICU stay that was commenced more than **2 hours** ago?
*[A phosphate infusion started **within the past** 2 hours is OK· Please consider any infusion that contained more than 5 mmol of phosphate.]*

3) Is the patient expected to be discharged from the study ICU today or tomorrow?

4) Was the patient admitted to the study ICU after a parathyroidectomy, performed during this hospital stay?

5) Has the patient received recent active treatment for **hyper**phosphatemia that may be associated with the onset of this current **hypo**phosphataemic event?
*[Common treatments for **hyper**phosphataemia include dialysis/RRT or the use of phosphate binders such as: calcium containing binders (calcium carbonate, calcium citrate), newer binders that don't contain aluminium or calcium (Sevelamar* (Renegal*) and Ranthanum Carbonate* (Fosrenol) or *Aluminium containing binders (generally not used anymore due to risks of aluminium absorption).]*

6) Has the patient received treatment for diabetic ketoacidosis during this current ICU admission?

7) Does the patient currently require treatment for hyperosmolar non-ketotic coma?

8) Is the patient currently receiving, or scheduled to receive, dialysis/renal replacement therapy?

9) Is the patient expected to receive palliative care only and is not expected to survive ICU or hospital discharge?

10) Is the patient moribund and not expected to survive 24 hours?

11) Is the patient brain dead or suspected to be brain dead?

12) Has the patient previously been enrolled and randomised into this study?

Appendix S2: Study Intervention: Caloric Management Protocol

Caloric Management Protocol Day 1 (first 24 h of energy management)

- ***Reduce*** current nutrition support to **20 kcals/hr.**
- Use the study web site (httpS://Research.EvidenceBased.Net/nrgCALC/) to calculate the energy content of the patient's current nutrition support (EN, PN plus any intravenous infusion containing ≥ 10% dextrose/glucose) in kcals per ml and re-calculate the patient's nutrition support rate to **reduce energy intake to 20 kcals / hr.**
- **Replace** phosphate deficit in accordance to study Phosphate Replacement Protocol.
- **Strongly recommend** daily administration of at least 100mg Thiamine IV.
- **Strongly recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, magnesium, and others, as clinically appropriate.

Caloric Management Protocol Day 2 (second 24 h of energy management)

- ***Continue*** current nutrition support at **20 kcals/hr.**
- **Replace** phosphate deficit in accordance to study Phosphate Replacement Protocol.
- **Strongly recommend** daily administration of at least 100mg Thiamine IV.
- **Strongly recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, magnesium, and others, as clinically appropriate.

At beginning of Day 3, plus additional days (next 24 h of energy management):

If most recent serum phosphate value does not rise above 0.71 mmol/L, replace phosphates as per Phosphate Protocol and continue Caloric Management as per Protocol Day 2 (above).

If most recent serum phosphate value rises above 0.71 mmol/L, initiate Day 1 of Gradual return to normal intake Protocol (see next page).

Note: Whilst patients are on the study Caloric Management Protocol, energy targets **must not** be exceeded. If targets are met with EN, PN and IV glucose (≥ 10% concentration), **oral consumption of high-energy / high-protein oral supplements** (Resource, Ensure, Sustagen etc), which may contain upwards of 2.0 kcal/ml, **may lead to Protocol targets being exceeded.** Use supplements with care. Patients should be monitored closely. **Total energy intake should be managed such that the Protocol set targets are not exceeded.**

Gradual return to normal intake protocol:

Calculate patient's eventual full-normal caloric goal using local hospital methods.

Gradual return to normal intake, Protocol Day 1 (first 24 h of energy increase)

- **Increase** nutrition support to **40 kcals/hr.**
- Use the study web site (httpS://Research.EvidenceBased.Net/nrgCALC/) to calculate the energy content of the patient's current nutrition support (EN, PN plus any intravenous infusion containing≥ 10% dextrose/glucose) in kcals per ml and re-calculate the patient's nutritional support rate to **increase energy intake to 40 kcals / hr.**
- Strongly recommend frequent monitoring of phosphate.
- If the patient's phosphate drops to 0·71 mmol/L or lower, replace phosphate as per Phosphate Replacement Protocol and revert to Caloric Management Protocol Day 1.
- **Recommend** daily administration of at least 100mg Thiamine IV.
- **Recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, and magnesium, as clinically appropriate.

Gradual return to normal intake, Protocol Day 2 (second 24 h of increase)

- Increase nutrition support to 60 kcals/hr, or 80% of goal *whichever is lower*.
- Use the study web site (*httpS://Research.EvidenceBased.Net/nrgCALC/*) to calculate the energy content of the patient's current nutrition support (EN, PN plus any intravenous infusion containing≥ 10% dextrose/glucose) in kcals per ml and re-calculate the patient's nutritional support rate to **increase energy intake to 60 kcals / hr or 80% of goal, whichever is lower**.
- Strongly recommend frequent monitoring of phosphate.
- If the patient's phosphate drops to 0·71 mmol/L or lower, replace phosphate as per Phosphate Replacement Protocol and revert to Caloric Management Protocol Day 1.
- **Recommend** daily administration of at least 100mg Thiamine IV.
- **Recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, and magnesium, as clinically appropriate.

Additional Days, until return to full normal intake is achieved

- **Increase** nutrition support to **80% of goal rate *OR*** if 80% has already been achieved, **increase to full goal rate,** as clinically appropriate.
- Strongly recommend frequent monitoring of phosphate.
- If the patient's phosphate drops to 0·71 mmol/L or lower, replace phosphate as per Phosphate Replacement Protocol and revert to Caloric Management Protocol Day 1.
- **Recommend** daily administration of at least 100mg Thiamine IV.
- **Recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, and magnesium, as clinically appropriate.

Appendix S3: Phosphate Replacement Protocol: Phosphate dosing table.

	Patient weight			
Serum Phosphate	**40 - 60kg**	**61 - 80kg**	**81 - 120kg**	**> 120kg**
0·71 to 0·55 mmol/L	10 mmol Phosphate IV over 6 hours*	15 mmol Phosphate IV over 6 hours*	20 mmol Phosphate IV over 6 hours*	25 mmol Phosphate IV over 6 hours*
0·54 to 0·32 mmol/L	20 mmol Phosphate IV over 6 hours*	30 mmol Phosphate IV over 6 hours*	40 mmol Phosphate IV over 6 hours*	50 mmol Phosphate IV over 6 hours*
below 0·32 mmol/L	30 mmol Phosphate IV over 6 hours*	40 mmol Phosphate IV over 6 hours*	50 mmol Phosphate IV over 6 hours*	60 mmol Phosphate IV over 6 hours*

If **potassium is > 4·0 mmol/L, use sodium phosphate** [#]; If potassium < 4·0 mmol/L, use of potassium phosphate may also be acceptable [##].

***** Rate may be increased, up to a maximum of 14·5 mmol/hr, at the discretion of local physician most responsible for the patient.

[#] Sodium phosphate solutions available in Australia contain a small quantity of potassium. For example, *DBL Sodium Phosphate and Potassium Phosphate Concentrated Injection (Hospira)* contains potassium ions in a final concentration of 0·13 mmol/ml. *This small quantity of potassium is safe in all patients*.

[##] Potassium phosphate may be used to correct both hypokalaemia and hypophosphataemia, but when larger doses of phosphate are required, potassium phosphate may provide excessive potassium. Consult the local physician most responsible for patient if you have concerns regarding use of potassium phosphate. We ***recommend*** use of sodium phosphate solutions for *all* patients, with hypokalaemia treated independently with an infusion of KCl. Refer to local protocols for the replacement of K.

Follow established local protocols and procedures to determine the appropriate time to re-asses patient's serum phosphate values post-infusion. However we ***strongly recommend*** that serum phosphate values should be checked at approximately 12 hours and 24 hours after the initiation of the phosphate infusion.

Additional phosphate infusions should be provided if serum phosphate drops to 0·71mmol/L or below. Dose additional phosphate infusions according to the above phosphate dosing table.

We **strongly recommend** that all **standard care** patients should receive at least **100mg Thiamine IV** each day they receive a phosphate infusion.

We **strongly recommend** cautionary clinical judgment when prescribing an ORAL dose of phosphate soon after an IV dose is administered, especially when serum phosphate values are not available.

IV: intravenous

Note: Patients with hypomagnesaemia may also require infusion of $MgSO_4$ or $MgCl_2$. Refer to local protocols for the replacement of Mg, or any other electrolytes, in these patients.

From: Taylor BE, Huey WY, Buchman TG, *et al.* Treatment of hypophosphatemia using a protocol based on patient weight and serum phosphorus level in a surgical intensive care unit. *J Am Coll Surg* 2004;198:198-204.

Appendix S4: https://research.EvidenceBased.net/nrgCALC Screen Capture

Total Energy Intake Calculator.

Use the Tab key or mouse to navigate fields. Press the HELP for help.

[**Instructions** | Glucose / Dextrose Solution | Enteral Nutrition]
[Normal PN | Complex PN | Complex PN in grams Load New Zealand nzCALC | **Total Energy**]

Instructions

The purpose of this web calculator is to help determine whether a patient is currently eligible for the Refeeding Syndrome Trial. One of the key elgibility criteria for the trial is:

4) Is the patient's current total energy intake from nutrition support at least 30 kcals per hour?
[Nutritional support is defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing ≥ 10% glucose/dextrose. For the purposes of this study, energy (calories) from propofol or boluses of glucose/dextrose solutions do not count towards energy intake.]

You can use this page to calculate energy intake from glucose solutions, enteral nutrition and/or parenteral nutrition.

After you have entered all required information, proceed to the **Total Energy** and review the **Current Total Energy** intake to determine whether the patient is eligible for enrollment based on Criteria 4 (above).

The **New Infusion Rate** fields on the **Total Energy** page can also be used to re-estimate infustion rates required to confirm with the recommendations of the Caloric Management Protocol.

You are responsible for the accuracy of the information you enter into this study tool. Please double check all your entries. Refer to the study Policy and Procedures Manual for additional instructions on use.

For use in the Refeeding Syndrome Trial only.
Created by Gordon S. Doig, Last updated 23 September 2010, Version 1. © EvidenceBased.net