Management of refeeding syndrome in critical illness: An AuSPEN endorsed multicentre randomised controlled trial.

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www.EvidenceBased.net/Refeeding

Outline

- Brief context and background
- Key elements of design
- Main results
- Summary

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- Recommended treatment for RS involves electrolyte replacement, thiamine supplementation and slow gradual achievement of caloric requirements.

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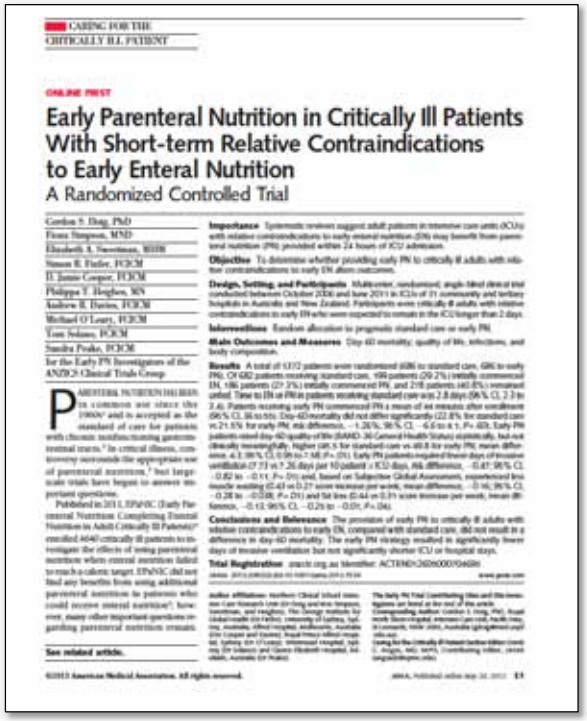

CARING FOR THE CRITICALLY ILL PATIENT

ONLINE FIRST

Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition

A Randomized Controlled Trial

Gordon S. Doig, PhD
Fiona Simpson, MND
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Simon R. Finfer, FCICM
D. Jamie Cooper, FCICM
Philippa T. Heighes, BN
Andrew R. Davies, FCICM
Michael O'Leary, FCICM
Tom Solano, FCICM
Sandra Peake, FCICM
for the Early PN Investigators of the ANZICS Clinical Trials Group

Importance Systematic reviews suggest adult patients in intensive care units (ICUs) with relative contraindications to early enteral nutrition (EN) may benefit from parenteral nutrition (PN) provided within 24 hours of ICU admission.

Objective To determine whether providing early PN to critically ill adults with relative contraindications to early EN alters outcomes.

Design, Setting, and Participants Multicenter, randomized, single-blind clinical trial conducted between October 2008 and June 2011 in ICUs of 31 community and tertiary hospitals in Australia and New Zealand. Participants were critically ill adults with relative contraindications to early EN who were expected to remain in the ICU longer than 2 days.

Interventions Random allocation to pragmatic standard care or early PN.

Main Outcomes and Measures Day-60 mortality; quality of life, infections, and body composition.

Results A total of 1372 patients were randomized (686 to standard care, 686 to early PN). Of 682 patients receiving standard care, 194 patients (29.2%) initially commenced EN, 186 patients (27.3%) initially commenced PN, and 218 patients (40.8%) remained ...

JAMA
The Journal of the American Medical Association

GS Doig and coauthors

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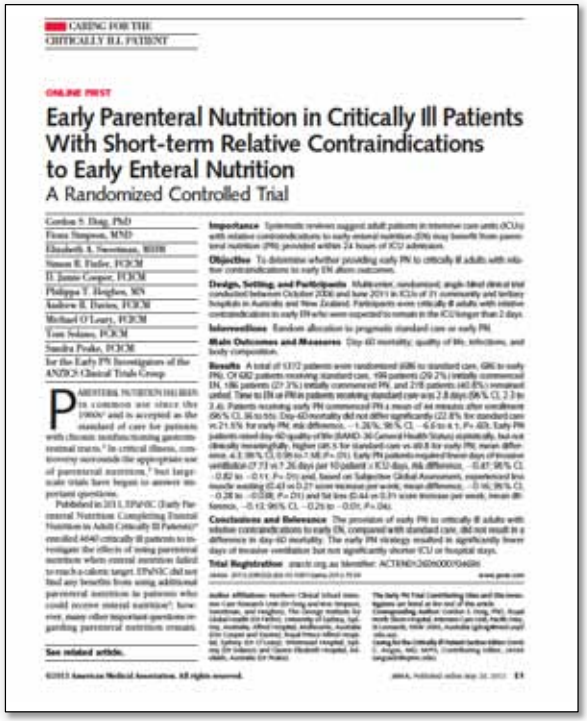

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PARENTERAL NUTRITION HAS BEEN in common use since the 1960s[1] and is accepted as the standard of care for patients with chronic intestine/stunting gastrointestinal tracts.[2] In critical illness, controversy surrounds the appropriate use of parenteral nutrition,[3] but large-scale trials have begun to answer important questions.

Published in 2011, EPaNIC (Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients)[4] enrolled 4640 critically ill patients to investigate the effects of using parenteral nutrition when enteral nutrition failed to reach a calorie target. EPaNIC did not find any benefits from using additional parenteral nutrition in patients who could receive enteral nutrition[5]; however, many other important questions regarding parenteral nutrition remain.

See related article.

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Conclusions and Relevance The provision of early PN to critically ill adults with relative contraindications to early EN, compared with standard care, did not result in a difference in day-60 mortality. The early PN strategy resulted in significantly fewer days of invasive ventilation but not significantly shorter ICU or hospital stays.

Trial Registration anzctr.org.au Identifier: ACTRN12609000704695

Author affiliations: Northern Clinical School Intensive Care Research Unit (Dr Doig and Miss Simpson, Sweetman, and Heighes), The George Institute for Global Health (Dr Finfer), University of Sydney, Sydney, Australia; Alfred Hospital, Melbourne, Australia (Drs Cooper and Davies); Royal Prince Alfred Hospital, Sydney (Dr O'Leary); Westmead Hospital, Sydney (Dr Solano); and Queen Elizabeth Hospital, Adelaide, Australia (Dr Peake).

The Early PN Trial Coordinating Office and the investigators are listed at the end of the article.

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Editorial on this Critically Ill Patient Section Editor: Derek C. Angus, MD, MPH. Contributing editor, Jama (angus@dom.edu).

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Doig GS, Simpson F, Sweetman EA et al. Early parenteral nutrition in critically ill patients with

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- We wanted to understand current practices for PN: patient selection, composition, dosing.
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- At the first 2 hospitals we visited, FS asked how often patients with RS were encountered and Intensivists responded "Never".

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100% (7/7) replied: “Yes”

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Simpson F, Doig GS, Sweetman EA and Heighes PT. Refeeding syndrome (RS) is under recognized and may be inappropriately managed in the Intensive Care Unit (ICU): results of a multicentre survey. Am J Respir Crit Care Med 179;2009:A6099.

Equipoise for a multi-centre clinical trial

Hypothesis:

In critically ill patients with refeeding syndrome, does energy restriction affect the duration of critical illness, and other measures of morbidity, compared to standard care plans?

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Power:

It was estimated a 336 patient clinical trial would have 90% power to detect a 6.4 day difference in ICU free days (SD=18.1 days).

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, Fiona Simpson, Philippa T Heighes, Rinaldo Bellomo, Douglas Chesher, Ian D Caterson, Michael C Reade, Peter W J Harrigan, for the Refeeding Syndrome Trial Investigators Group**

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/m² *vs* ≤18 kg/m²). 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).

Lancet Respir Med 2015; 3: 943–52

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See Comment page 904

*see appendix for the full list of investigators

Northern Clinical School Intensive Care Research Unit (G S Doig PhD, F Simpson PhD, P T Heighes MNE), **and The Boden Institute of Obesity, Nutrition Exercise, and Eating Disorders** (Prof I D Caterson FRACP), **University of Sydney, Sydney, NSW, Australia; School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia** (Prof R Bellomo MD); **New South Wales Health, Pathology, Sydney, NSW, Australia** (D Chesher PhD); **Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, QLD,**

Doig GS, Simpson F, Heighes PT et al. 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 Respiratory Medicine* 2015;3:943-952.

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Key exclusion criteria:

- Other explanations for phos drop (ICU admit post-parathyroidectomy, recent RRT, use of phosphate binders for hyperphosphataemia, diabetic ketoacidosis, hyperosmolar non-ketotic coma etc.)

Study Intervention

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Pragmatic Standard Care:

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.

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If serum phosphate did not need to be replaced by the end of this 2 day period (defined by study protocol, Appendix 3a) caloric intake was gradually returned to normal by following the study Gradual Return to Normal Intake Protocol (Appendix 3b).

All patients

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	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 [##].*

Taylor BE, Huey WY, Buchman TG, Boyle WA, Coopersmith CM. 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(2):198-204.

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- 339 patients were enrolled and randomised
- At time of enrolment:
  - Mean age was 60 years,
  - 40% were female
  - Mean APACHE II score was 18.0
  - 96% of patients had *at least two key signs* associated with Refeeding Syndrome
    - *hypophosphatemia plus:* hypokalemia (26.6%), hyperglycemia (51.7%), respiratory failure (91.2%), or required diuretics for the management of fluid balance (29.6%).

Baseline balance

	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/m²)		
Mean	28 (6·7)	28 (7·3)
<18 kg/m²	5 (3%)	6 (4%)
SGA		
Muscle wasting	1·3 (0·7)	1·4 (0·8)
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Baseline balance

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)*	5·0 (3·8)†
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History of high alcohol intake‡	22 (13%)	18 (11%)

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Maximum insulin infusion rate (units per h)	5·6 (4·3)*	5·0 (3·8)†
Semipermanent (surgically placed) feeding tube	11 (7%)	19 (12%)
History of high alcohol intake‡	22 (13%)	18 (11%)

Baseline balance

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)*	5·0 (3·8)†
Semipermanent (surgically placed) feeding tube	11 (7%)	19 (12%)
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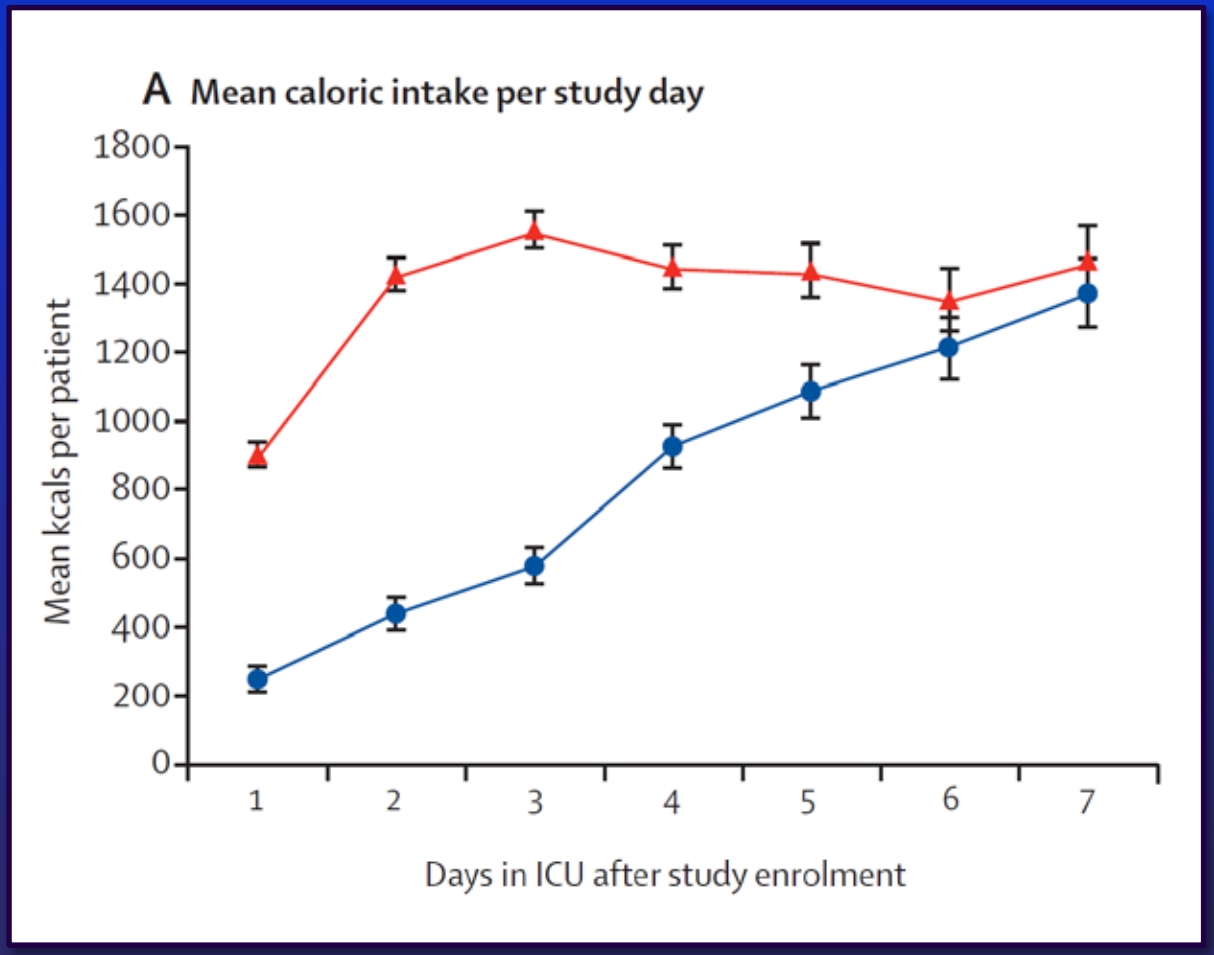
Process measures

Process measures



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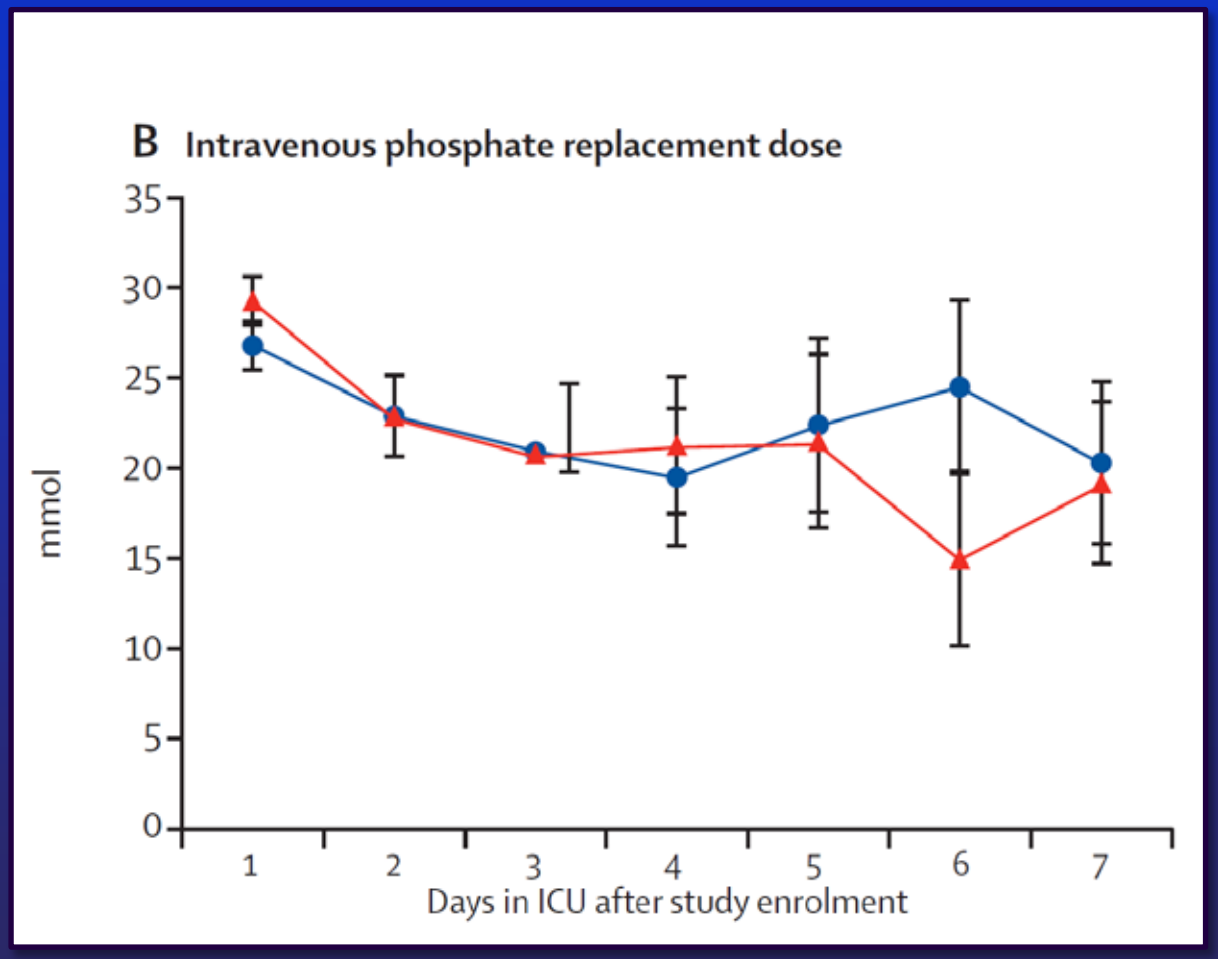
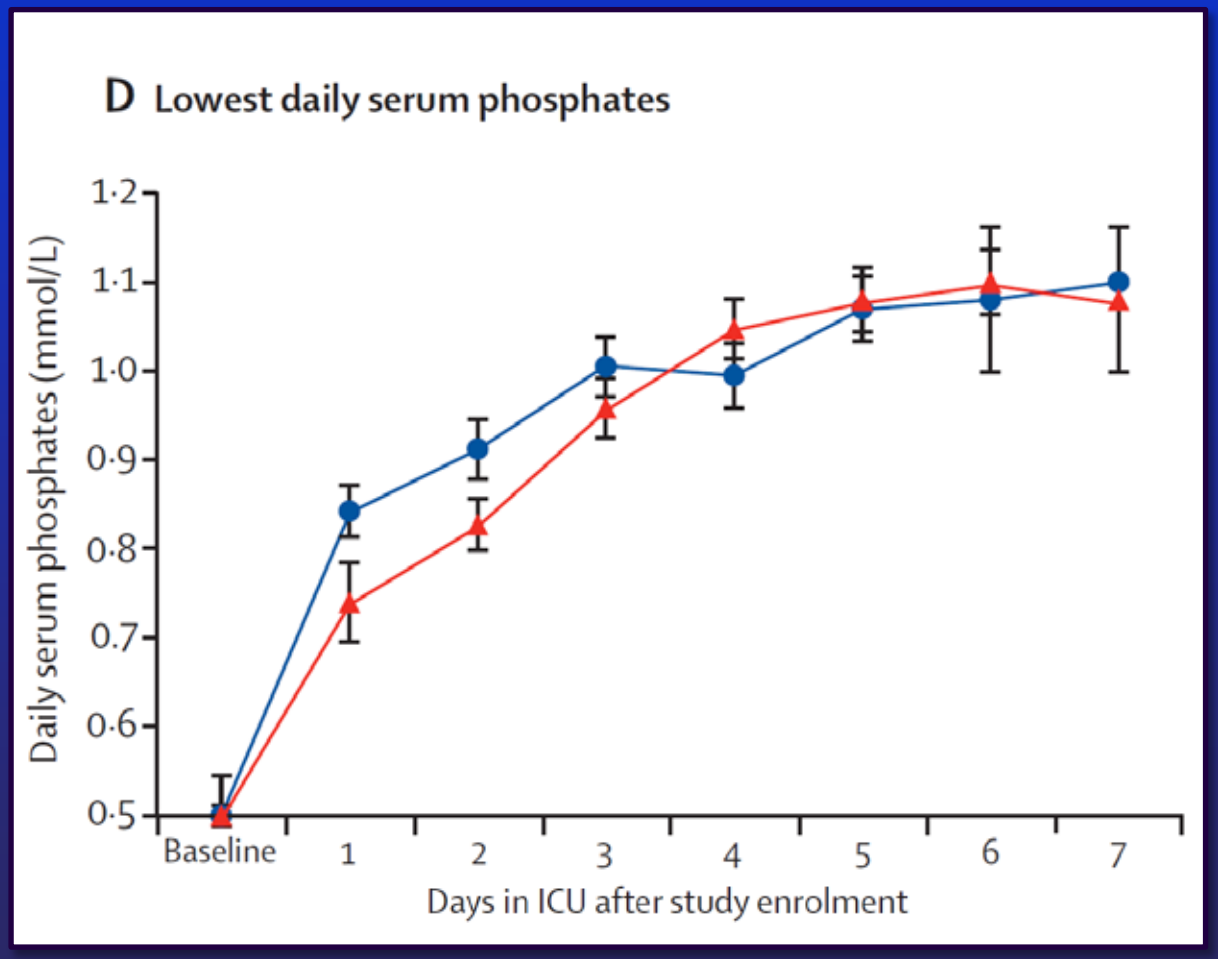


Caloric Management

Standard care

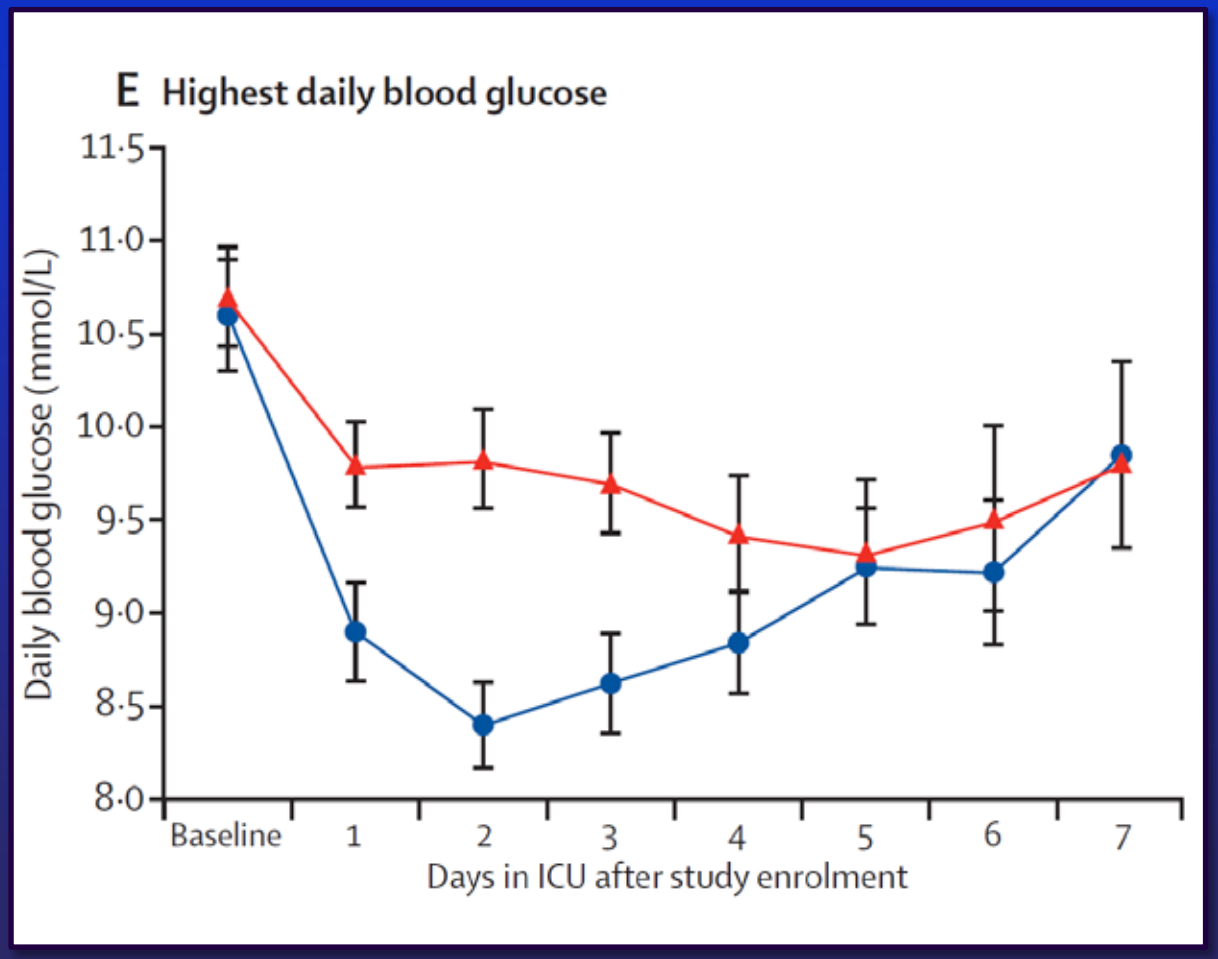
Process measures



Caloric Management

Standard care

Process measures



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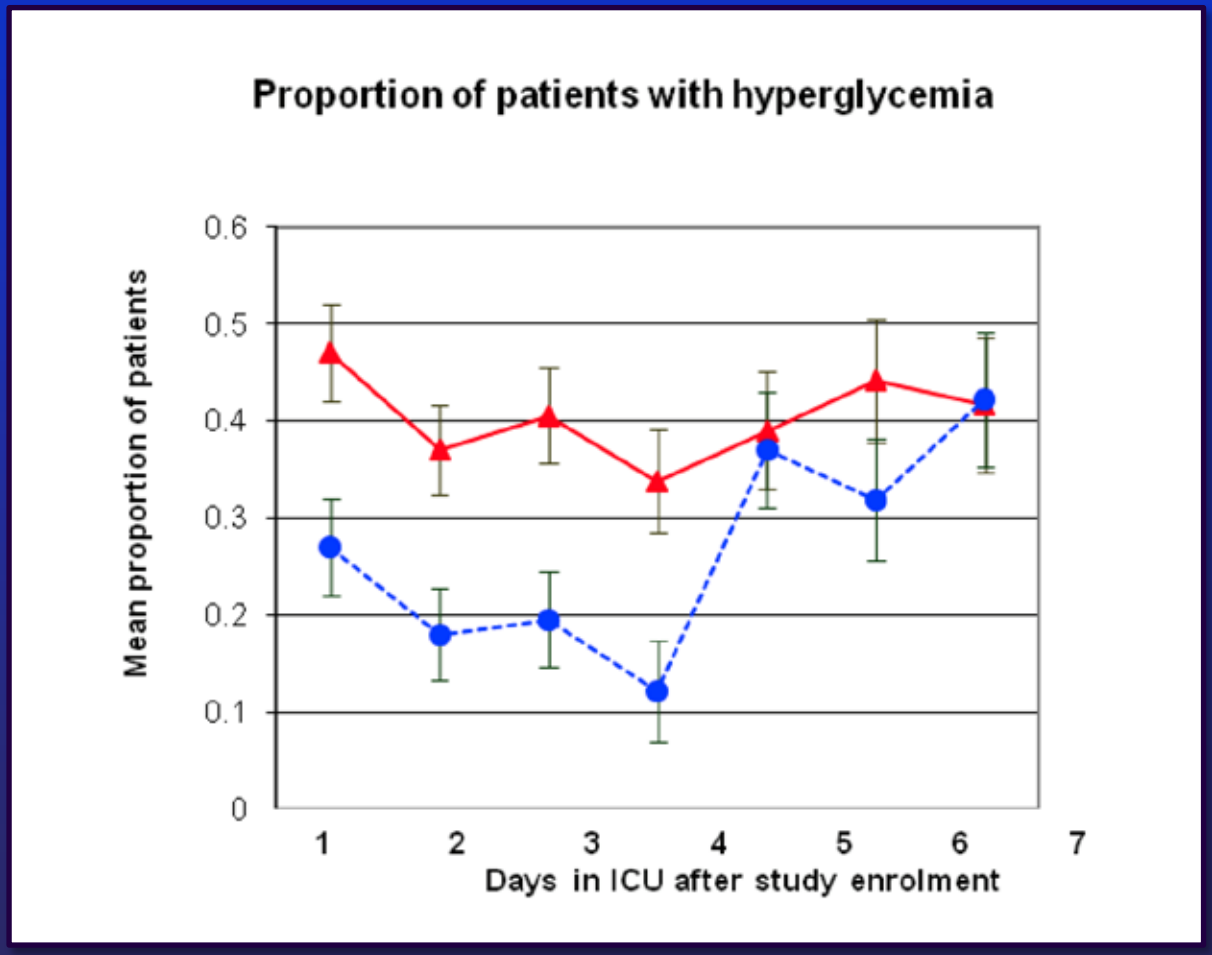
Standard care

Process measures



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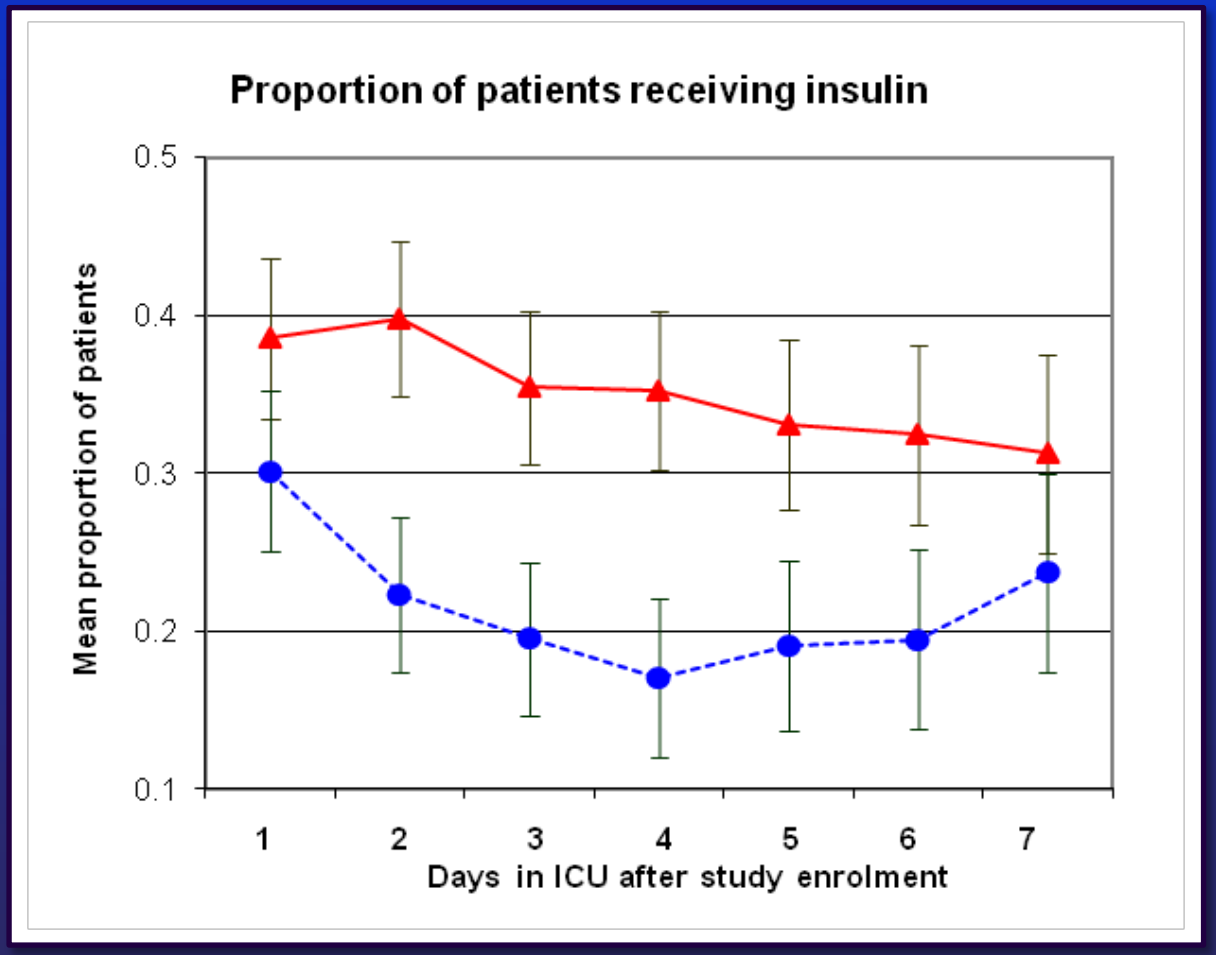

Process measures

Caloric restriction led to:

Process measures

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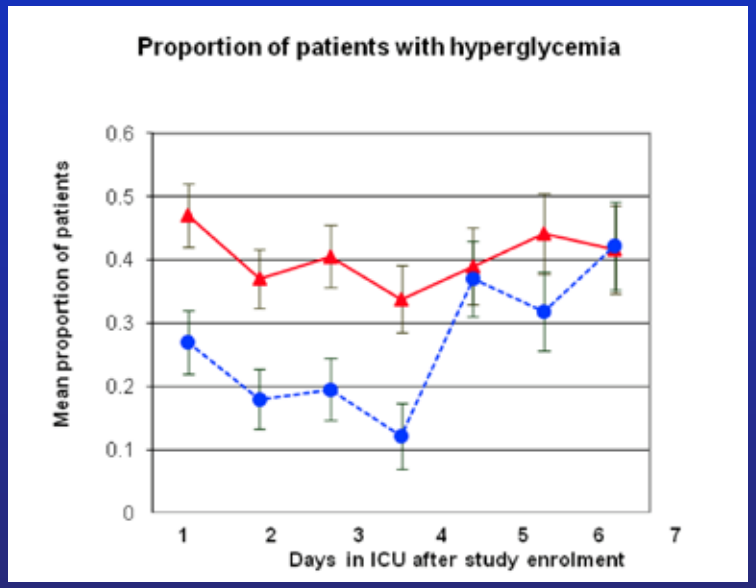
Significantly less hyperglycaemia



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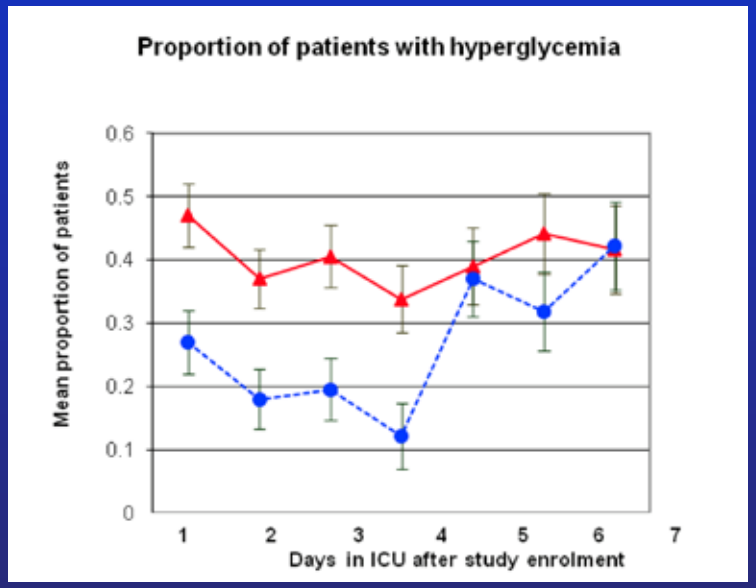
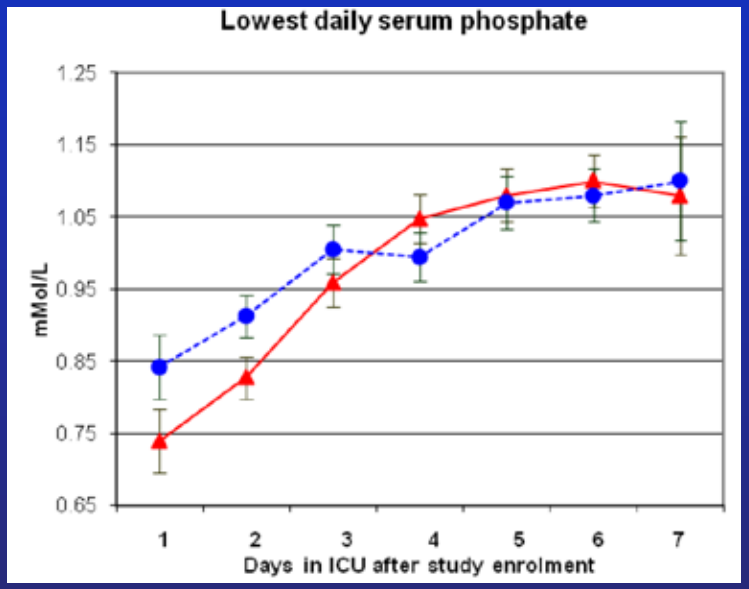


Significantly better serum phosphate



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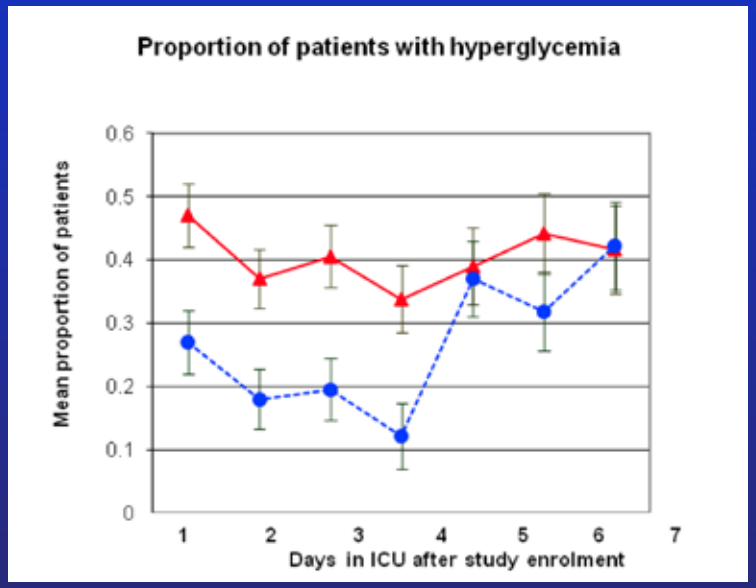

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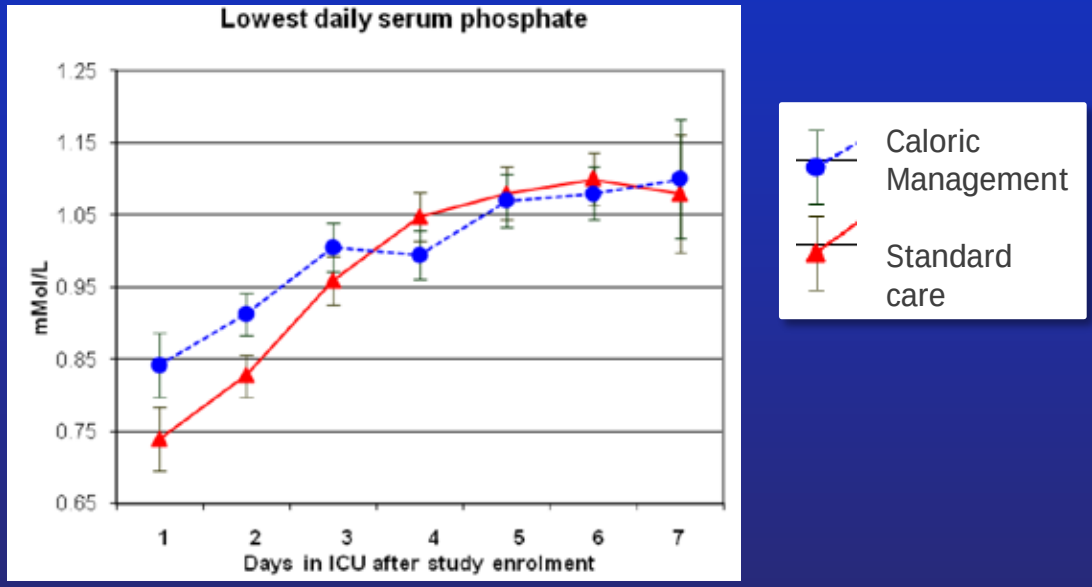

- Hyperglycaemia predisposes to infections

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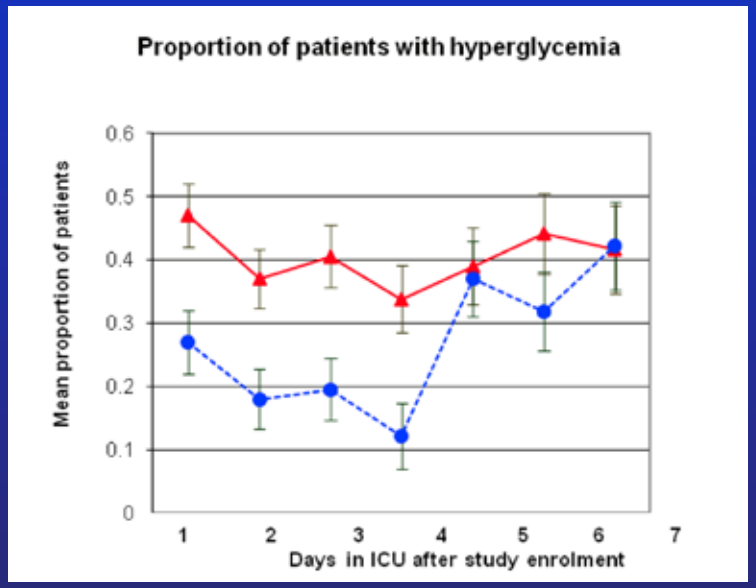

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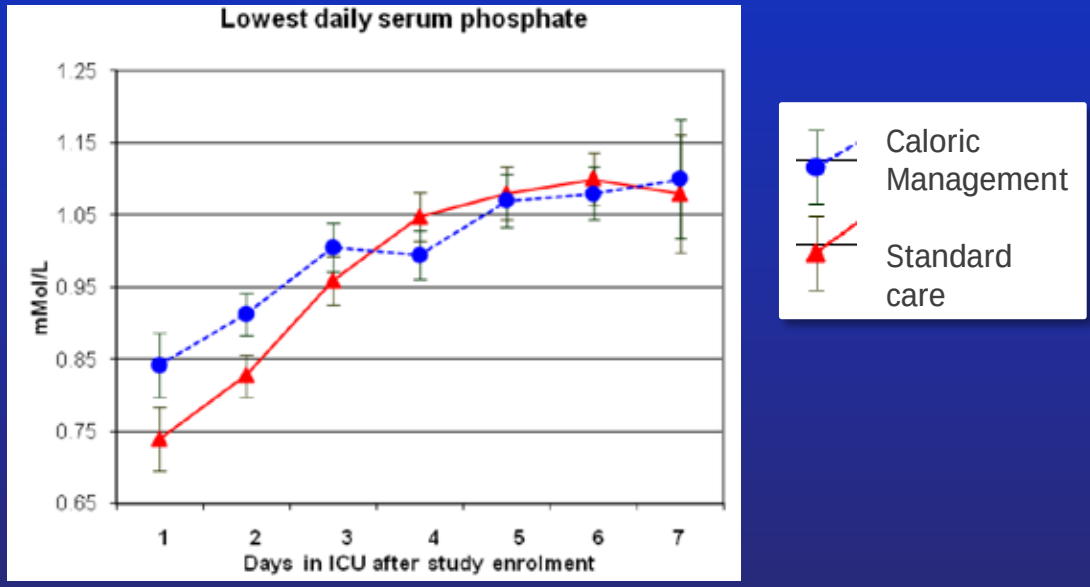

- Hyperglycaemia predisposes to infections
- Hypophosphatemia compromises white cell function
  - impaired chemotactic, phagocytic and bactericidal ability

Infectious complications

Infectious complications

	Standard care (165 patients)	Caloric management (166 patients)	Risk difference (95% CI)	p value
Catheter*	4 (2%)	4 (2%)	0·0% (–10·7 to 10·7)	1·00
Catheter tip*	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†	52 (32%)	35 (21%)	–10·4% (–19·8 to –1·1)	0·0342
CPIS probable‡ pneumonia	34 (21%)	25 (15%)	–5·5% (–13·8 to 2·7)	0·20
CPIS confirmed§ pneumonia	22 (13%)	14 (8%)	–4·9% (–11·6 to 1·2)	0·16
Any major infection¶	27 (16%)	13 (8%)	–8·5% (–15·5 to –1·6)	0·0187

CPIS = Clinical Pulmonary Infection Score. **Major Infection** = attributable excess mortality > 15%.

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Cohen J, Cristofaro P, Carlet J, Opal S. New method of classifying infections in critically ill patients. *Critical Care Medicine* 2004;32(7):1510-1526.

Composite primary outcome

Days alive after discharge from ICU (ICU free days):

Composite primary outcome

Days alive after discharge from ICU (ICU free days):

- Overall survival time (60 day follow-up)
- Alive / dead at 60 day follow-up
- Time spent in ICU
- Alive / dead at ICU discharge

Composite primary outcome

Days alive after discharge from ICU (ICU free days):

- Overall survival time (60 day follow-up)

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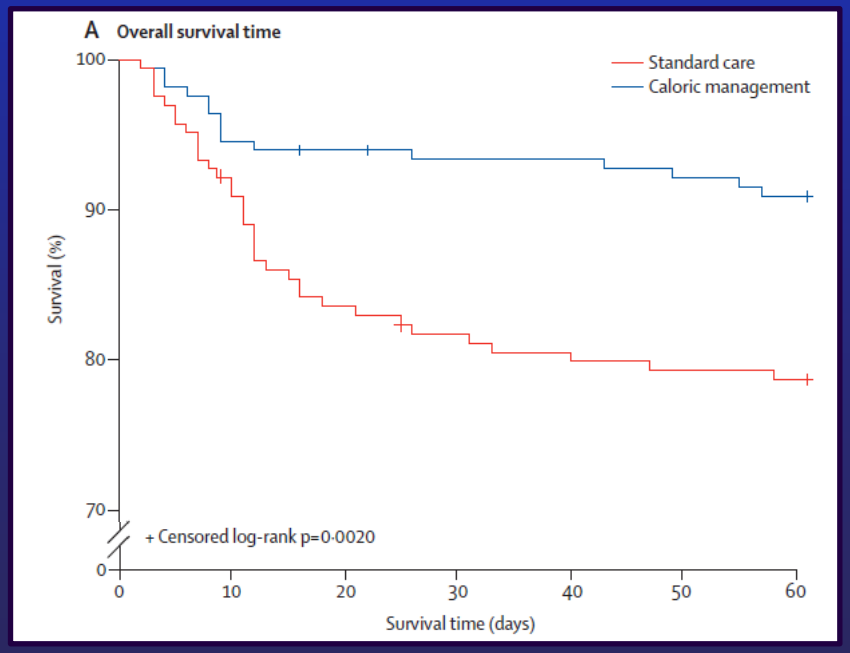

Composite primary outcome

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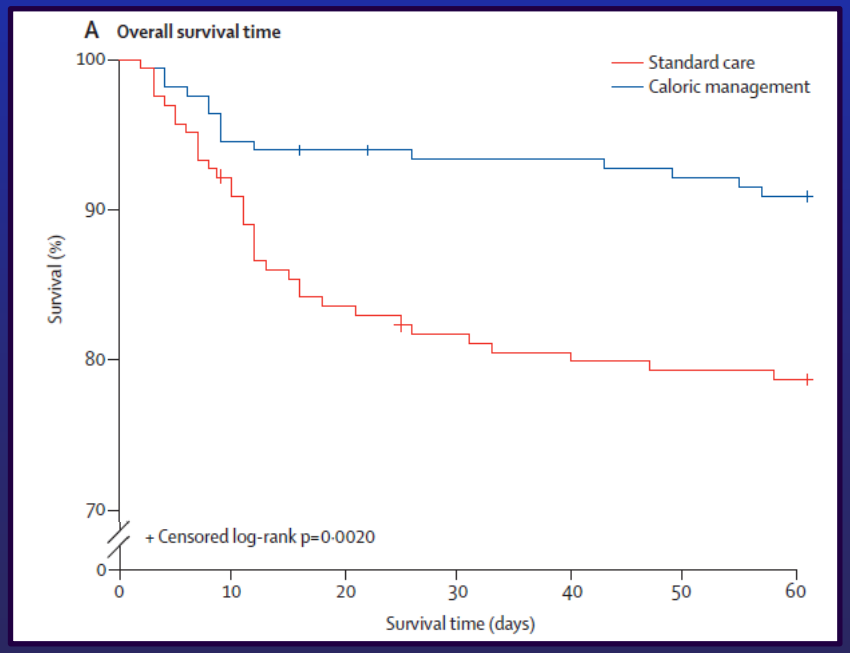
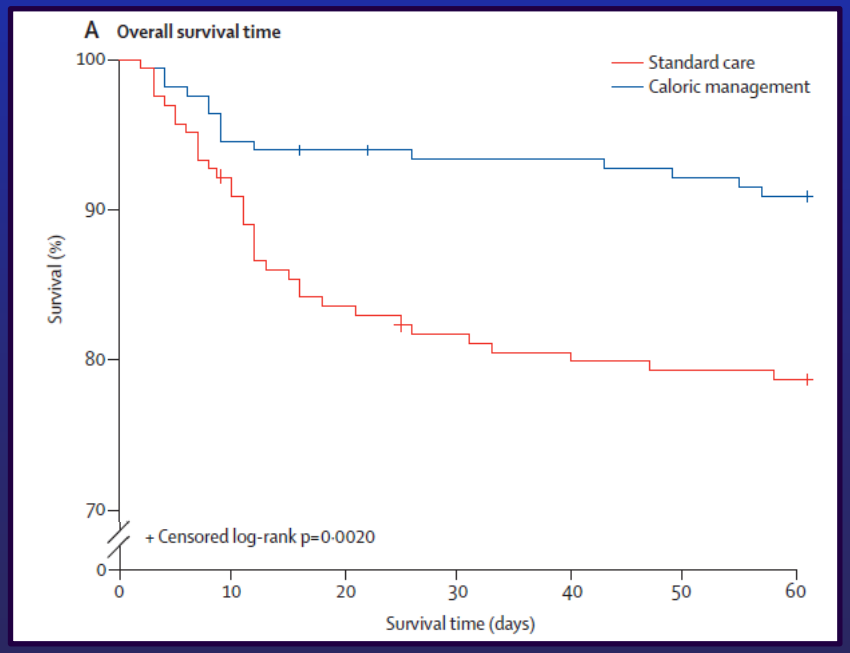
- Overall survival time (60 day follow-up)
  - Control 48·9 vs. 53·6 days , P=0·002 Log-Rank Test



Composite primary outcome

Days alive after discharge from ICU (ICU free days):

- Overall survival time (60 day follow-up)
  - Control 48·9 vs. 53·6 days , P=0·002 Log-Rank Test
- Alive / dead at 60 day follow-up



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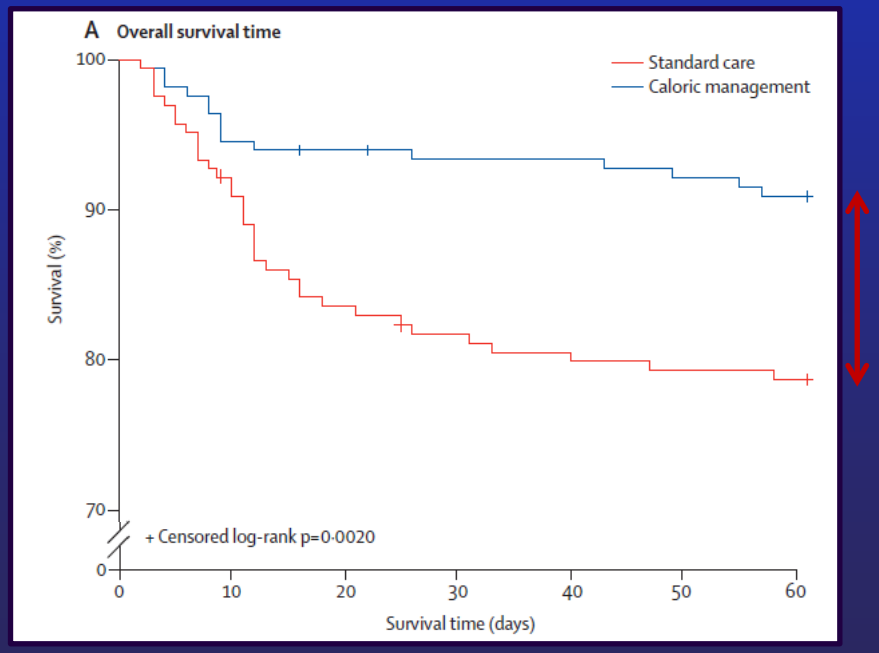
- Overall survival time (60 day follow-up)
  - Control 48·9 vs. 53·6 days , P=0·002 Log-Rank Test
- Alive / dead at 60 day follow-up



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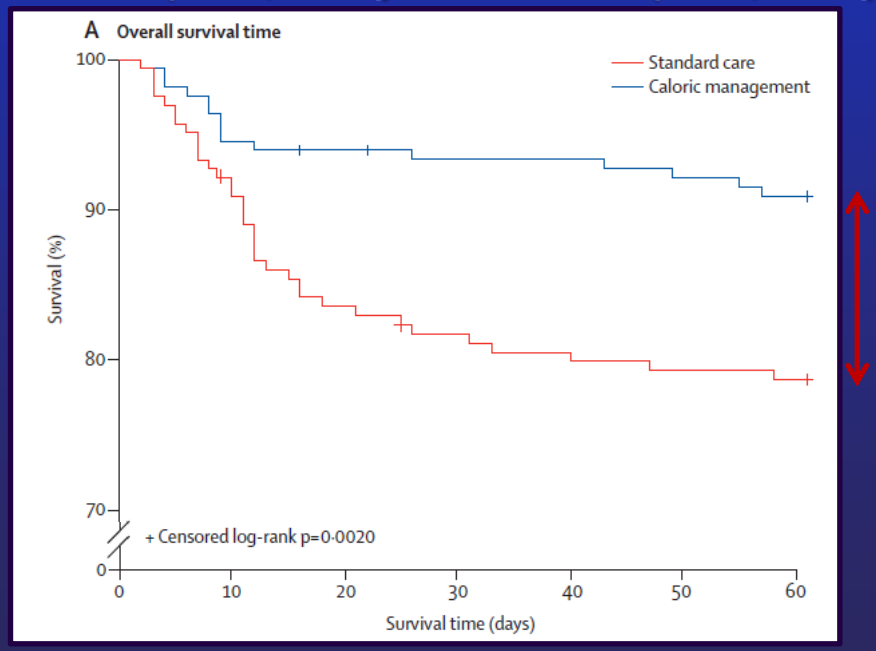

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- Alive / dead at ICU discharge
  - Control 90.9% (150/165) vs. 94.6% (157/166) survival , P=0.21

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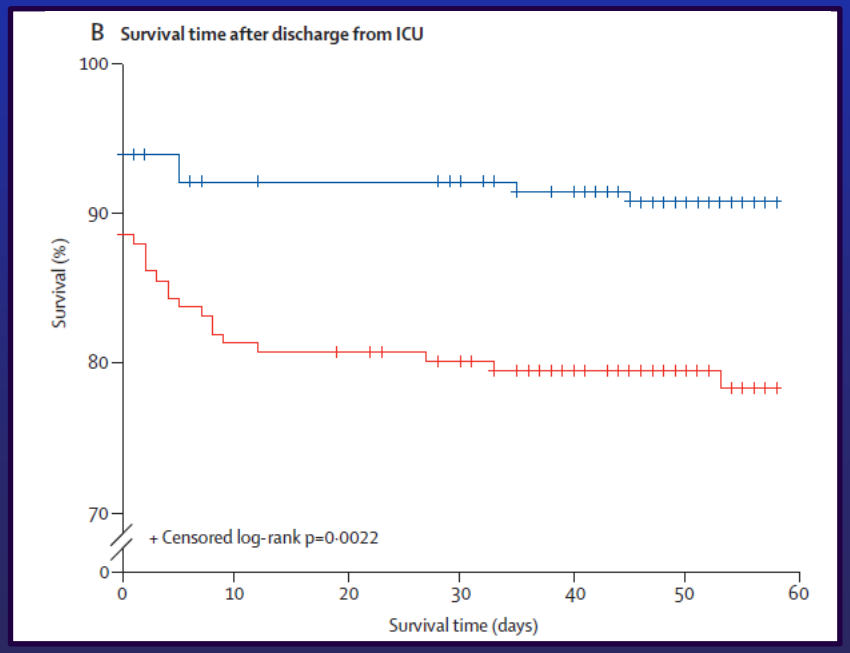
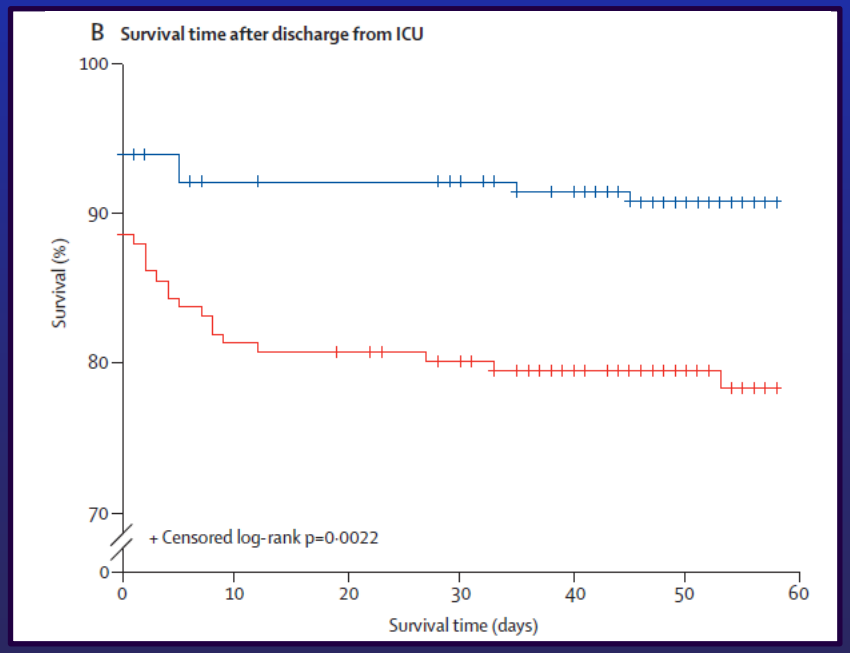


Composite primary outcome

Days alive after discharge from ICU (ICU free days):

- Control 39.9 vs. 44.8 days, P=0.21



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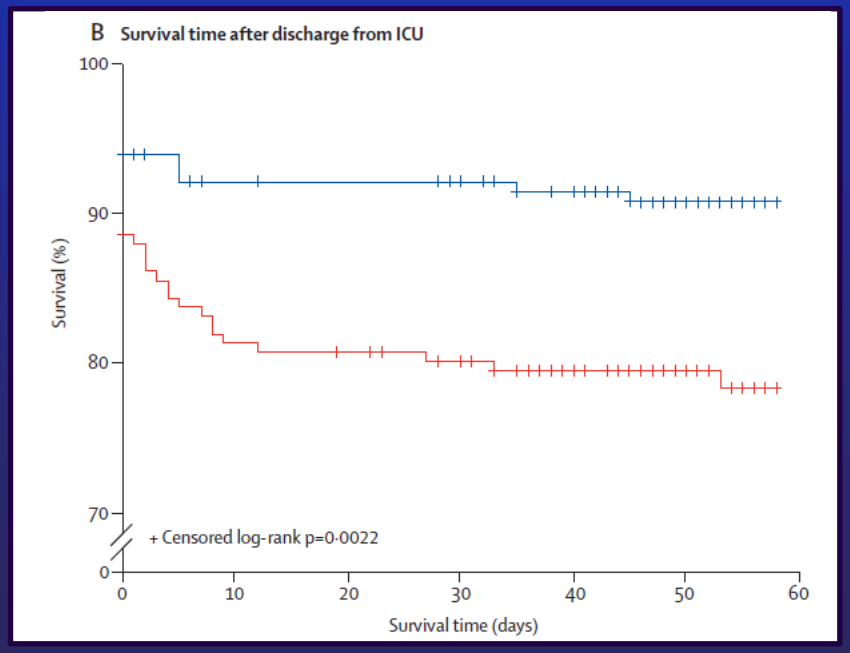

Composite primary outcome

Days alive after discharge from ICU (ICU free days):

- Control 39.9 vs. 44.8 days, P=0.21

But:

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Composite primary outcome

Days alive after discharge from ICU (ICU free days):

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More patients were *discharged alive from hospital*:

- Control 81.8 (135/165) vs. 91% (151/166), P=0.02

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More patients were *alive at 60 day follow-up*:

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More patients were *discharged alive from hospital*:

- Control 81.8 (135/165) vs. 91% (151/166), P=0.02

More patients were *alive at 60 day follow-up*:

- Control 78.5% (128/163) vs. 90.8% (149/164) survival , P=0.002

More patients were *alive at 90 day follow-up*:

- Control 78.5% (128/163) vs. 87.2% (143/164), P=0.041

Summary

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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.

See www.EvidenceBased.net/Refeeding for complete details, reported in Statistical Analysis Plan.

Caloric Management Protocol

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.
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See www.EvidenceBased.net/Refeeding for complete details, reported in Statistical Analysis Plan.

All patients

To ensure any differences in outcomes were attributable to the primary intervention (caloric management), we implemented the same phosphate replacement protocol in all patients.

We also recommended 100mg Thiamine for all patients, prior to phosphate replacement.

	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 [##].*

Taylor BE, Huey WY, Buchman TG, Boyle WA, Coopersmith CM. 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(2):198-204.

Baseline balance

	Standard care (n=165 patients)	Caloric management (n=166 patients)
(Continued from prevous page)		
Source of admission to ICU		
Operating room	60 (36%)	57 (34%)
Emergency department	38 (23%)	50 (30%)
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)

Follow-up