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

Dr. Gordon S. Doig,
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www.EvidenceBased.net/Refeeding

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I will also show this QR code at the end of the talk

Outline

- Brief history of RF
- Context for our clinical trial
- Key elements of design
- Main results
- Summary

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- As a *syndrome*, patients present with a constellation of signs however hypophosphatemia is considered to be the “hallmark sign” of RS.
- Recommended treatment for RS involves electrolyte replacement, thiamine supplementation and slow gradual achievement of caloric requirements.

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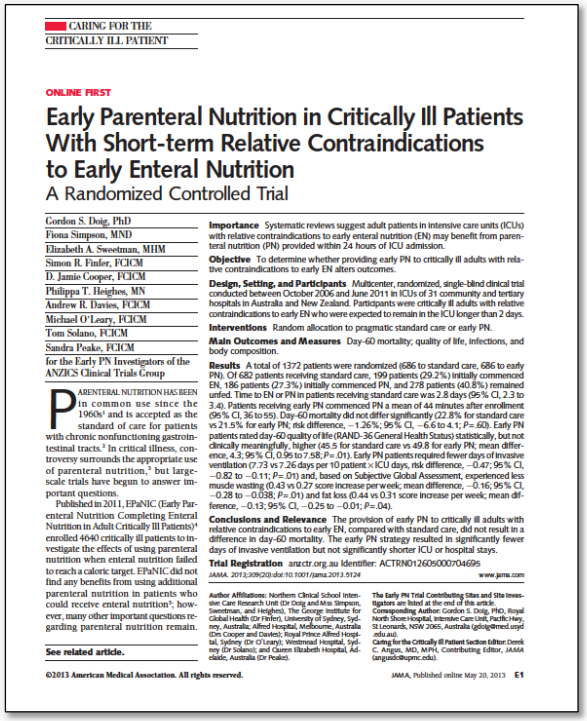

CARING FOR THE CRITICALLY ILL PATIENT

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
Elizabeth A. Sweetman, MHM
Simon R. Finfer, FCICM
D. Jamie Cooper, FCICM
Philippa T. Heighes, MN
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 2006 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, 199 patients (29.2%) initially commenced EN, 186 patients (27.3%) initially commenced PN, and 278 patients (40.8%) remained unfed. Time to EN or PN in patients receiving standard care was 2.8 days (95% CI, 2.3 to 3.4). Patients receiving early PN commenced PN a mean of 44 minutes after enrollment (95% CI, 36 to 55). Day-60 mortality did not differ significantly (22.8% for standard care vs 21.5% for early PN; risk difference, −1.26%; 95% CI, −6.6 to 4.1; $P=.60$). Early PN patients rated day-60 quality of life (RAND-36 General Health Status) statistically, but not clinically meaningfully, higher (45.5 for standard care vs 49.8 for early PN; mean difference, 4.3; 95% CI, 0.95 to 7.58; $P=.01$). Early PN patients required fewer days of invasive ventilation (7.73 vs 7.26 days per 10 patient × ICU days, risk difference, −0.47; 95% CI, −0.92 to −0.11; $P=.01$) and, based on Subjective Global Assessment, experienced less muscle wasting (0.43 vs 0.27 score increase per week; mean difference, −0.16; 95% CI, −0.28 to −0.038; $P=.01$) and fat loss (0.44 vs 0.31 score increase per week; mean difference, −0.13; 95% CI, −0.25 to −0.01; $P=.04$).

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: ACTRN01260500070469

JAMA. 2013;309(20):doi:10.1001/jama.2013.5124 www.jama.com

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 Contributing Sites and Site Investigators are listed at the end of this article.

Corresponding Author: Gordon S. Doig, PhD, Royal North Shore Hospital, Intensive Care Unit, Pacific Hwy, St Leonards, NSW 2065, Australia (gdoig@med.usyd.edu.au).

Caring for the Critically Ill Patient Section Editor: Derek C. Angus, MD, MPH, Contributing Editor, *JAMA* (angusdc@upmc.edu).

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Site selection visits commenced in 2006.

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- We wanted to understand current practices for PN: patient selection, composition, dosing.
  - FS asked scripted questions about nutritional practices, GSD asked scripted questions about other aspects of practice and research resources.
- At the first 2 hospitals we visited, FS asked how often patients with RS were encountered and Intensivists responded "Never".

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FS: How often do you encounter Refeeding Syndrome in your ICU?

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100% (7/7) replied: “Yes”

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51.5% (17/33) responded “No”

48.5% (16/33) responded “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.

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Patients who had caloric intake reduced had a significantly shorter ICU stay (RR=0.43, p<0.001), a reduced duration of mechanical ventilation (RR=0.27, p<0.001) and a reduced need for antibiotics (RR=0.45, p<0.001).

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,**

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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

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.

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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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- 13 participating hospitals throughout Australia and New Zealand.
- 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)
Fat loss	1·4 (0·7)	1·5 (0·8)

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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)
Fat loss	1·4 (0·7)	1·5 (0·8)

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%)
History of high alcohol intake‡	22 (13%)	18 (11%)

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Process measures

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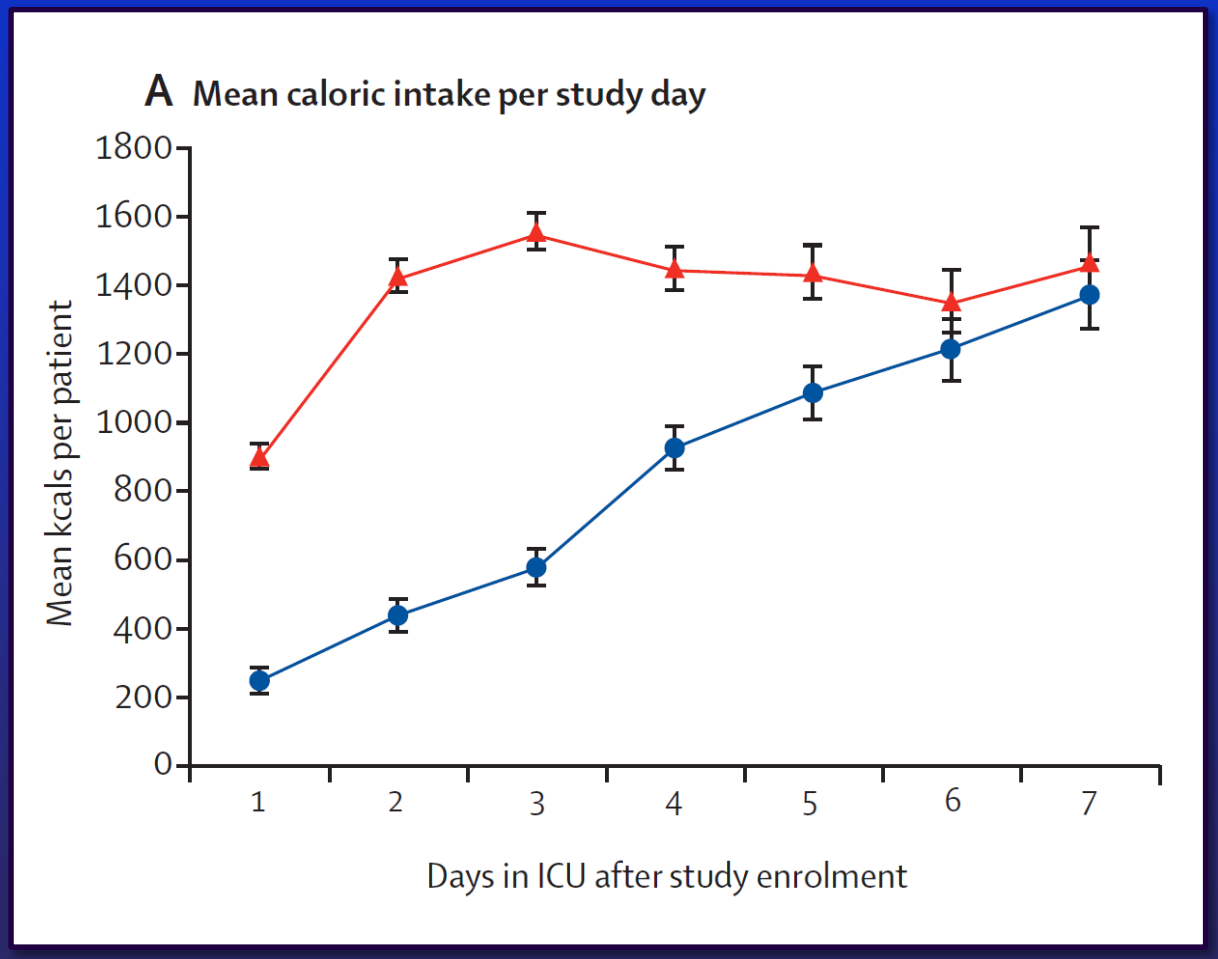

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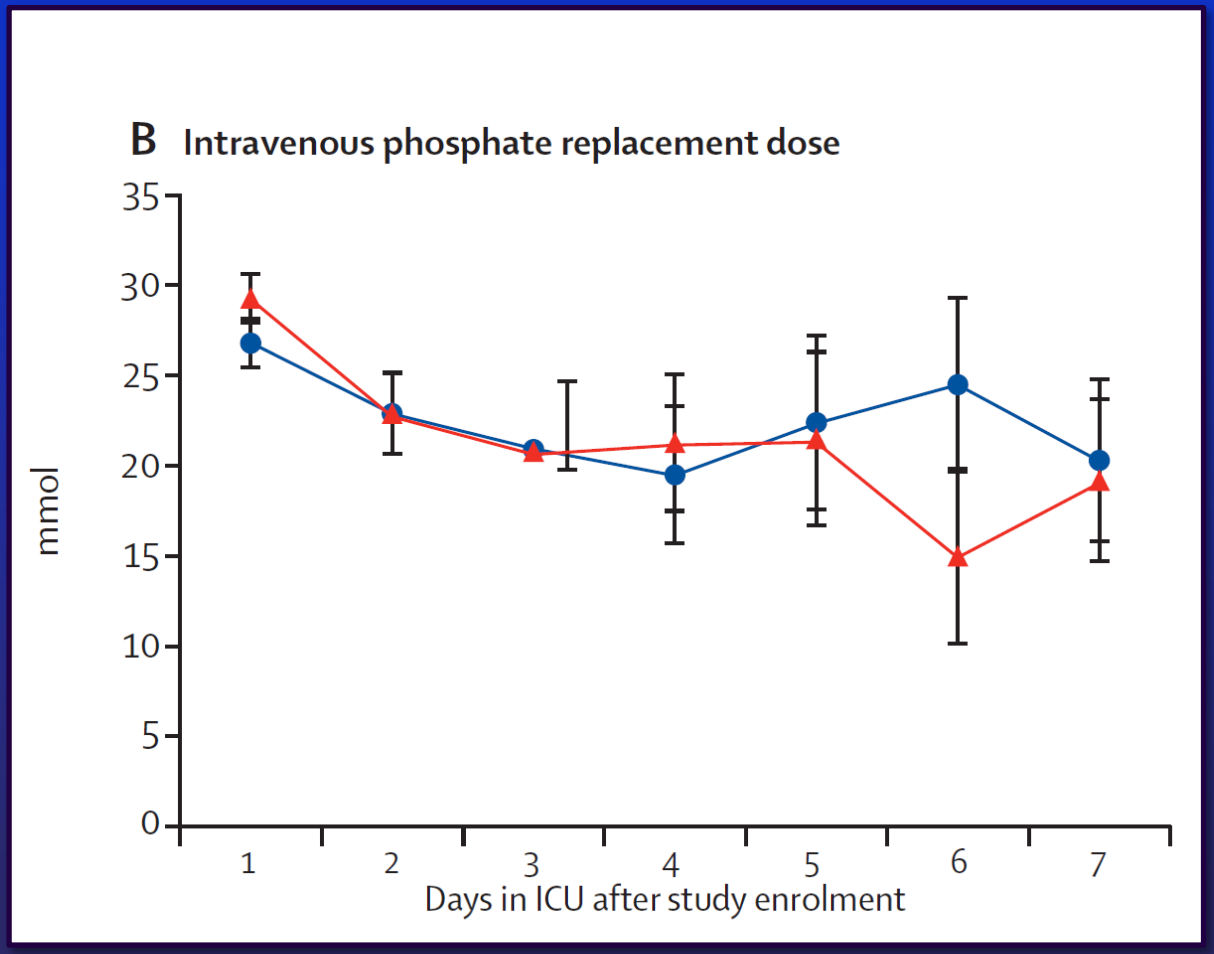
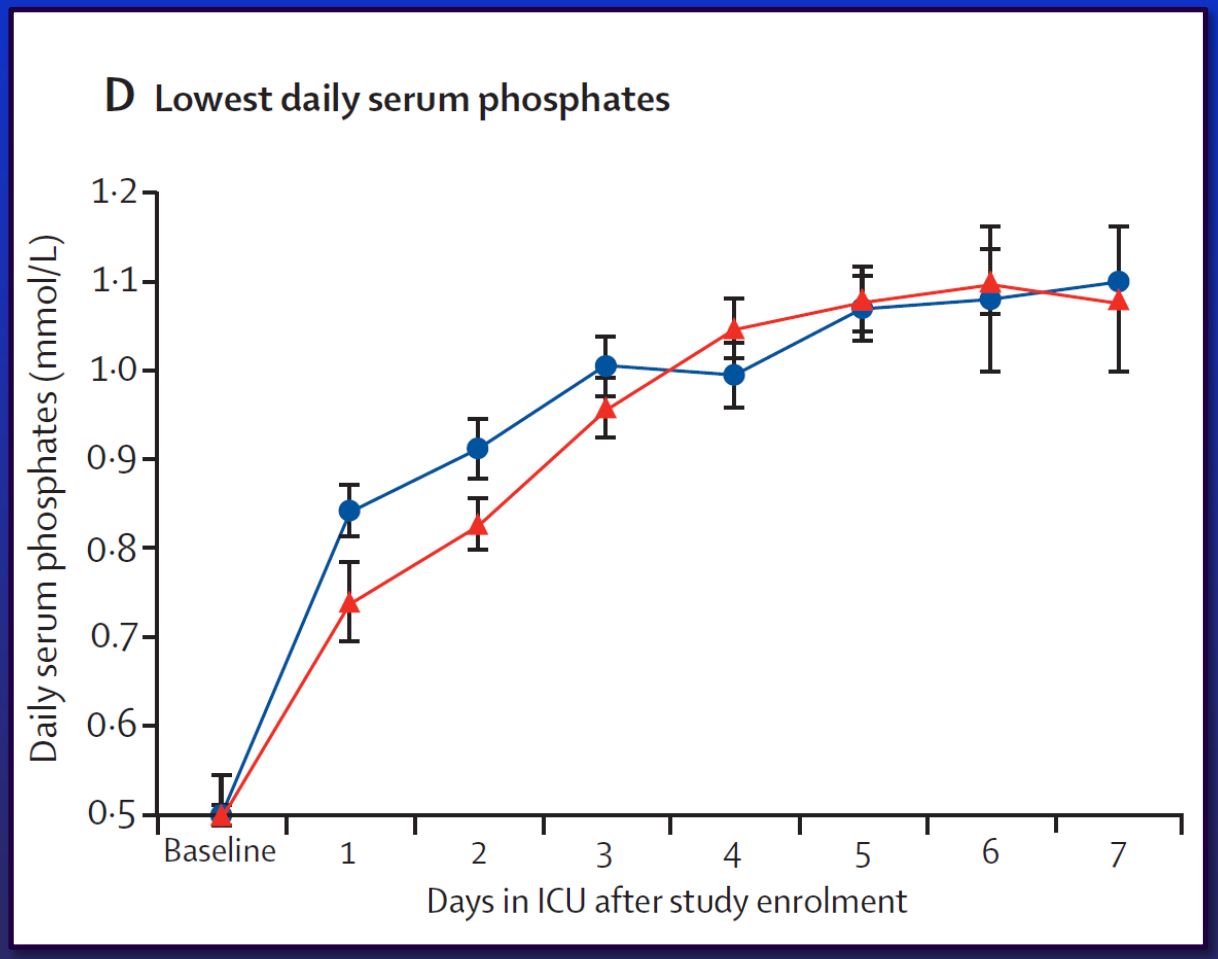


Caloric Management

Standard care

Process measures



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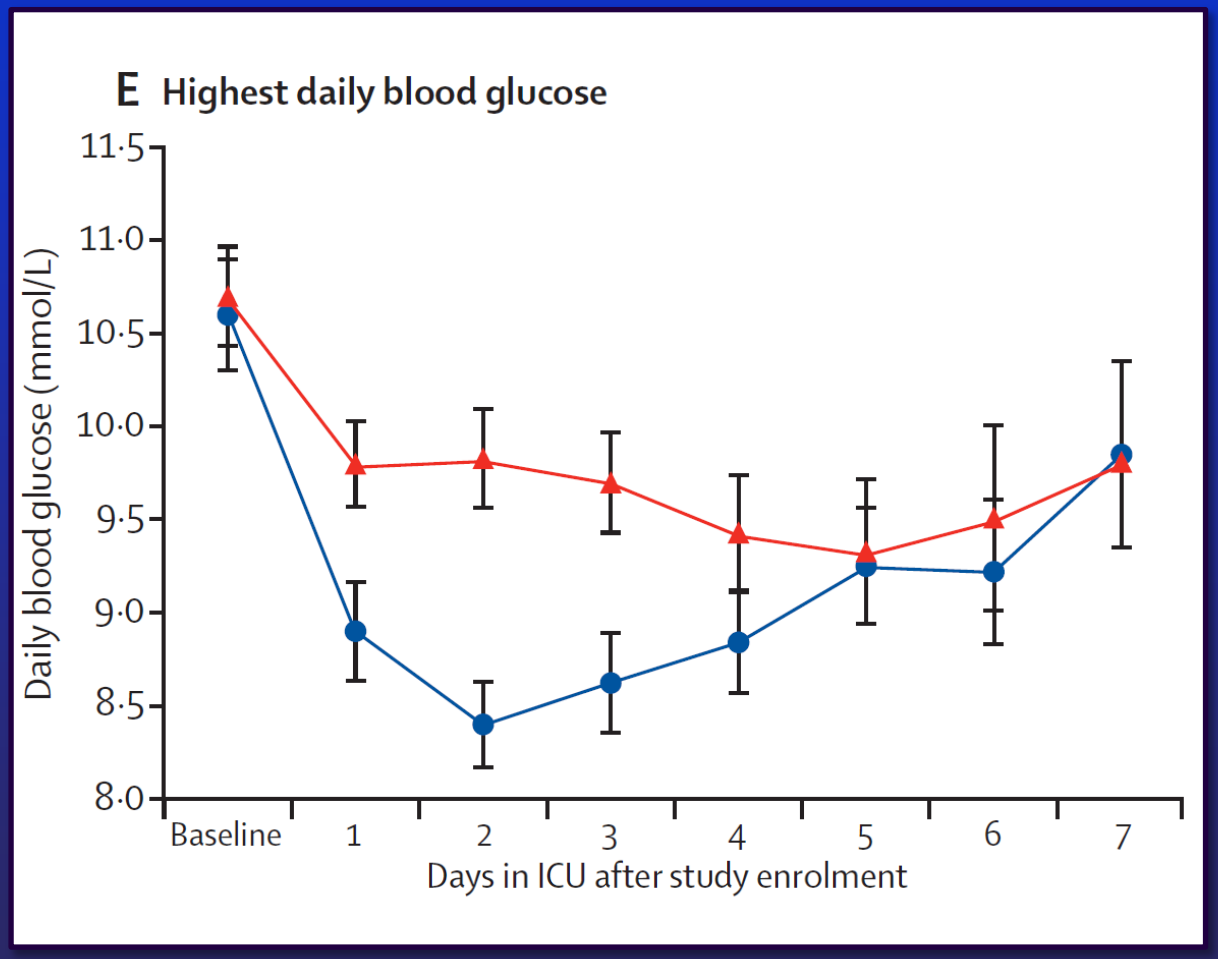

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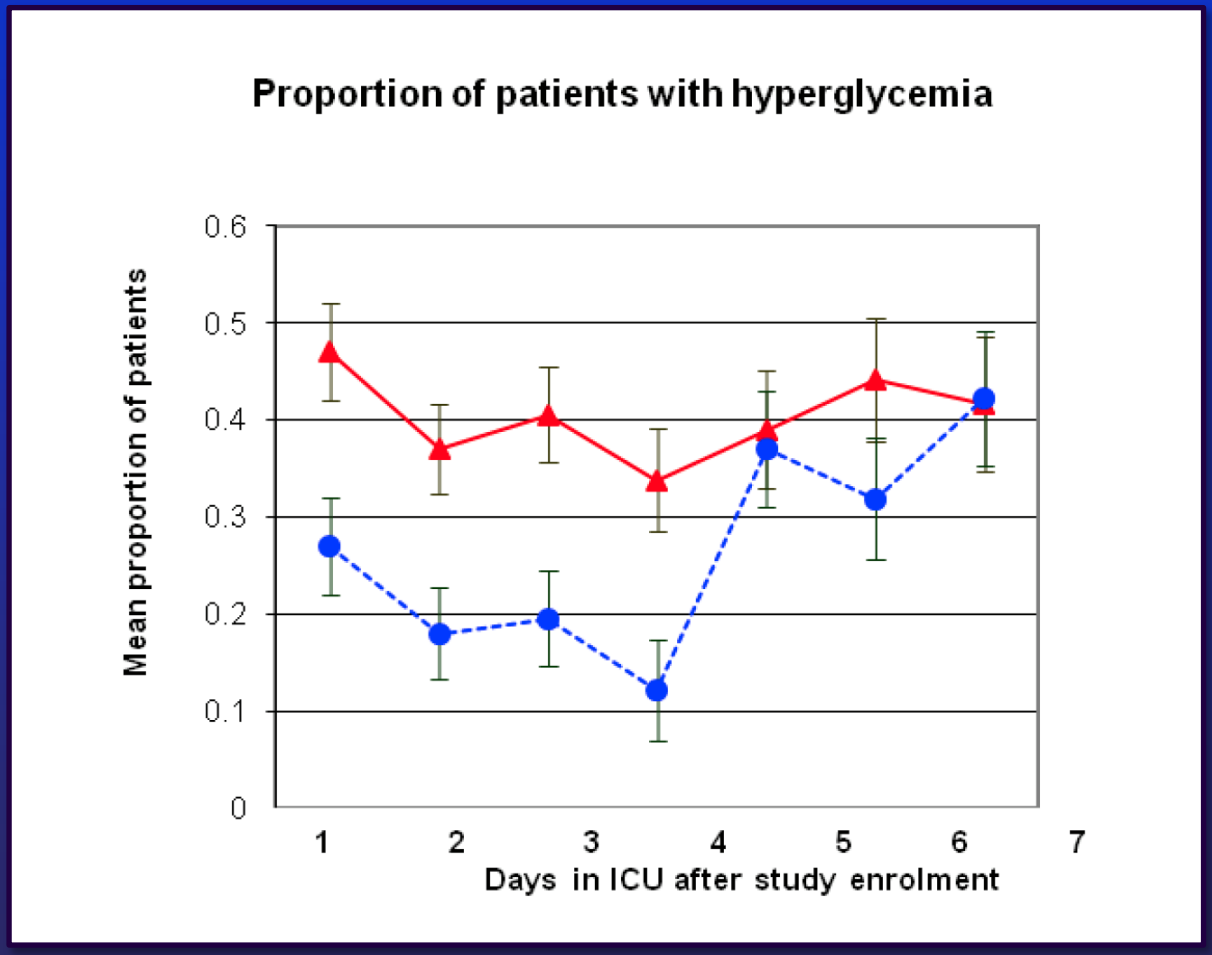
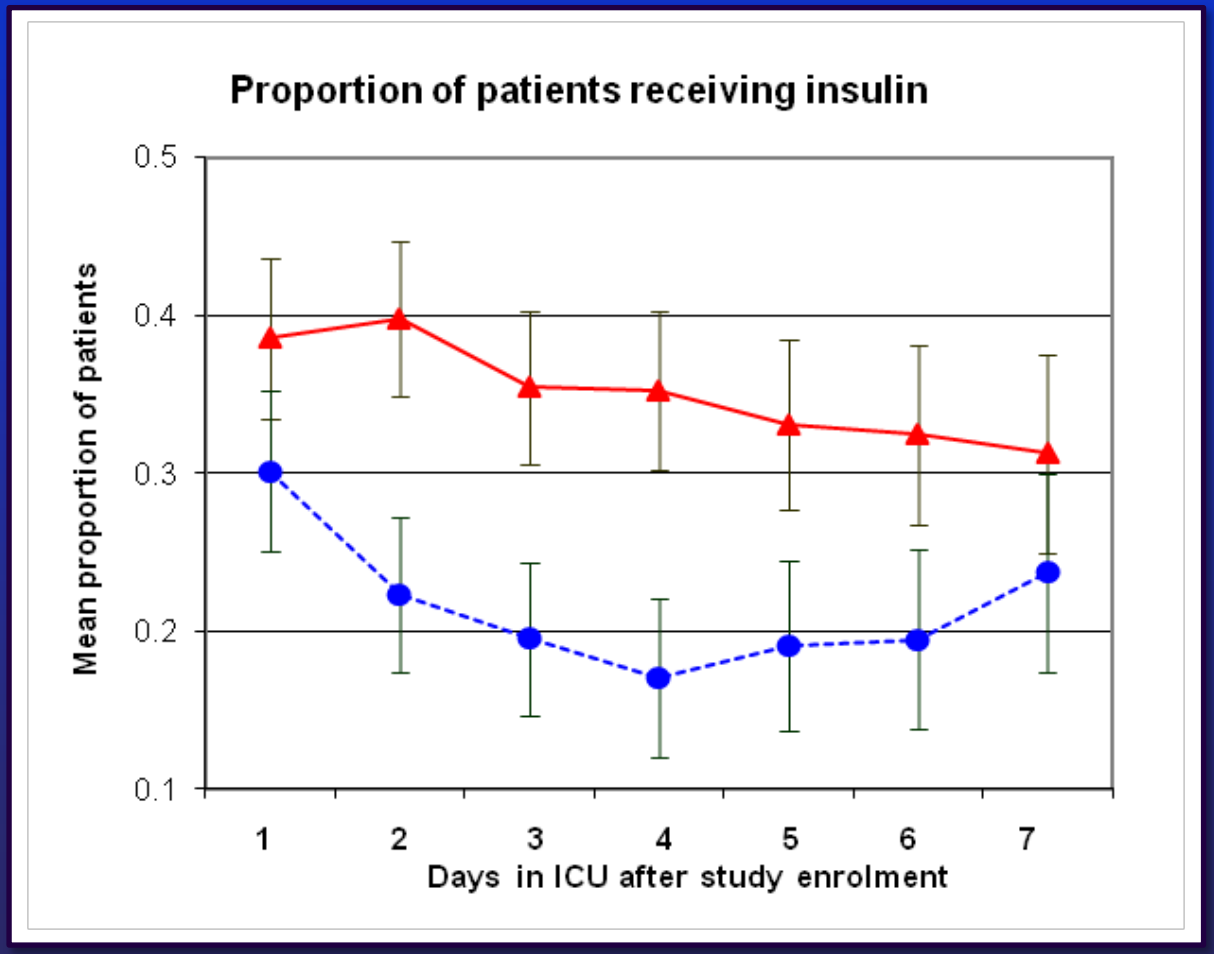


Process measures



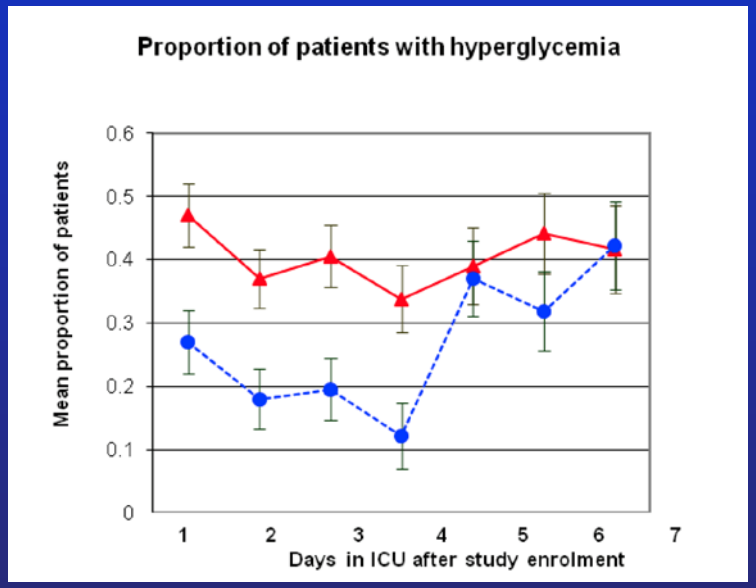
Process measures

Caloric restriction led to:

Process measures

Caloric restriction led to:

Significantly less hyperglycaemia



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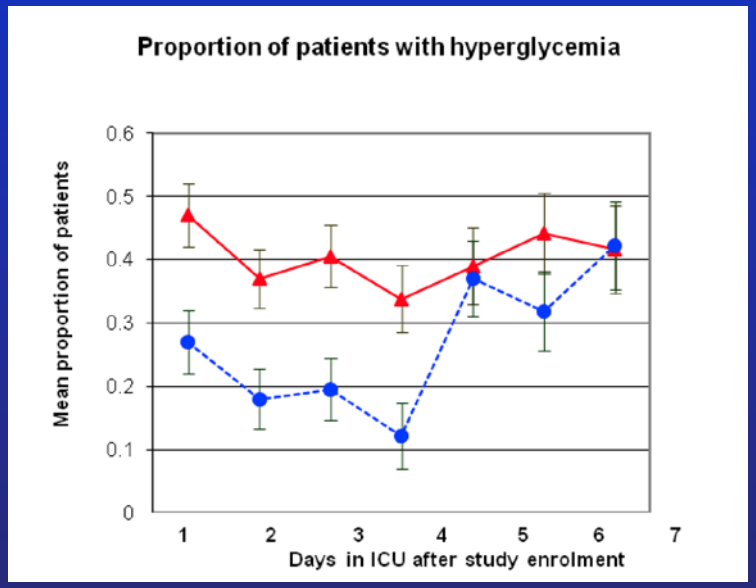
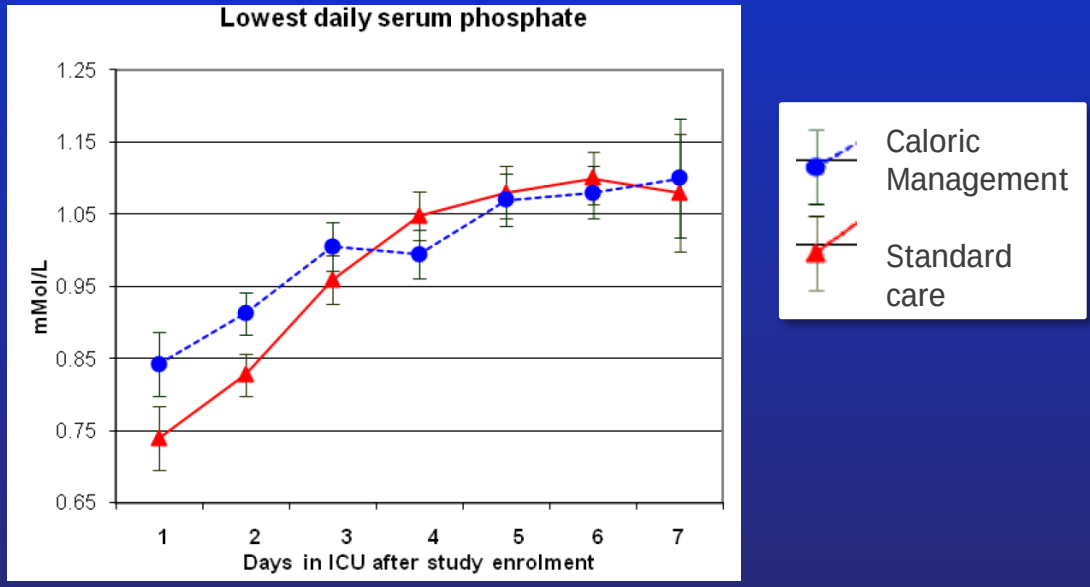


Significantly better serum phosphate



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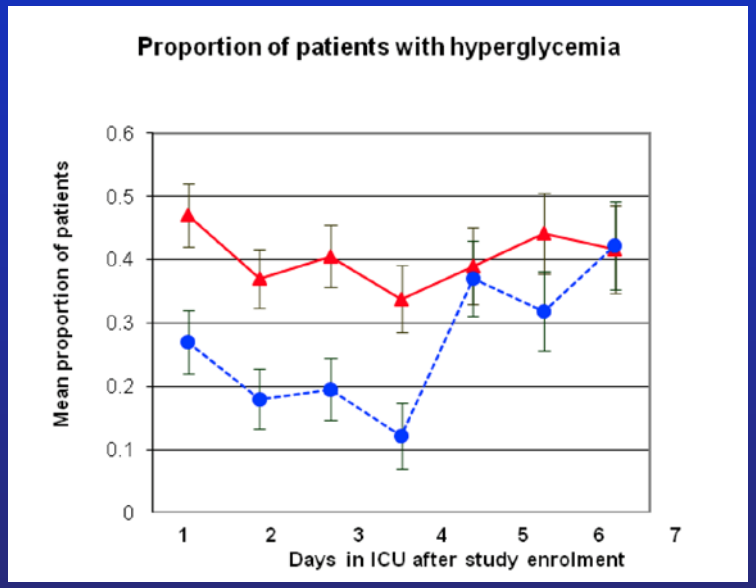

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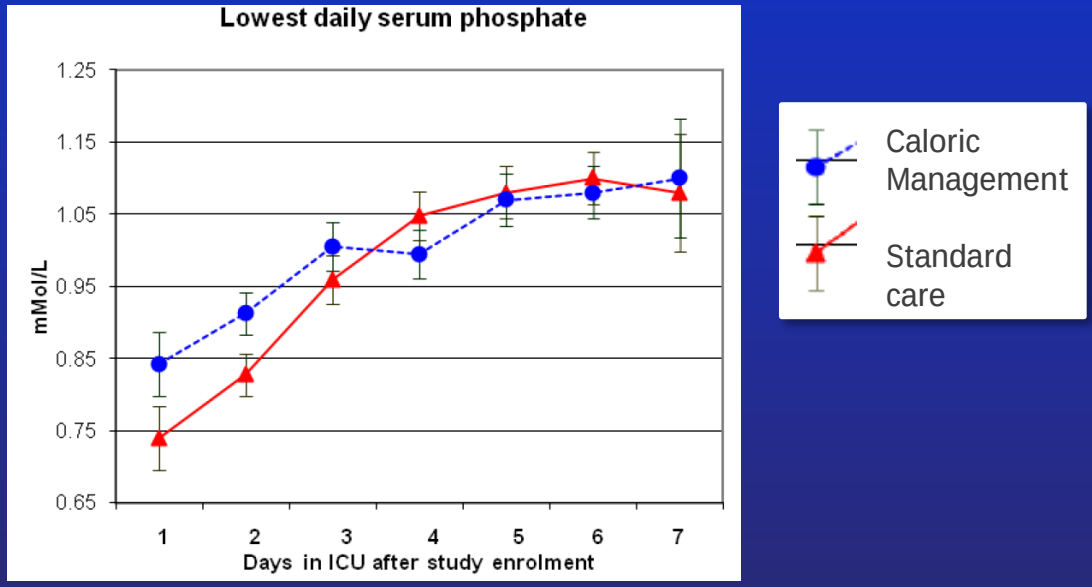

- Hyperglycaemia predisposes to infections

Process measures

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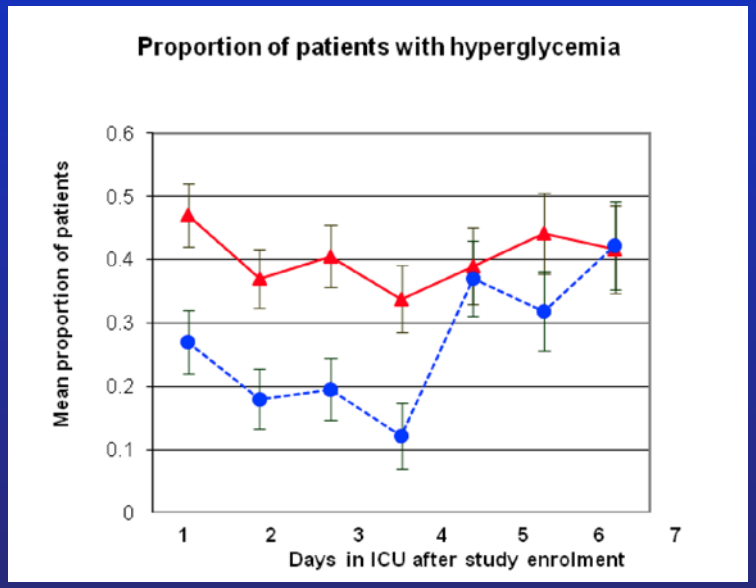

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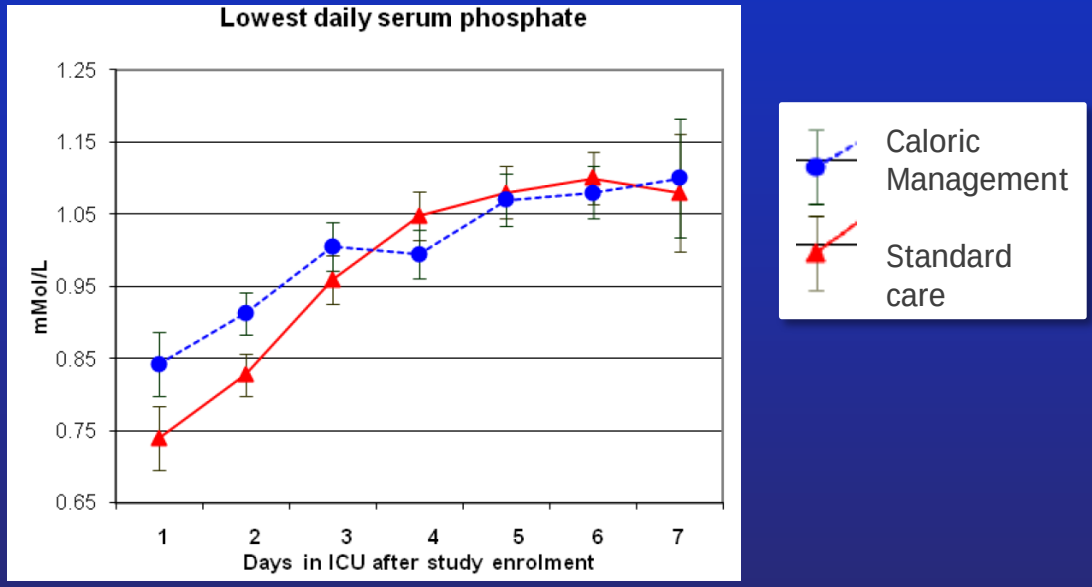

- Hyperglycaemia predisposes to infections
- Hypophosphatemia compromises white cell function
  - impaired chemotactic, phagocytic and bactericidal ability

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

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%.

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):

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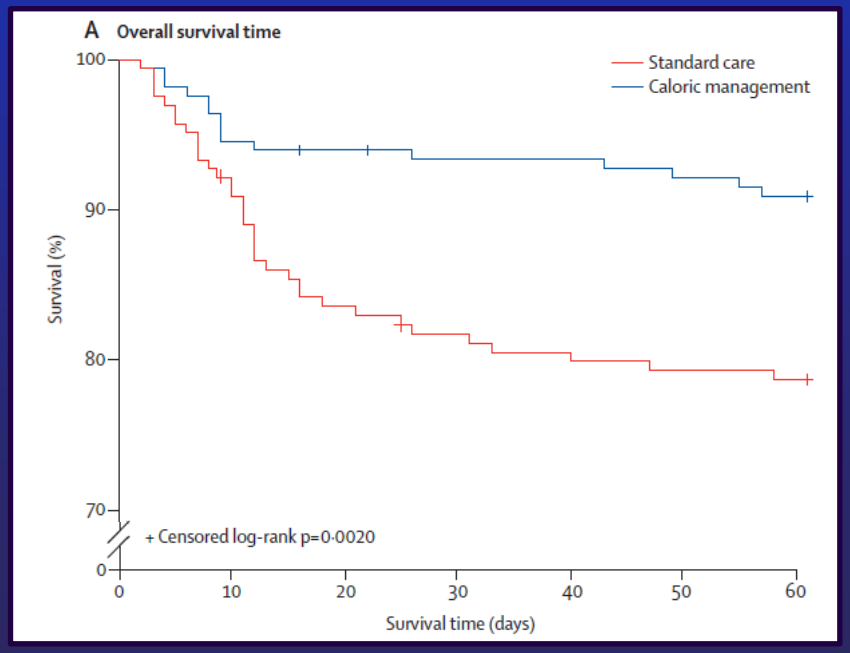
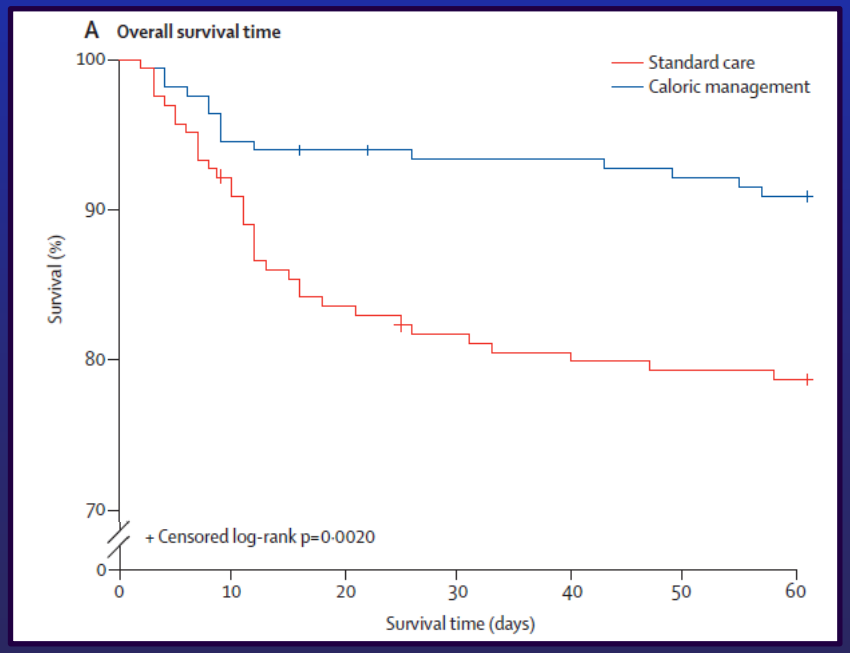


Composite primary outcome

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



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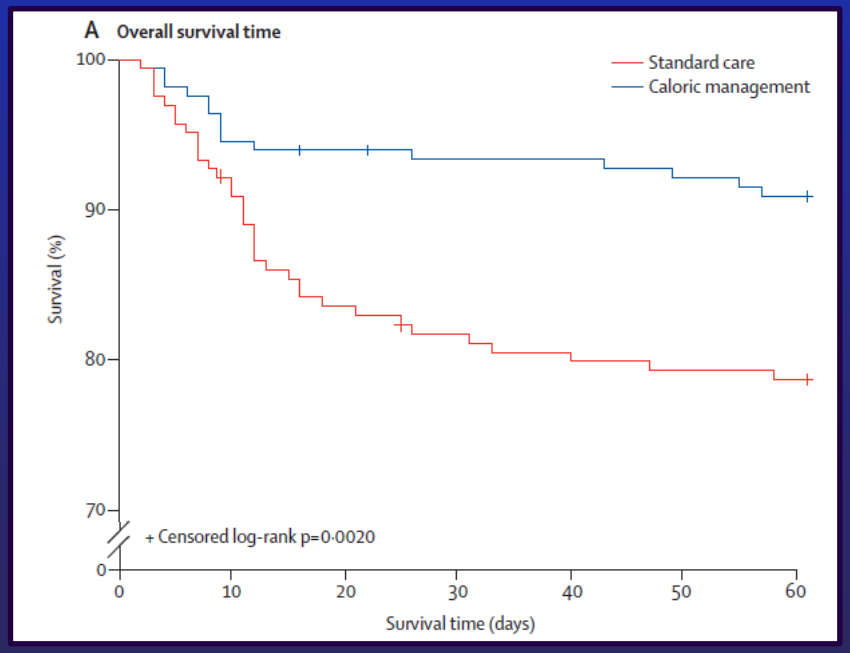

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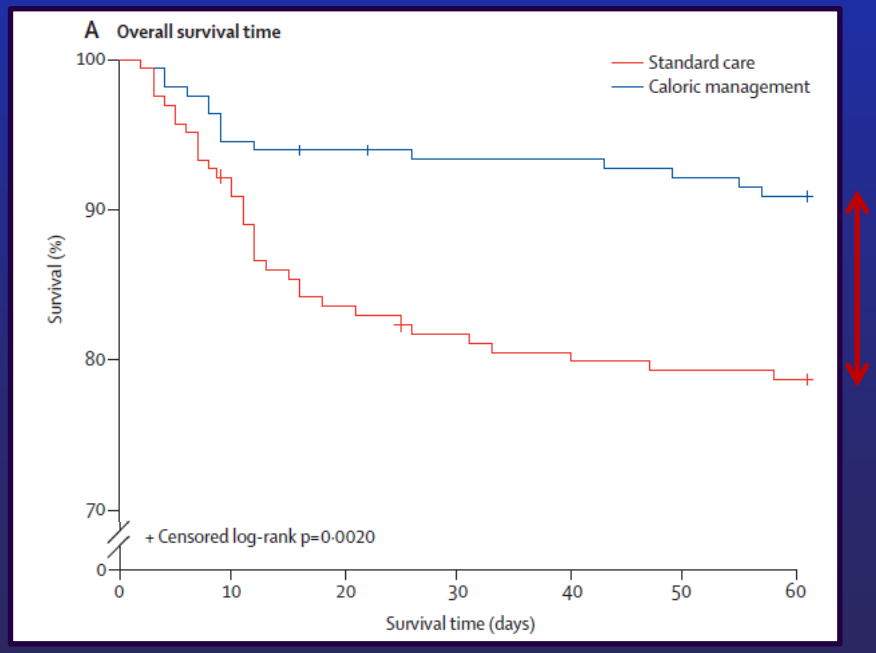

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Days alive after discharge from ICU (ICU free days):

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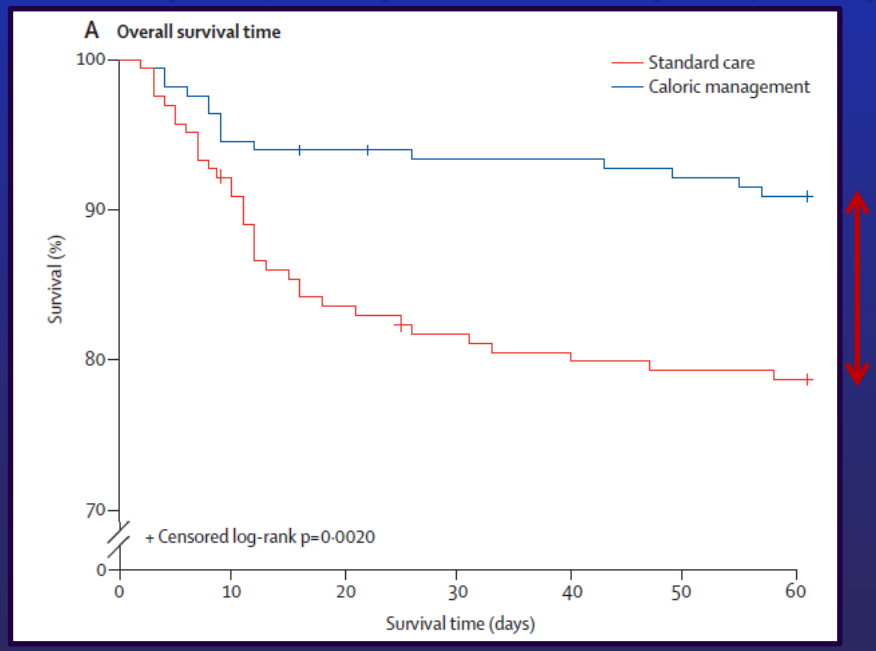
  - Control 78.5% (128/163) vs. 90.9% (149/164) survival , P=0.002



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  - Control 10.0 vs. 11.4 days, P=0.14

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Composite primary outcome

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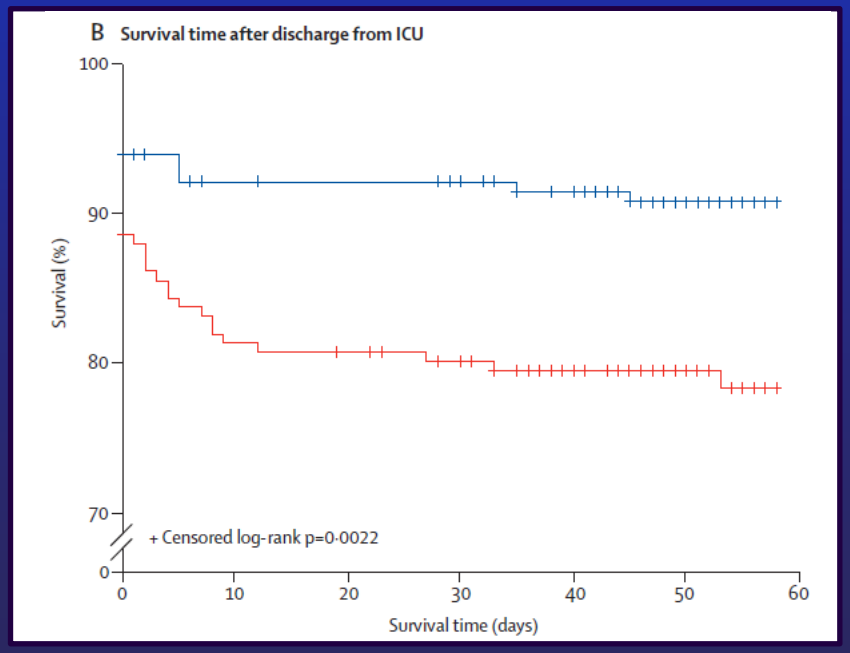
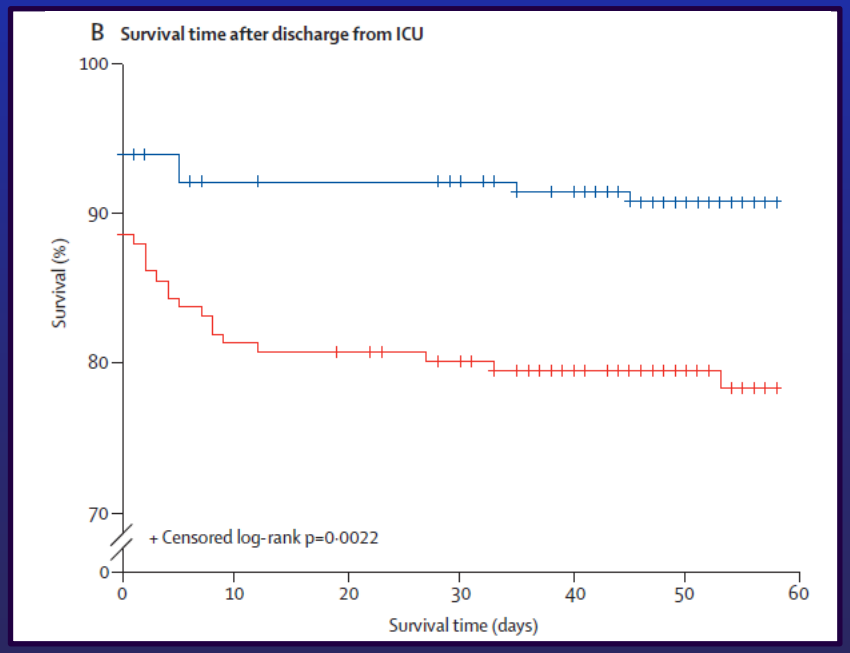


Composite primary outcome

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

- Control 39.9 vs. 44.8 days, P=0.21



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- Control 39.9 vs. 44.8 days, P=0.21

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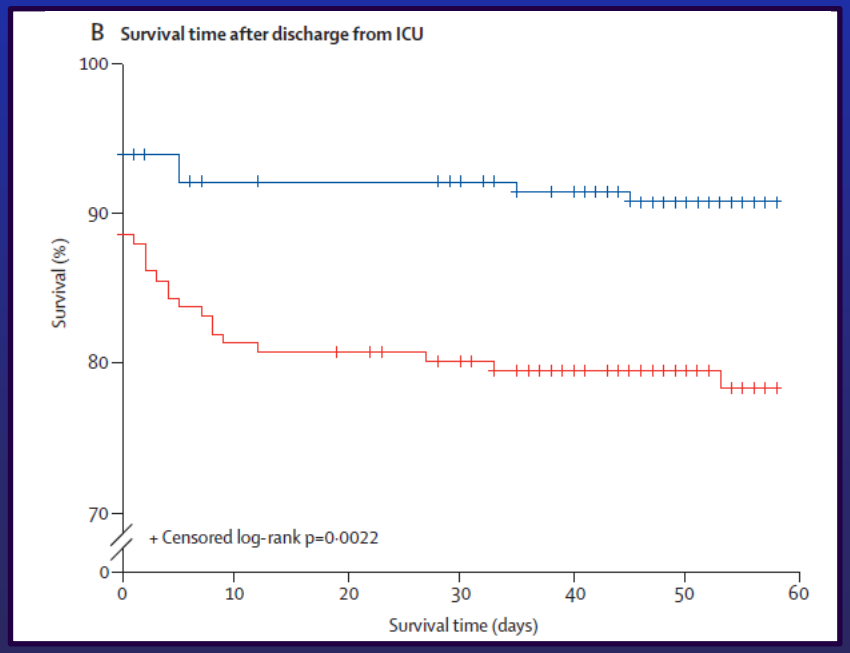

Composite primary outcome

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

- Control 39.9 vs. 44.8 days, P=0.21

But:

Overall survival time (60 day follow-up) was increased:

- 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):

- Control 39.9 vs. 44.8 days, P=0.21

But:

Overall survival time (60 day follow-up) was increased:

- Control 48·9 vs. 53·6 days , P=0·002 Log-Rank Test

More patients were *discharged alive from hospital*:

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

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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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*:

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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:

Overall survival time (60 day follow-up) was increased:

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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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Recommendation 56

- In patients with refeeding hypophosphatemia (< 0.65 mmol/l or a drop of > 0.16 mmol/l), electrolytes should be measured 2-3 times a day and supplemented if needed.

  Grade recommendation: GPP - strong consensus (100% agreement)

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Recommendation 57

- In patients with refeeding hypophosphatemia energy supply should be restricted for 48 h and then gradually increased.

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Questions??

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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.

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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 [##].*

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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.

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Caloric Management Protocol

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

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- **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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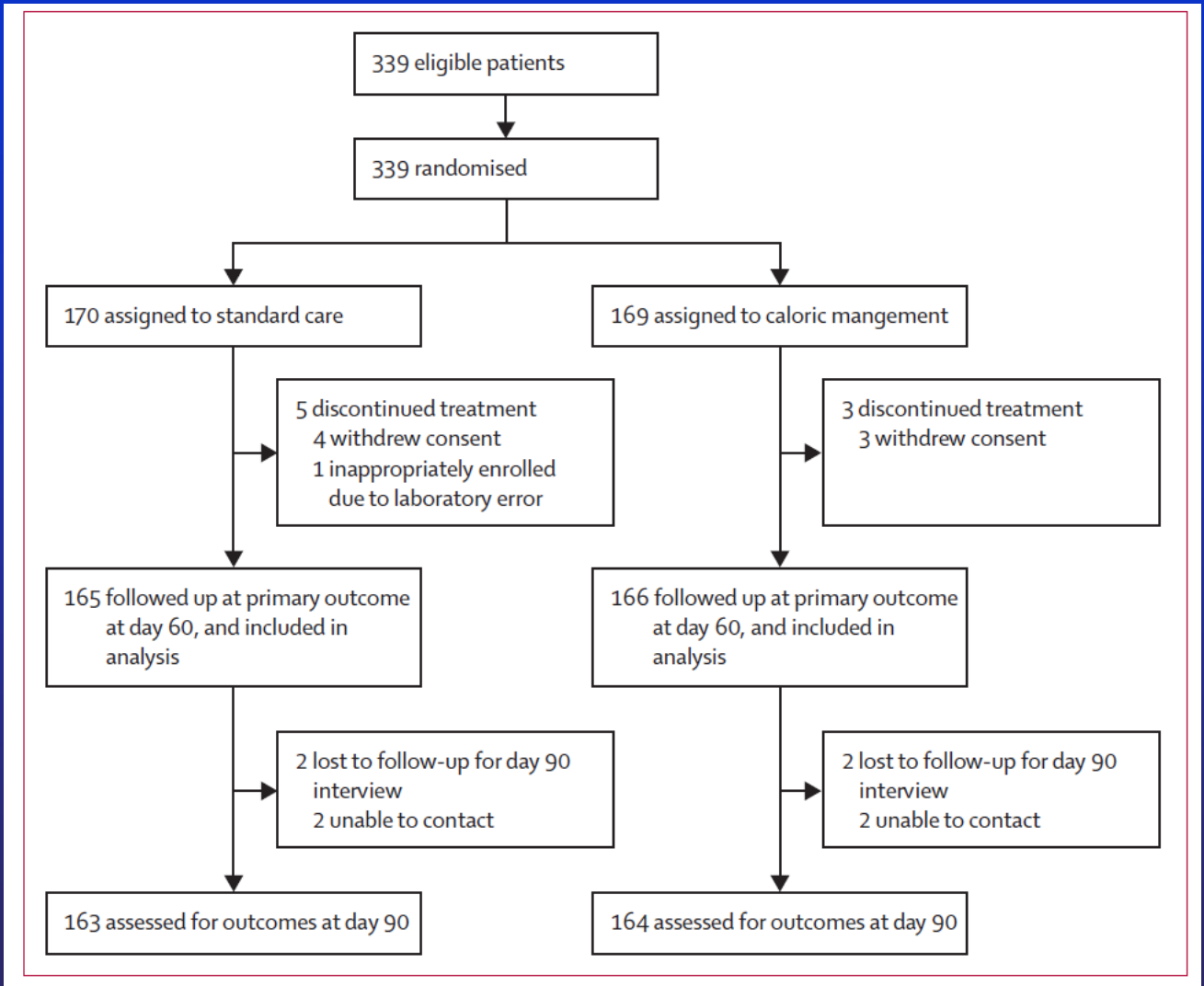
Follow-up



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