Refeeding Syndrome in the ICU: New insights in pathophysiology, diagnosis and treatment

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Disclosures

Arthur R.H. van Zanten M.D., PhD:

received honoraria for advisory board meetings, lectures and travel expenses from:

Abbott Nutrition

Baxter

B|BRAUN SHARING EXPERTISE

DANONE NUTRICIA

FRESENIUS KABI caring for life

Nestlé Nutrition

NOVARTIS MEDICAL NUTRITION

Inclusion fees for patients in the MetaPlus trial published in JAMA, August 2014, from Nutricia were paid to the local ICU research foundation.

ICU Nutrition Academy in the Netherlands and website www.criticalcarenutrition.nl

What is refeeding syndrome?

Special Articles

STARVATION IN WESTERN HOLLAND : 1945 *

G. C. E. BURGER, MD † NETHERLANDS
H. R. SANDSTEAD, MD ‡ UNITED STATES
SIR JACK DRUMMOND, D SC § UNITED KINGDOM

REPORTS of severe shortages of food and starvation began to come from Western Holland to the liberated area towards the end of October, 1944. Preparations were therefore begun to meet this problem. The SHAEF Mission, on the advice of the Netherlands Military Administration, invited a group of Allied nutrition experts to join them in this work. In coöperation with Dutch health authorities the following plans were carried out :

1. Three nutrition survey teams were assigned by SHAEF to the Netherlands to make both proliminary and detailed investigations of the nutritional status of the population.
2. Stocks of special foods were imported, including protein hydrolysates, vitaminised glucose, and powdered skim milk.
3. Fifty-one Dutch medical feeding units were assembled, trainod, and equipped.
4. Arrangements were made for the early despatch of the feeding units into occupied Holland.
5. All specialists in Western Holland who had experience of nutrition problems were assembled soon after liberation.

was pale and often showed a dun pigmentation. Petechiæ were common, and older subjects especially had large superficial hæmorrhages in the skin of the back of the hands and of the face. These hæmorrhages leave no pigmentation on absorption.

Hunger œdema was absent in a considerable proportion of the patients. If it appeared in the face it was sometimes difficult to diagnose in a patient whom one had never seen before. The fact that it was always attended with chemosis was an aid to diagnosis. Œdema occ
on
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showed well-marked cyanosis. Gangrene of the skin occurred often, particularly in the toes.

No phenomena that would justify a diagnosis of scurvy were seen. In the majority there were no other signs of vitamin deficiency, except occasional redness and tenderness of the tip of the tongue, which may have been due to nicotinic-acid deficiency.

The heart was normal, often with a slow pulse-rate down to 40 per min. and with a systolic blood-pressure down to 80 mm. Hg. No specific signs were found in the lungs but serious cases often acquired a terminal dry

Three types of death were observed : (1) sudden, unexplained, early after admission to the hospital ; (2) unexpected, after the patient appeared to be on the way to recovery, a turn for the worse leading to death in about an hour ; (3) a slow death, the patient lapsing into coma, as in any exhausting disease. In most cases

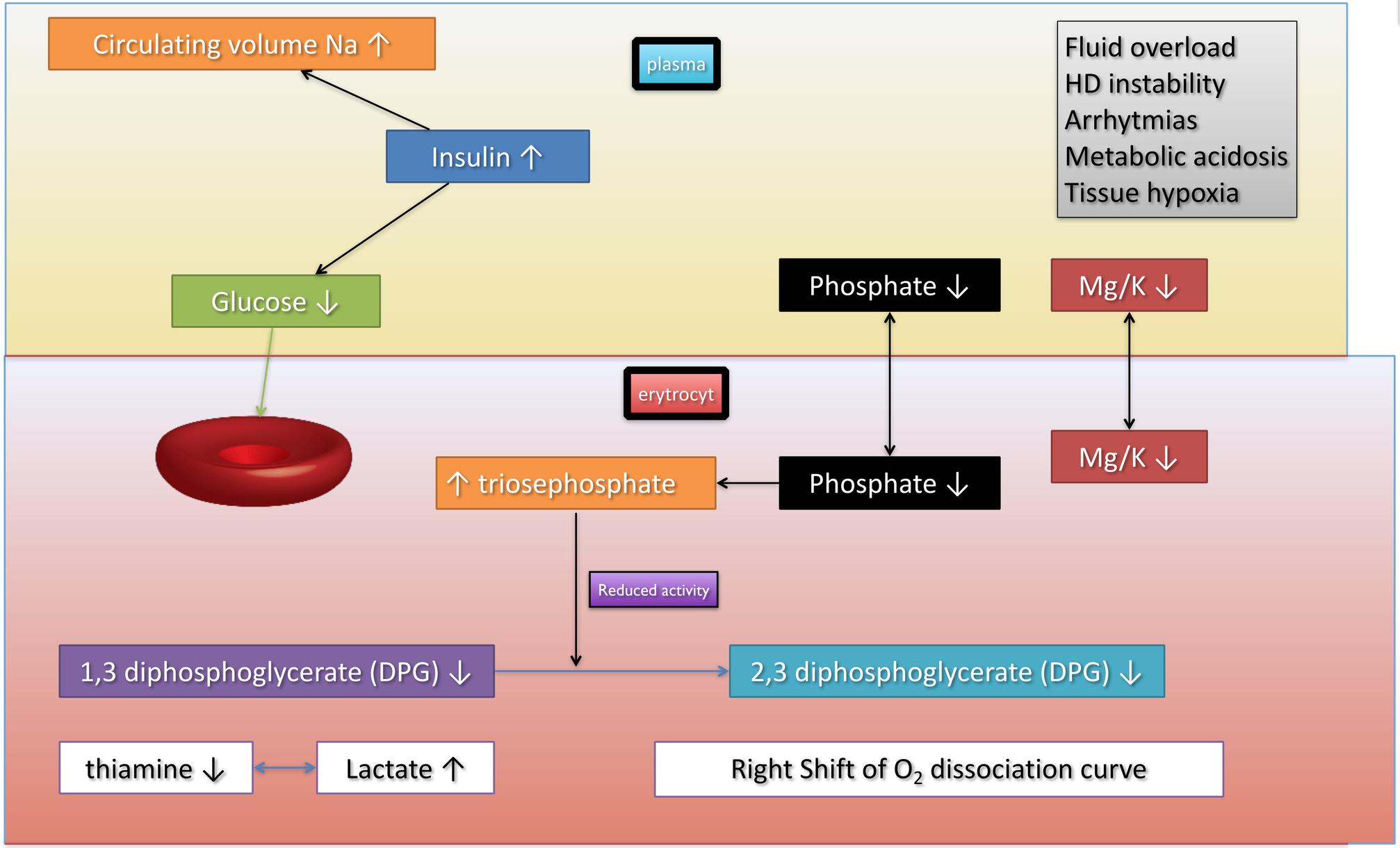
Burger GC et al Lancet 1945;9:282

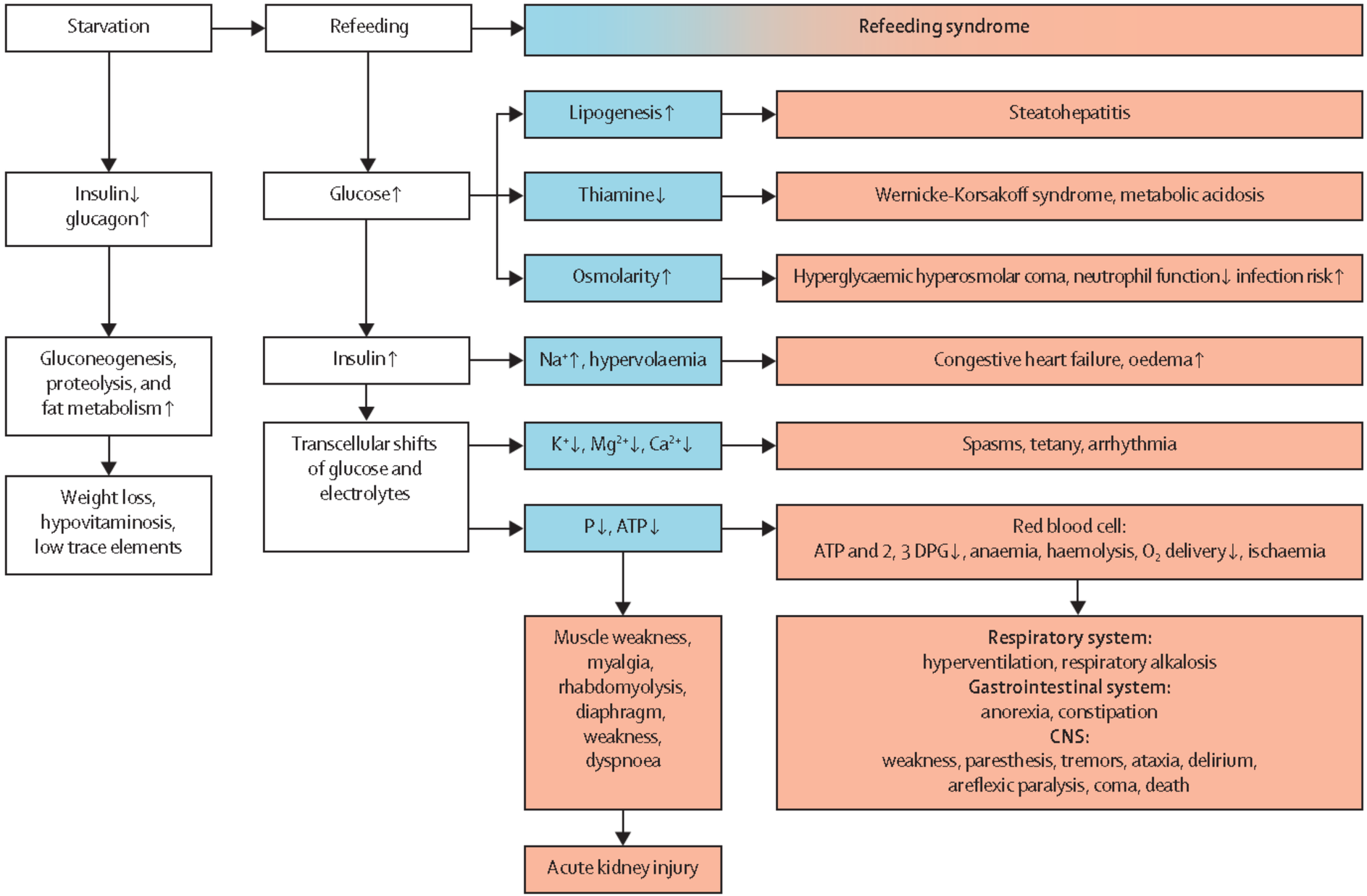
What is refeeding syndrome?

- Refeeding syndrome comprises metabolic disturbances that occur during reintroduction of feeding after a period of starvation or fasting.
- Clinical symptoms are due to biochemical abnormalities, typically consisting of fluid and electrolyte imbalances, such as hypokalemia, hypomagnesaemia and with hypophosphatemia.
- Additionally, abnormalities in glucose metabolism, insulin resistance and vitamin B1 (thiamine) deficiency are frequently encountered.

van Zanten AR. Lancet Respir Med. 2015 Dec;3(12):904-5.

Refeeding syndrome





van Zanten AR. Lancet Respir Med. 2015 Dec;3(12):904-5.

The Netherlands Journal of Medicine

EDITORIAL

How relevant is refeeding syndrome?

A.R.H. van Zanten

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van Zanten AR. Neth J Med. 2016 Mar;74(3):102-3.

The Netherlands Journal of Medicine

ORIGINAL ARTICLE

Incidence of refeeding syndrome in internal medicine patients

B.V.C. Kraaijenbrink[1]*, W.M. Lambers[2], E.M.H. Mathus-Vliegen[3], C.E.H. Siegert[4]

[1]Department of Internal Medicine, Tergooi, Hilversum, the Netherlands, [2]Department of Internal Medicine, VU Medical Centre, Amsterdam, the Netherlands, [3]Department of Gastroenterology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands, [4]Department of Internal Medicine, OLVG West, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)6-20884159, fax: +31 (0)88-7532060, email: bvckraaijenbrink@gmail.com

Kraaijenbrink BV et al. Neth J Med. 2016 Mar;74(3):116-21

Refeeding Syndrome in internal medicine patients

- Incidence of refeeding syndrome is relatively high in patients acutely admitted to the department of internal medicine.
- Of all patients admitted 8% developed refeeding syndrome.
- Patients with malignancy or previous malignancy increased risk of developing RFS.
- Clinicians should be aware of this risk when feeding these patients.
- When taking the occurrence of hypophosphataemia as a hallmark, no other objective parameters were identified in this study that may help to identify at risk patients at admission or during the hospital stay.

Kraaijenbrink BV et al. Neth J Med. 2016 Mar;74(3):116-21

Main clinical questions

- What is the incidence of refeeding syndrome during critical illness?
- Can we identify patients at risk (compare with NICE criteria)?
- Is caloric restriction warranted, as fluid balance and electrolytes can be controlled for excellently in the ICU environment?

Patients at risk of developing refeeding problems: useful in the ICU?

NICE criteria (UK)

Patient has one or more of the following:

- BMI < 16 kg/m^2
- Unintentional weight loss >15% within the last 3-6 months
- Little or no nutritional intake for more than 10 days
- Low levels of phosphate, potassium or magnesium prior to feeding

Or patient has 2 or more of the following:

- BMI < 18.5 kg/m^2
- Unintentional weight loss >10% within the last 3-6 months
- Littel or no nutritional intake for more than 5 days
- A history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics

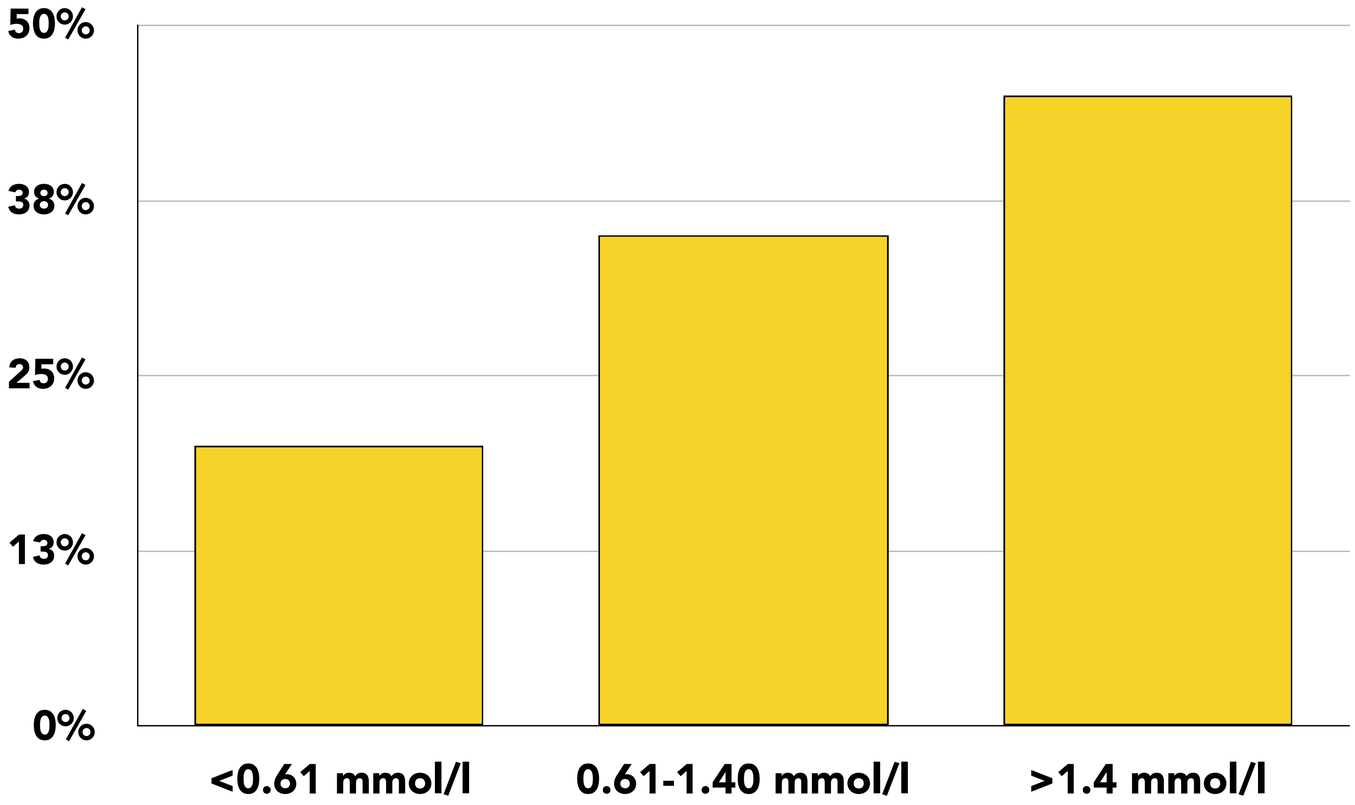
Practice guidelines recommend:
start feeding at 50% of energy target during first 3 days

Koekkoek WAC, Van Zanten ARH.
Curr Opin Clin Nutr Metab Care. 2018 Mar;21(2):130-137.

Hypophosphatemia in critically ill patients

2730 adult critically ill patients and 10,504 phosphate measurements

Hypophosphatemia behaves like a general marker of illness severity and not as an independent predictor of ICU or in-hospital mortality in critically ill patients.



MV logistic regression analysis, hypophosphatemia not independently associated with ICU mortality (aOR, 0.86 [95% CI, 0.66-1.10]; P = .24) and hospital mortality (aOR, 0.89 [0.73-1.07]; P = .21).

Suzuki S J Crit Care. 2013 Aug;28(4):536.e9-19.

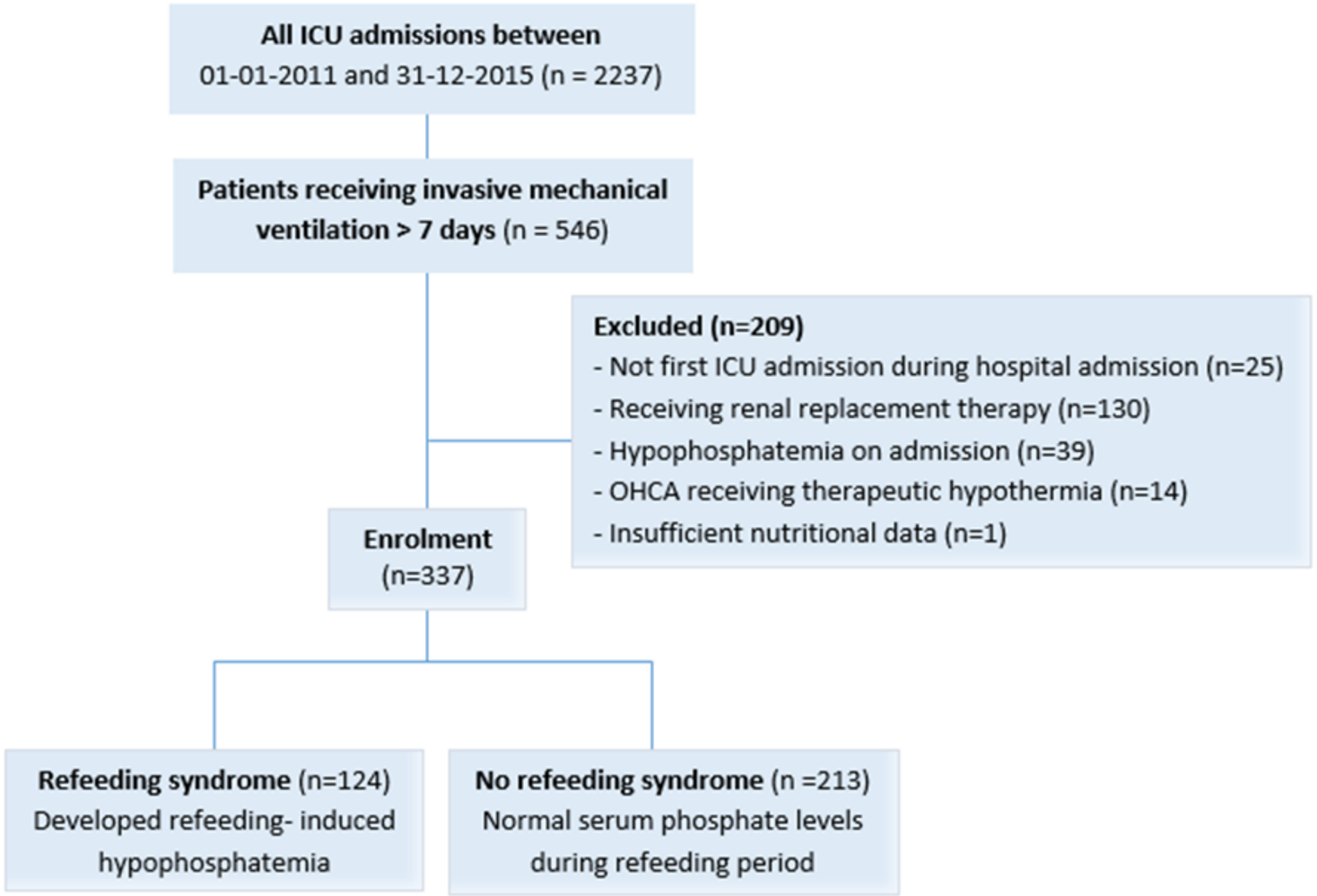
Is refeeding syndrome relevant during critical illness?

Diagnosis:

serum phosphate level below 0·65 mmol/l within 72h after start nutritional support. Change >0·16 mmol/l decrease from any previous level.

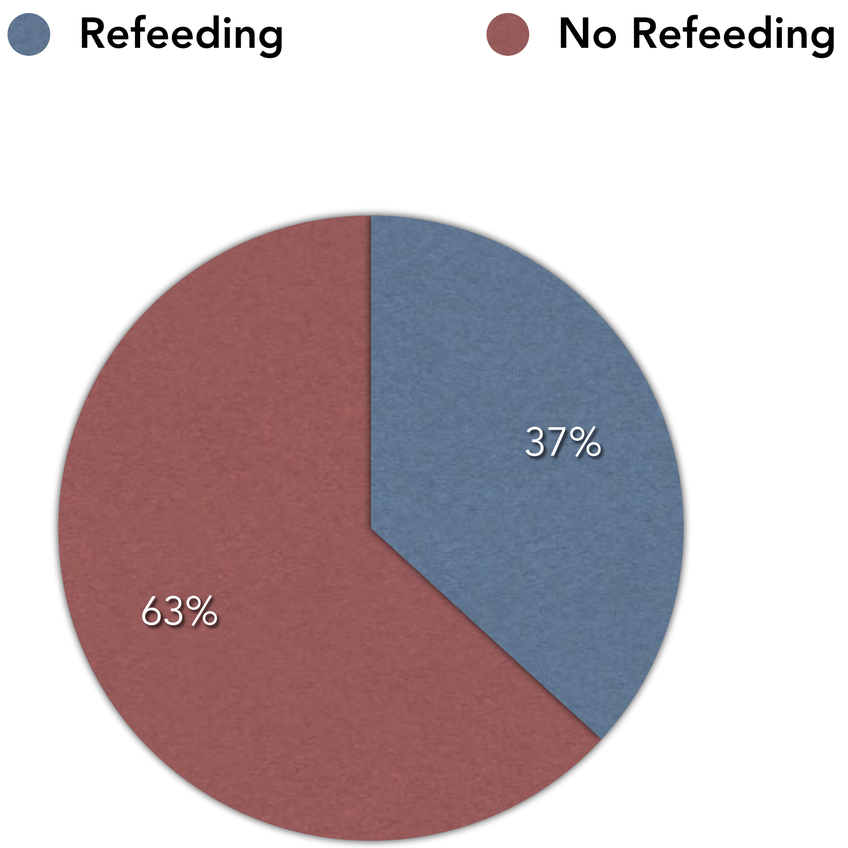
Exclusion:

Patients with other major causes of hypophosphataemia: ongoing dialysis, recent parathyroidectomy, or treatment for hyperphosphataemia.



Olthof L, Koekkoek K, ..Van Zanten AR
Clin Nutr 2017 http://dx.doi.org/10.1016/j.clnu.2017.08.001

Refeeding syndrome in critically ill patients is common



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Clin Nutr 2017 http://dx.doi.org/10.1016/j.clnu.2017.08.001

Baseline characteristics

		Total	RFS (n = 124)	No RFS (n = 213)	p Value
Age (years)	mean (SD)	66.5 (13.4)	66.4 (13.2)	66.6 (13.6)	0.94
Gender, female	N (%)	126 (37.4%)	50 (40.3%)	76 (35.7%)	0.39
BMI on admission kg/m^2					
	mean (SD)	27.0 (5.6)	26.6 (5.7)	27.2 (5.5)	0.31
BMI<18.5 kg/m^2	N (%)	14 (4.2%)	8 (6.5%)	6 (2.8%)	0.11
APACHE II-score[a]	mean (SD)	21.6 (6.5)	21.3 (5.8)	21.7 (6.9)	0.56
SOFA score[b]	mean (SD)	6.9 (2.8)	6.6 (2.7)	7.1 (2.9)	0.17
Baseline blood test					
Leukocytes ($\times 10^9$)	median [IQR]	14.6 [9.2–17.6]	14.1 [9.8–19]	12.6 [8.7–17.4]	0.12
Creatinine (μmol/L)		88.5 [63.3–122]	86.0 [66.3–110.5]	90.5 [61–127.8]	0.50
CRP (mg/L)		131 [32.3–249.8]	117 [20.5–229.5]	145 [37–264.3]	0.10
Bilirubin (mmol/L)		8.5 [6–13]	9 [6–14]	8 [6–13]	0.48
Albumin (g/L)		27 [21–33]	28 [22–34.3]	26 [21–32]	0.10
Highest glucose in first 24 h (mmol/L)		7.5 [6.4–8.7]	7.5 [6.5–8.7]	7.5 [6.3–8.7]	0.62
Baseline electrolytes					
Sodium (mmol/L)	median [IQR]	138 [135–141]	139 [136–142]	138 [134–141]	0.095
Potassium (mmol/L)	median [IQR]	3.8 [3.4–4.2]	3.7 [3.5–4.3]	3.9 [3.2–4.1]	0.004*
Magnesium (mmol/L)	median [IQR]	0.73 [0.62–0.83]	0.69 [0.58–0.8]	0.74 [0.63–0.85]	0.004*
Phosphate (mmol/L)	median [IQR]	1.17 [0.9–1.5]	1.14 [0.9–1.4]	1.20 [0.9–1.5]	0.320
Admission type					
Medical	N (%)	210 (62.3%)	75 (60.5%)	135 (61.2%)	0.85
Elective surgery		61 (18.1%)	23 (18.5%)	38 (17.8%)	
Emergency surgery		66 (19.6%)	26 (21.0%)	40 (18.8%)	
Charlson comorbidity index[c]	Mean (SD)	3.8 (2.4)	3.7 (2.1)	3.9 (2.5)	0.54
NUTRIC-score[d]	Mean (SD)	4.5 (1.8)	4.4 (1.6)	4.5 (1.9)	0.72
Nutritional parameters					
3-day caloric intake	Mean (SD)	2718 (1226)	2562 (1052)	2811 (1313)	0.067
7-day caloric intake (kcal)	Mean (SD)	9597 (2506)	9463 (2102)	9676 (2716)	0.42
Caloric target, (kcal*day)	Mean (SD)	1581 (289)	1562 (299)	1593 (272)	0.33
7-day caloric adequacy	Mean (SD)	87.9% (22.9)	87.5% (25.8)	88.1% (17.2)	0.79
Non nutritional to total caloric intake	Median [IQR]	4.0% [1.5–7.5]	4.6% [1.9–8.1]	3.6% [1.3–7.4]	0.11
Time to start nutrition (hours)	Median [IQR]	5.9 [2.6–14.4]	6.4 [2.9–15]	5.3 [2.4–13.3]	0.32

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Magnesium (mmol/L)	median [IQR]	0.73 [0.62–0.83]	0.69 [0.58–0.8]	0.74 [0.63–0.85]	0.004*
Phosphate (mmol/L)	median [IQR]	1.17 [0.9–1.5]	1.14 [0.9–1.4]	1.20 [0.9–1.5]	0.320

Statistically significant but not clinically relevant

RFH/RFS patients cannot be identified on ICU admission

Olthof L, Koekkoek K, ..Van Zanten AR
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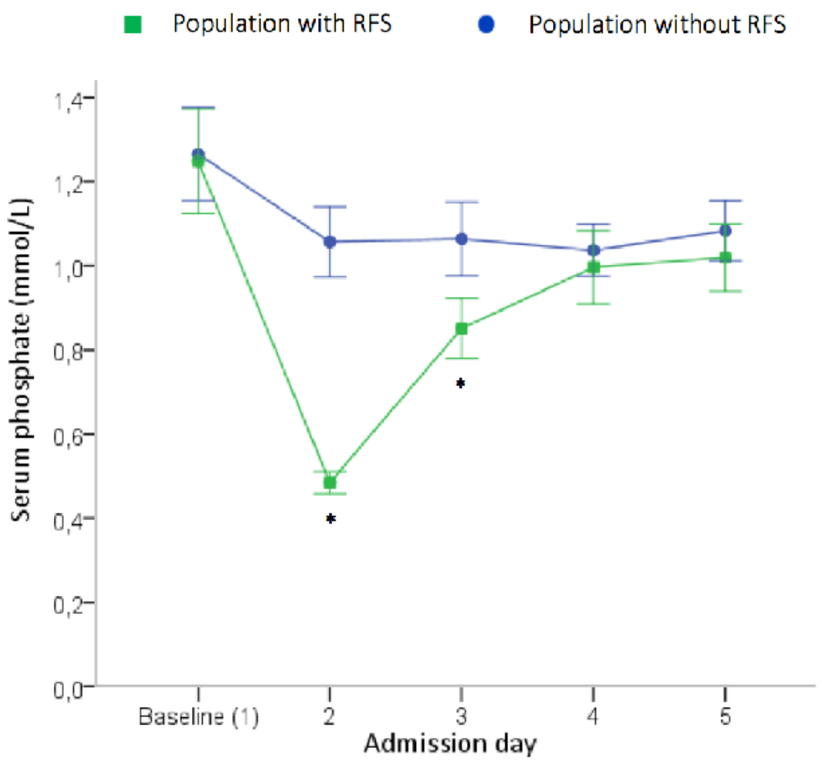
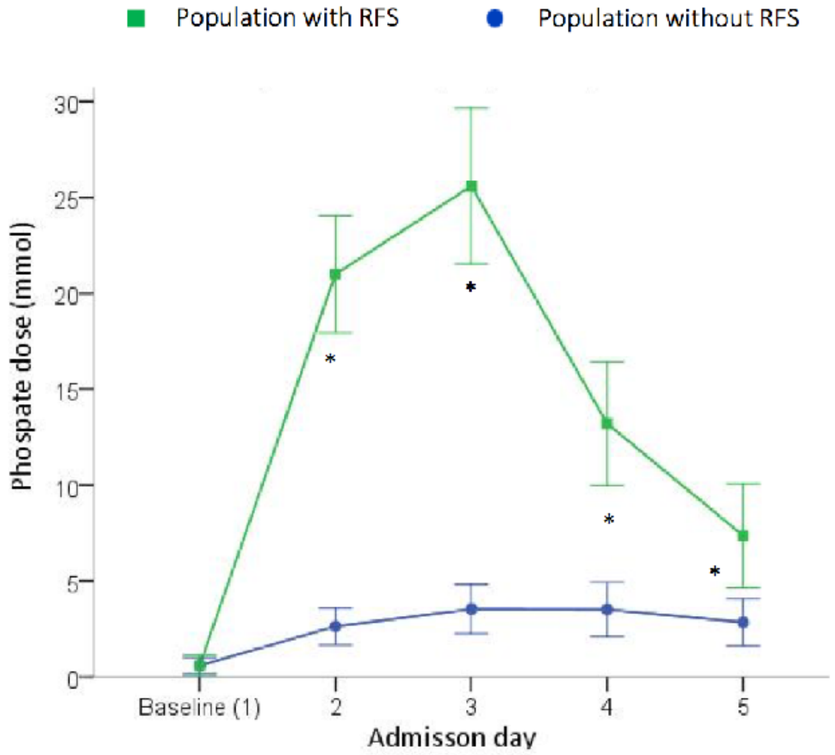
Phosphate levels and supplementation in RFS patients

n=337



Phosphate level

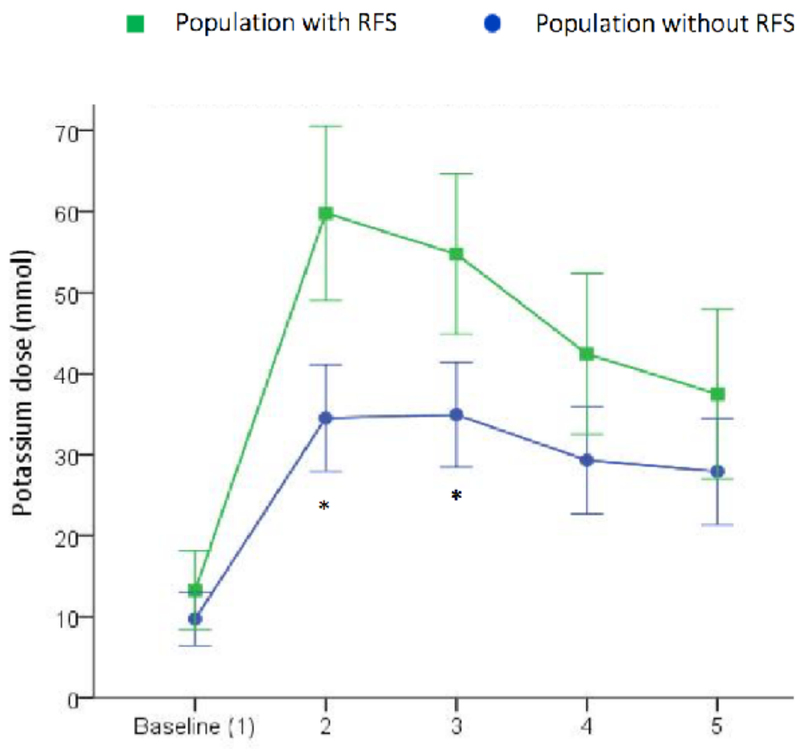


Phosphate supplementation

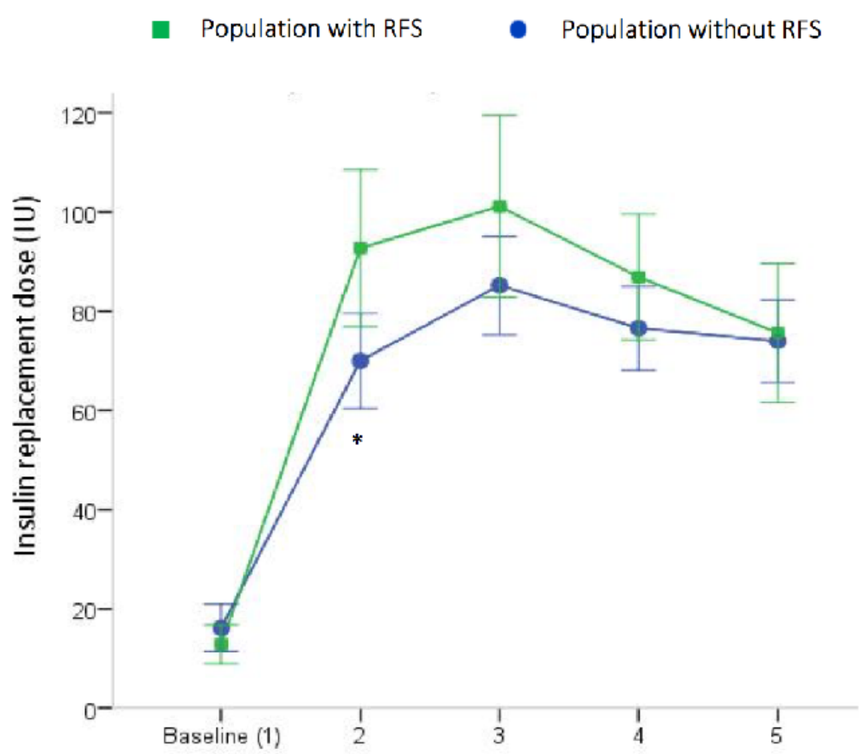
Olthof L, Koekkoek K, ..Van Zanten AR
Clin Nutr 2017 http://dx.doi.org/10.1016/j.clnu.2017.08.001

Potassium and insuline supplementation in RFS patients

n=337



Potassium supplementation



Insulin supplementation

Olthof L, Koekkoek K, ..Van Zanten AR
Clin Nutr 2017 http://dx.doi.org/10.1016/j.clnu.2017.08.001

Outcomes RFS vs no RFS

Mortality N (%)	Total (n=337)	Without RFS (n=213)	With RFS (n=124)	P value
ICU	55 (16.3%)	34 (16,0%)	21 (16.9%)	0.82
Hospital	79 (23.4%)	49 (23,0%)	30 (24.4%)	0.80
3 months	103 (30.6%)	62 (29.1%)	41 (33.1%)	0.45
6 months	109 (32.3%)	67 (31.5%)	42 (33.9%)	0.65

Table 3. Secondary outcomes

		Total (n=337)	Without RFS (n=213)	With RFS (n=124)	P value
LOS [a]	Median [IQR]				
- ICU		15 [11.0]	15 [12.0]	15 [10.0]	0.56
- hospital		26 [22.0]	28.0 [23.5]	24.0 [17.0]	0.066
TDA [b]	Median [IQR]				
- ICU		14.4 [11.1]	14.5 [12.2]	13.6 [10.9]	0.26
- hospital		29.5 [21.3]	31 [23]	27.5 [17.5]	0.19
Duration of MV [c]	Median [IQR]	10.0 [7.0]	10.0 [6.8]	10.0 [7.0]	0.69

ICU = Intensive Care Unit; a LOS = length of stay in days; b TDA = time to discharge alive in days
. c MV = mechanical ventilation in days.

Olthof L, Koekkoek K, ..Van Zanten AR
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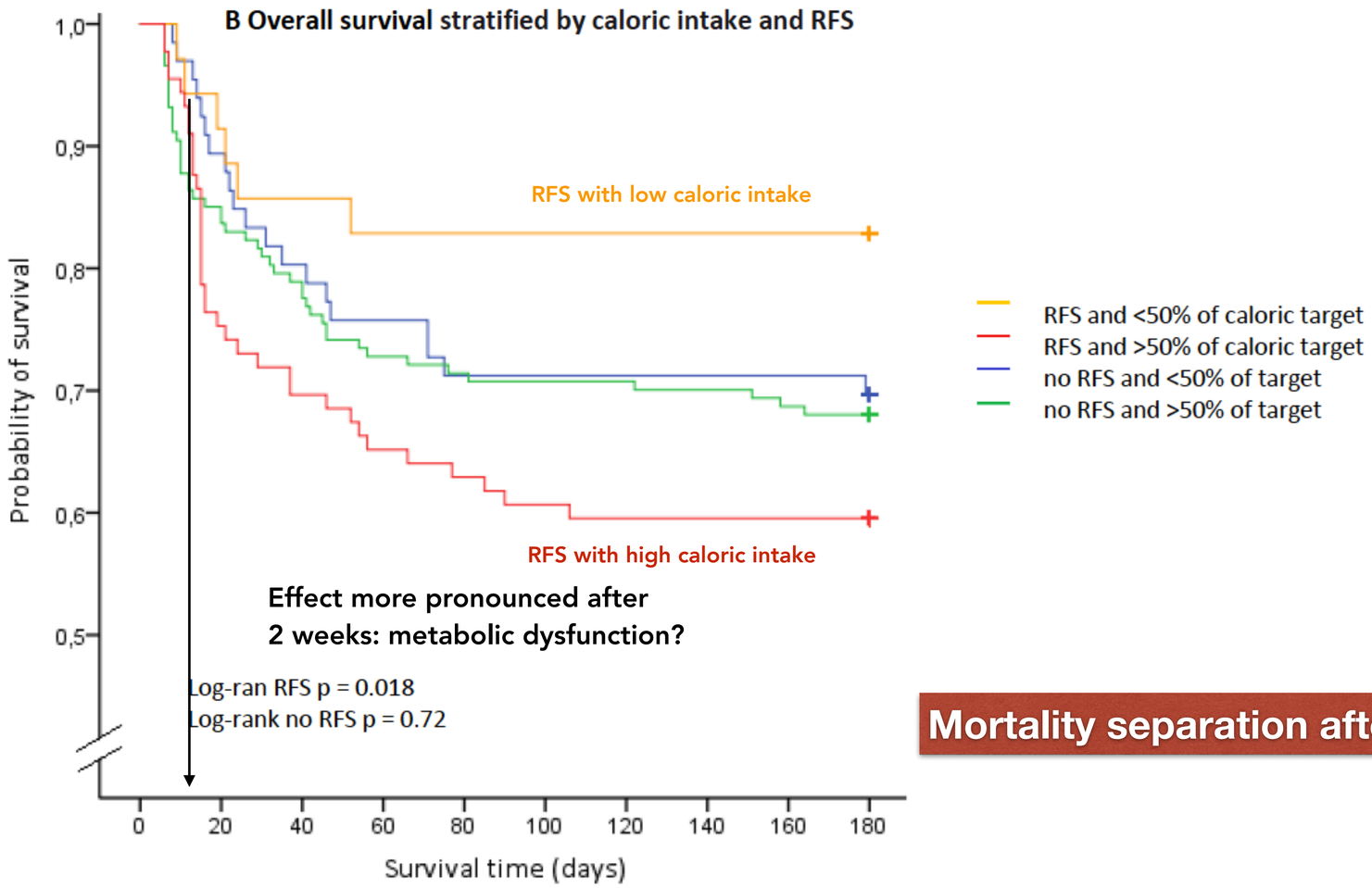
ICU patients with and without refeeding syndrome



Mortality separation after 2 weeks

Lower caloric intake is associated with better 6-month survival only in refeeding syndrome patients and not in those patients without RFS

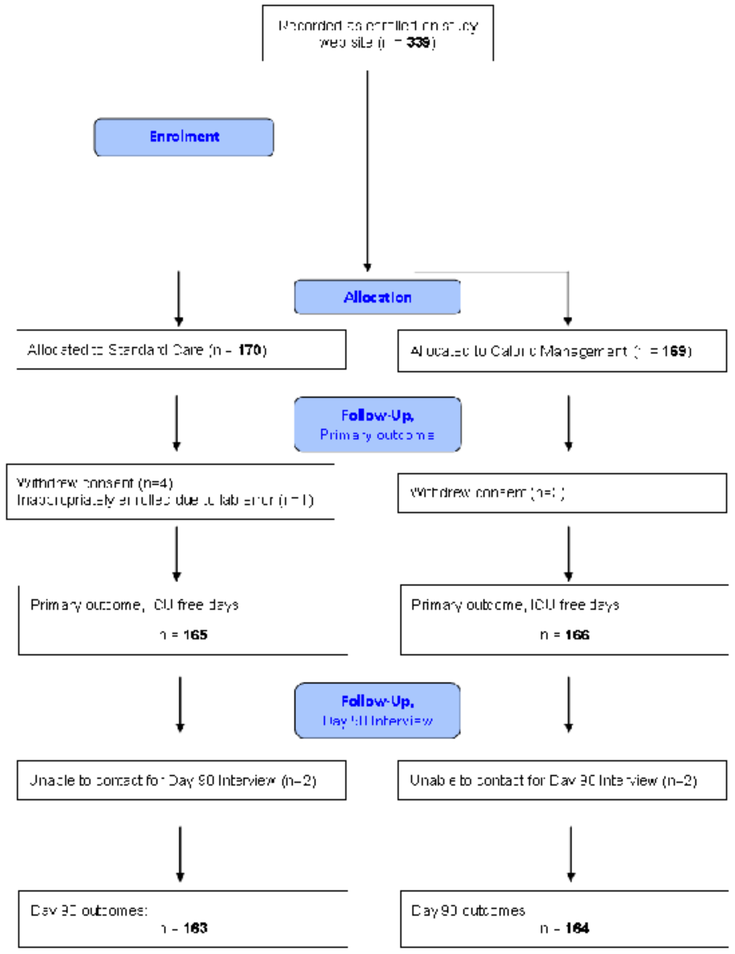
Olthof L, Koekkoek K, ..Van Zanten AR
Clin Nutr 2017 http://dx.doi.org/10.1016/j.clnu.2017.08.001

6-month mortality in RFS patients

Refeeding Syndrome population				
Variable	Univariate COX regression		Multivariate cox regression	
	HR (95%CI)	P value	HR (95%CI)	P value
Caloric intake < 50% target	0.38 (0.16–0.91)	0,030	0.39 (0.16-0.95)	0,037
Charlton Comorbidity Index	1.23 (1.07-1.40)	0,003	1.14 (0.94-1.38)	0.19
NUTRIC score	1.34 (1.09-1.64)	0,006	0.89 (0.62-1.27)	0.51
Age on admission	1.05 (1.01-1.08)	0,004	1.03 (0.99-1.07)	0.12
APACHE II score	1.07 (1.01-1.12)	0,014	1.10 (1.102-1.19)	0,017

Olthof L, Koekkoek K, ..Van Zanten AR
Clin Nutr 2017 http://dx.doi.org/10.1016/j.clnu.2017.08.001

Refeeding Syndrome the "only" RCT



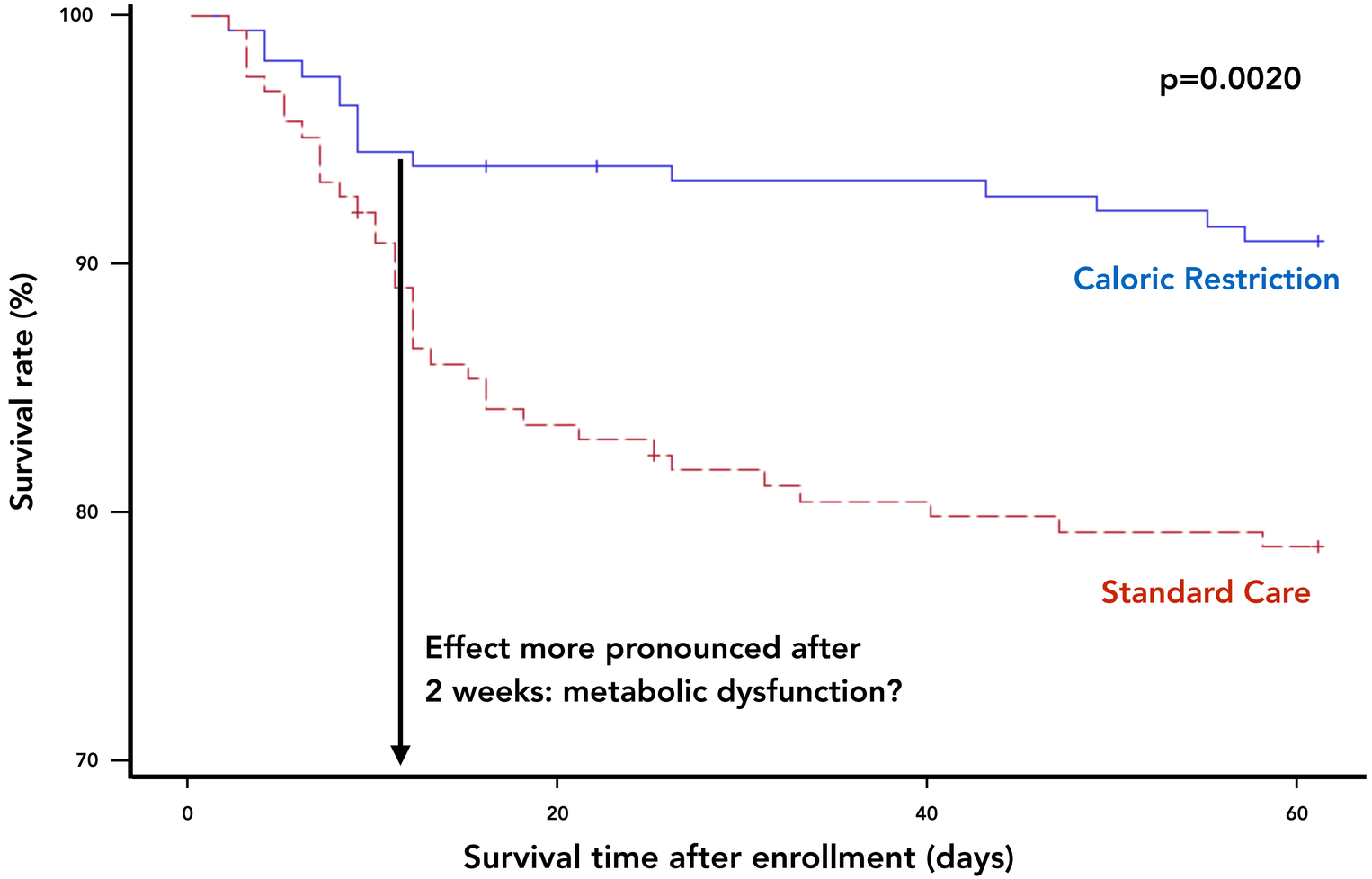
Inclusion:
serum phosphate level decreased to below 0·65 mmol per litre within 72 hours of commencing nutritional support.
Change required to be greater than 0·16 mmol per litre decrease from any previous level.

Exclusion:
Patients with other major causes of hypophosphataemia, such as ongoing dialysis, recent parathyroidectomy, or treatment for hyperphosphataemia were excluded from enrolment.

Caloric Management Protocol reduced energy intake to 20 kilocal/h for at least 2 days.
After 2 days, if phosphate levels did not need to be supplemented, energy intake returned to normal.

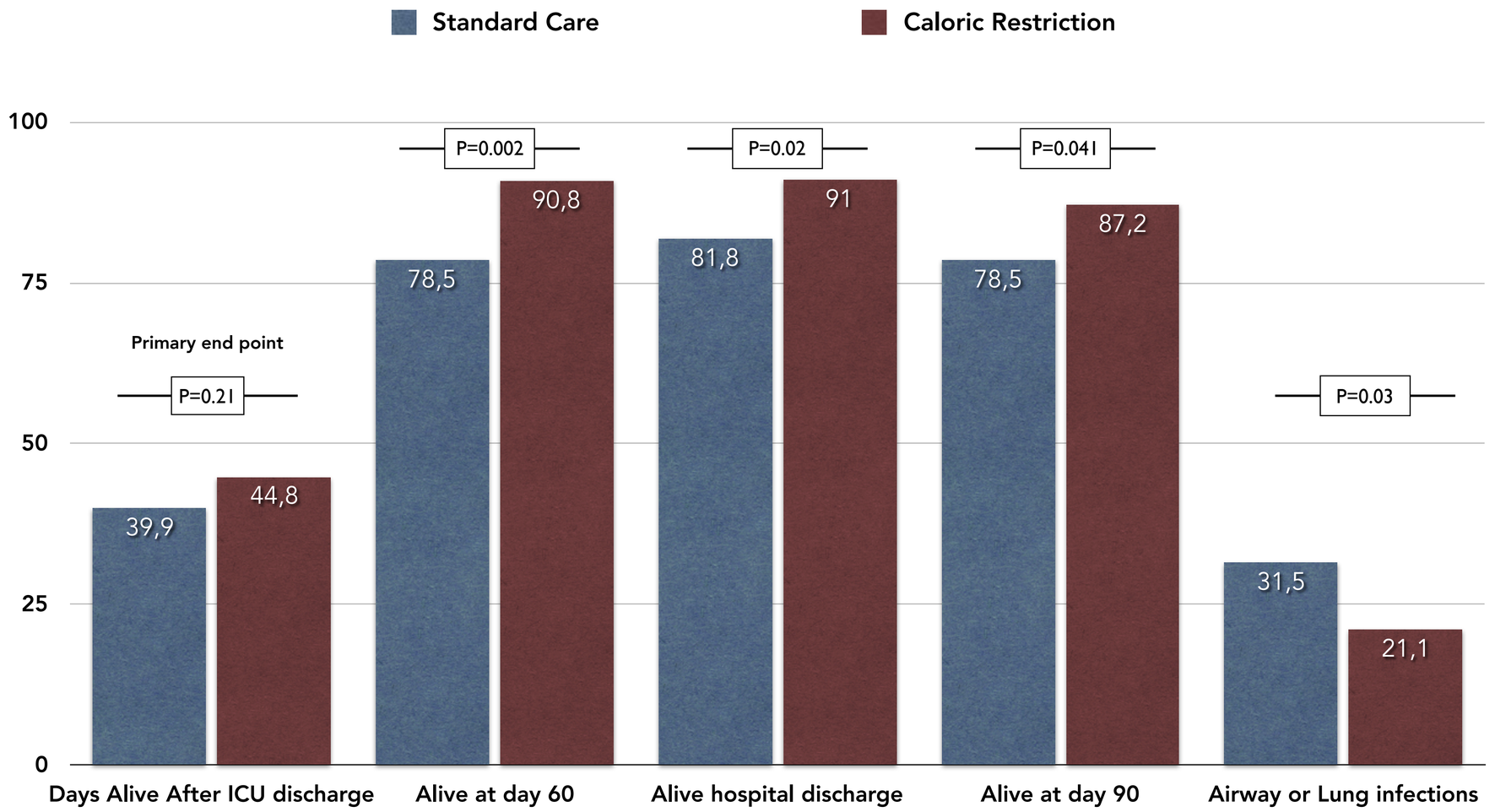
Doig GS, et al. Lancet Respir Med. 2015.

Caloric restriction and survival after inclusion



Doig GS, et al. Lancet Respir Med. 2015.

Caloric restriction during treatment for refeeding syndrome



Doig GS, et al. Lancet Respir Med. 2015.

Any contradictory data?

Other data in search of the holy grail?

Refeeding Hypophosphatemia or Refeeding Syndrome?

- **Combined cases (n=63 patients) showed that hypophosphatemia was a consistent finding but that other abnormalities were not consistently identified.**
- **Refeeding hypophosphatemia is not accompanied by a consistent pattern of biochemical or clinical abnormalities among case reports or case series of patients reported to have refeeding syndrome.**

In the Olthof and Doig studies > 90-95% of patients not only had RH but also low levels of potassium and magnesium and decreased insulin sensitivity,

Skipper A. Nutr Clin Pract. 2012 Feb;27(1):34-40.

Other findings

Asia Pac J Clin Nutr 2018;27(2):329-335

Original Article

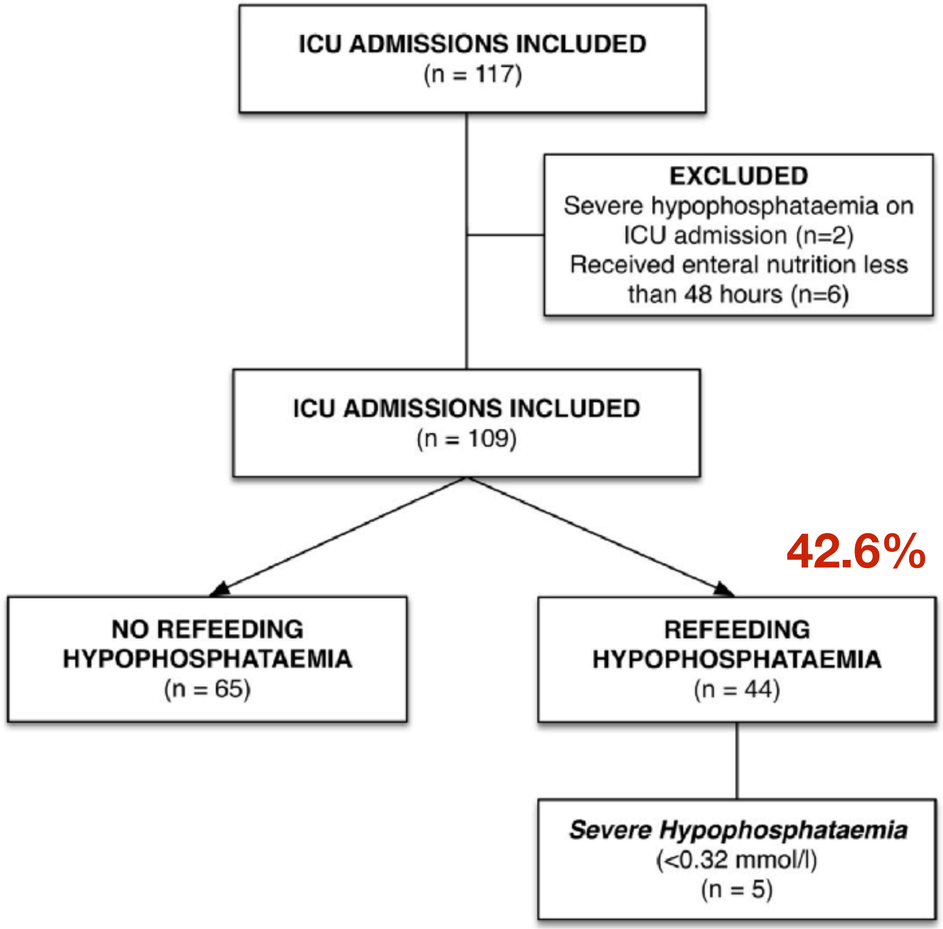
Refeeding hypophosphataemia after enteral nutrition in a Malaysian intensive care unit: risk factors and outcome

Azrina Md Ralib MBChB, MMed, PhD, Mohd Basri Mat Nor MBBCh.BAO, MMed, EDIC

Department of Anaesthesiology and Intensive Care, Kulliyyah of Medicine, International Islamic University Malaysia

Ralib A. Asia Pac J Clin Nutr 2018;27(2):329-335

Other findings



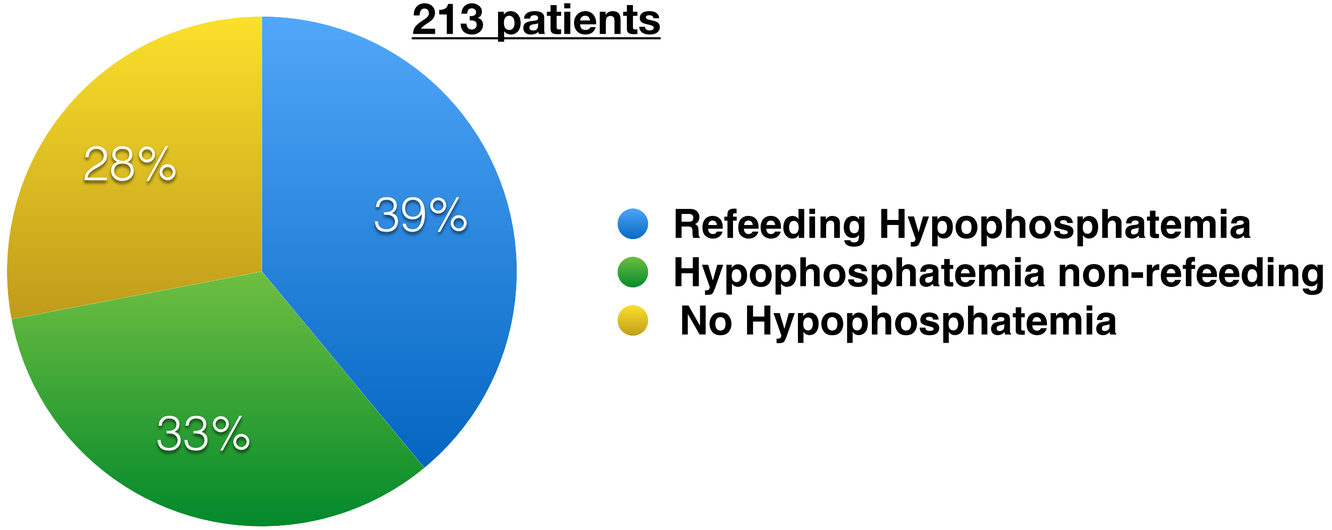
After refeeding, patients with RH had lower serum phosphate, magnesium and albumin, and higher supplementation of phosphate, potassium and calcium. Suggests RFS

There were no differences in mortality, length of hospital or ICU stay. Not analyzed for intake

Ralib A. Asia Pac J Clin Nutr 2018;27(2):329-335

Other findings in Surgical ICU

213 patients



Refeeding hypophosphatemia

<2.0 mg/dL= 0.65 mmol/l and

decrement > 0.5 mg/dL=0.15 mol/l

Nutrition parameters did not differ between groups; most patients were initiated on EN within 48 hours of SICU admission, and timing of EN initiation was not a significant predictor for the development of RH.

The median hospital length of stay (LOS) was 21 and 24 days for those with and without RH, respectively (P = .79);

RH remained a nonsignificant predictor for hospital LOS in the multivariable analysis.

Associations with intake?

Fuentes E et al. Nutr Clin Pract 2017 Apr;32(2):252-257.

Post-hoc RFS analysis from the Permit trial by Arabi and coworkers

PermiT (Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients)

- Both study groups reflect underfeeding strategies (mean caloric intake in the underfeeding and full-feeding groups, 11 kcal vs. 16 kcal per kilogram of body weight per day, respectively; recommended target, 25 kcal per kilogram of body weight per day)
- Mean protein intake achieved (0.7 g per kilogram of body weight per day in both groups) was far below the recommended intake of 1.2 to 2.0 g per kilogram of body weight per day.

Van Zanten AR. Am J Respir Crit Care Med 2017 195(5):691-692.

Post-hoc RFS analysis from the Permit trial by Arabi and coworkers

Variables	Permissive Underfeeding	Standard Feeding	Adjusted Odds Ratio (95% CI)	*P* Value	*P* Value for Interaction
90-d mortality*					
Hypophosphatemia on admission	29/125 (23.2)	23/110 (20.9)	1.36 (0.71–2.62)	0.36	0.10
Normal or elevated phosphate	65/197 (33.0)	64/190 (33.7)	0.86 (0.55–1.34)	0.51	
Refeeding syndrome	19/101 (18.8)	33/123 (26.8)	0.58 (0.30–1.13)	0.11	
New renal replacement therapy					
Hypophosphatemia on admission	2/117 (1.7)	5/105 (4.8)	0.40 (0.06–2.72)	0.35	0.86
Normal or elevated phosphate	25/180 (13.9)	30/163 (18.4)	0.47 (0.24–0.94)	0.03	
Refeeding syndrome	2/90 (2.2)	7/115 (6.1)	0.59 (0.10–3.41)	0.55	
ICU-associated infections					
Hypophosphatemia on admission	57/126 (45.2)	41/111 (36.9)	1.41 (0.84–2.38)	0.20	0.35
Normal or elevated phosphate	67/199 (33.7)	77/191 (40.3)	0.75 (0.50–1.13)	0.17	
Refeeding syndrome	2/90 (2.2)	7/115 (6.1)	1.02 (0.59–1.78)	0.93	

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit.
Data are presented as n/N (%). Hypophosphatemia on admission: ≤0.70 mmol/L on Day 1; normal or elevated phosphate: >0.70 mmol/L on Days 1, 2, and 3; refeeding syndrome: >0.70 mmol/L on Day 1 and then ≤0.70 mmol/L on Day 2 or 3.
*Ninety-day mortality was not available in nine patients.

slightly different definition used

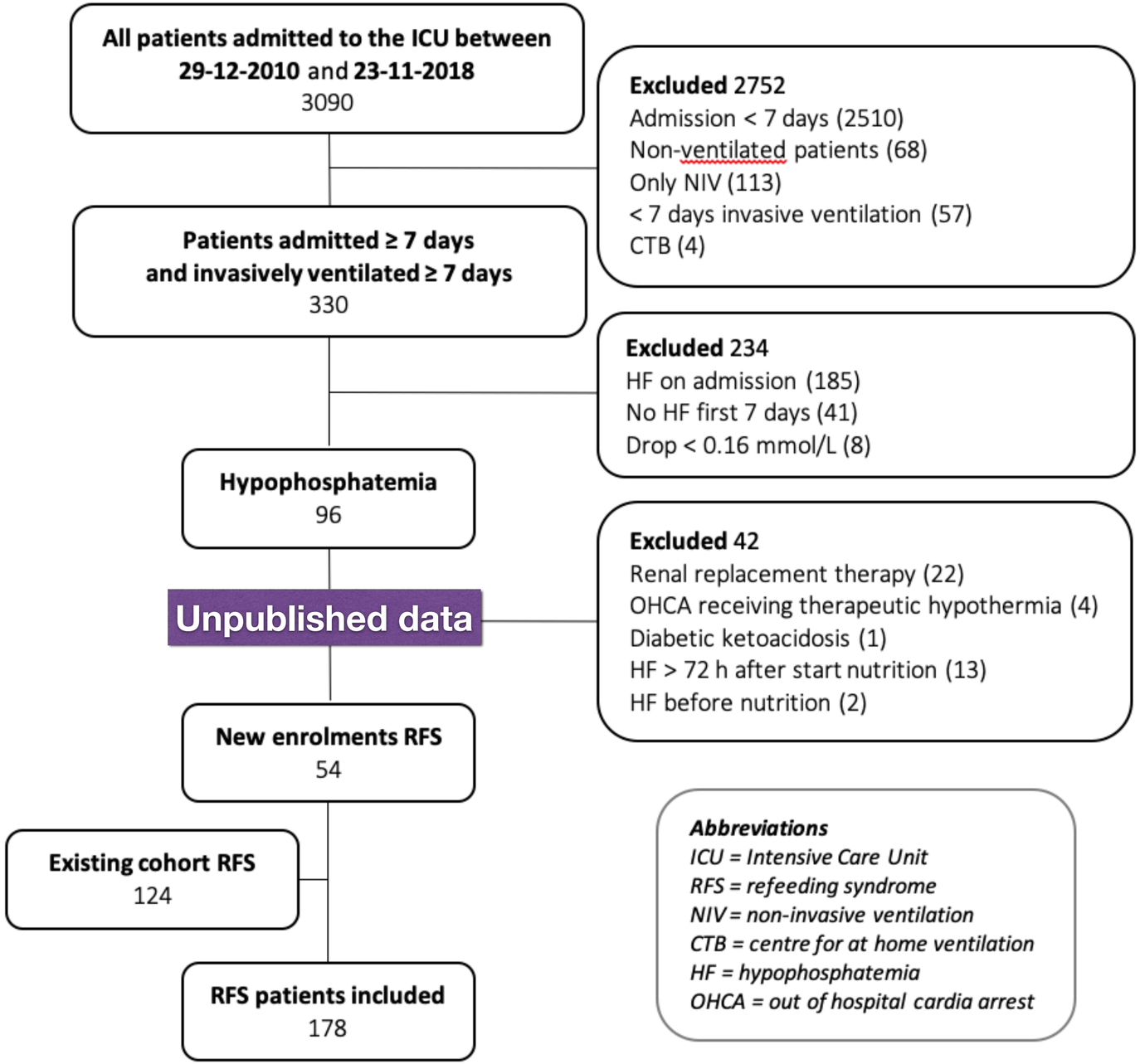
Arabi YM et al. Am J Respir Crit Care Med 2017 195(5):692-693.

Post-hoc RFS analysis from the Permit trial by Arabi and coworkers

Interpretation why the full feeding negative effect may not have been seen

- Not fully fed versus trophic (separation of groups <400 kcal/day)
- Day 1 above 0.70 mmol/l and below on day 2 or 3, not used 0.65 mmol/l and minimum drop of 0.15 mmol/l
- No exclusion of other factors inducing hypophosphatemia
- Trends show similar observations favoring the hypocaloric strategy
- post-hoc analysis
- study not designed to study RFS

Van Zanten AR. Am J Respir Crit Care Med 2017 195(5):691-692.



Outcomes of ICU patients with refeeding hypophosphatemia: calories vs macronutrients

Are outcomes of ICU patients with refeeding hypophosphatemia related to carbohydrate intake following the pathophysiology?

Slingerland-Boot R, Rooijakkers EF, Van Zanten AR

Variable	RFS patients	< 50% caloric target	> 50% caloric target	*p* Value [a]
Number of patients	178	58	120	
Age, years	68.0 [57-76]	67 [54-74]	69 [59-76]	0.323
Gender, male	106 (59.6%)	36 (62.1%)	70 (58.3%)	0.634
Weight on admission, kg	78 [67-90]	82 [73.5-90.3]	76.5 [65.6-87]	**0.018**
Length on admission, cm	172 [166-178]	175 [167-180]	172 [165-178]	0.183
BMI on admission, kg/m^2	26.1 [23.1-29.3]	27.2 [24.6-29.4]	25.3 [22.7-29.0]	**0.027**
BMI <18.5, kg/m^2	8 (4.5%)	2 (3.4%)	6 (5%)	0.640
APACHE II score (n=172)	20.9 (5.7)	20.7 (6.2)	21.0 (2.6) (n=114)	0.760
SOFA score	7.1 (2.8)	7.7 (2.9)	6.7 (2.6)	**0.023**
CCI	3.6 (2.2)	3.5 (2,3)	3.7 (2.2)	0.574
NUTRIC score	4.5 (1.6)	4.4 (1.7)	4.6 (1.6)	0.554
Baseline blood test				
Leukocytes, x10^9/L	13.8 [9.5-18.6]	13.7 [9.6-20.2]	13.8 [9.6-17.5]	0.617
Creatinine, µmol/L	88 [67-110.3]	96.5 [69.8-119]	79.5 [67-107]	*0.067*
CRP, mg/L (n=174)	114.5 [31-219.8]	87 [15.5-195.8]	131.5 [32.3-228] (n=116)	0.113
Bilirubin, mmol/L (n=173)	9 [6-14]	11 [7-21] (n=55)	8 [6-12] (n=118)	*0.052*
Albumin, g/L (n=175)	27 [21-33]	26 [20-32] (n=55)	28.5 [22-35]	*0.065*
Highest glucose first 24h, mmol/L (n=166)	8.1 [6.7-10.3]	9.3 [7.4-12.7] (n=56)	7.8 [6.5-9.9] (n=110)	**0.003**
Baseline electrolytes, mmol/L				
Sodium	139 [135-142]	140 [135-142]	138 [136-142]	0.559
Potassium	3.7 [3.3-4.1]	3.7 [3.3-4.1]	3.7 [3.2-4.1]	0.867
Magnesium (n=172)	0.69 [0.59-0.80]	0.67 [0.50-0.75] (n=55)	0.72 [0.60-0.81] (n=117)	*0.056*
Phosphate	1.10 [0.89-1.33]	1.05 [0.83-1.32]	1.12 [0.92-1.34]	0.386
Admission type				
Medical	110 (61.8%)	32 (55.2%)	78 (65%)	0.366
Elective surgery	32 (18%)	11 (19%)	21 (17.5%)	
Emergency surgery	36 (20.2%)	15 (25.9%)	21 (17.5%)	

Unpublished data

RFS = Refeeding syndrome, < 50% caloric target = less than 50 percent of caloric target reached at day 3, > 50% caloric target = more than 50 percent of caloric target reached at day 3, n = number of patients, BMI = Body Mass Index, APACHE II score (first 24 hours of admission) = Acute Physiology and Chronic Health Evaluation II score; SOFA score (first 24 hours of admission) = Sequential Organ Failure Assessment score; CCI = Charlson Comorbidity Index predicts 10-year mortality from 22 comorbid conditions, NUTRIC score = Nutrition Risk In Critically ill score, CRP = C-reactive protein. Values: mean (standard deviation), median [interquartile range] i.e. 1st – 3rd quartile, N (%).

[a] *p* Values were calculated using Independed Samples t-test, Mann-Whitney U test or chi-square test where appropriate.

Bold = $p < 0.05$, italic = $p < 0.10$.

Slingerland-Boot R, Rooijakkers EF, Van Zanten AR

Variable	RFS patients	< 50% caloric target	> 50% caloric target	*p* Value [a]
Number of patients	178	58	120	
Time till start nutrition, hours	7.0 [3.3-16.6]	15.7 [6.5-27.6]	5.4 [2.9-11.7]	**0.000**
Caloric targets, kcal				
Caloric target per day	1739 (305)	1777 (314)	1720 (301)	0.247
Cumulative target day 1-3	4167 (875)	4277 (963)	4114 (828)	0.246
Cumulative target day 1-7	11123 (2009)	11385 (2118)	10996 (1950)	0.226
Protein targets, kcal and gr				
Protein target per day, kcal	454 (80)	470 (71)	446 (84)	*0.067*
Protein target per day, gr	114 (20)	117 (18)	112 (21)	*0.067*
Cumulative protein target day 1-3, kcal	1086 (222)	1130 (229)	1065 (217)	*0.067*
Cumulative protein target day 1-3, gr	272 (56)	283 (57)	266 (54)	*0.067*
Cumulative protein target day 1-7, kcal	2902 (520)	3009 (484)	2850 (531)	*0.056*
Cumulative protein target day 1-7, gr	725 (130)	752 (121)	712 (133)	*0.056*

Unpublished data

Slingerland-Boot R, Rooijakkers EF, Van Zanten AR

Variable	RFS patients	< 50% caloric target	> 50% caloric target	*p* Value [a]
Number of patients	178	58	120	
Macronutrients (non)-nutritional, kcal				
3-day caloric intake	2386 [1732-3311]	1515 (503)	2928 [2340-3673]	**0.000**
3-day protein intake	472 [285-692]	259 (133)	623 (247)	**0.000**
3-day carbohydrate intake	1153 [785-1546]	699 [604-1020]	1422 [1084-1728]	**0.000**
3-day lipid intake	745 [476-1085]	462 [333-598]	914 [634-1295]	**0.000**
7-day caloric intake	9275 (2338)	7726 (2079)	10023 (2079)	**0.000**
7-day protein intake	2025 (569)	1710 (522)	2177 (528)	**0.000**
7-day carbohydrate intake	4166 [3322-5209]	3624 [2875-4451]	4513 [3530-5428]	**0.000**
7-day lipid intake	2758 [1991-3559]	2268 [1691-2891]	3175 [2207-3977]	**0.000**
Macronutrients (non)-nutritional, gr				
3-day protein intake	117.9 [71.1-173.0]	Unpublished data	155.8 (61.9)	**0.000**
3-day carbohydrate intake	288.1 [196.2-386.6]	174.8 [150.9-255.0]	355.4 [271.0-431.9]	**0.000**
3-day lipid intake	82.7 [52.9-120.6]	51.3 [37.0-66.4]	101.5 [70.4-143.8]	**0.000**
7-day protein intake	506.2 (142.1)	427.6 (130.6)	544.2 (131.9)	**0.000**
7-day carbohydrate intake	1041.5 [830.5-1302.3]	906.0 [718.8-1112.8]	1128.1 [882.4-1356.9]	**0.000**
7-day lipid intake	306.4 [221.2-395.4]	251.9 [187.9-321.2]	352.8 [245.3-441.9]	**0.000**
Caloric and protein adequacy, %				
3-day caloric adequacy	58.6 [46.0-80.0]	36.3 [29.7-45.6]	71.2 [58.5-87.9]	**0.000**
7-day caloric adequacy	84.6 (19.5)	69.5 (19.6)	91.8 (14.8)	**0.000**
3-day protein adequacy	46.7 [27.4-65.2]	25.1 [13.6-31.4]	59.1 (20.6)	**0.000**
7-day protein adequacy	72.6 [58.7-85.1]	58.5 [45.7-71.0]	78.7 [67.3-89.3]	**0.000**
Non-nutritional to total caloric load, %				
3-day glucose	10.2 [2.5-20.3]	20.6 [9.0-30.9]	15.0 [6.2-27.5]	**0.000**
7-day glucose	4.5 [2.0-8.5]	7.2 [4.1-12.2]	3.5 [1.4-6.9]	**0.000**
3-day propofol	4.3 [0.34-13.9]	8.0 [0.07-16.0]	3.5 [0.6-13.2]	0.384
7-day propofol	3.1 [0.9-7.2]	3.5 [1.1-6.8]	2.9 [0.7-8.0]	0.742

RFS = Refeeding syndrome. Caloric or protein adequacy = percentage realized calorie or protein intake compared to 100% of caloric or protein target respectively. Values: mean (standard deviation), median [interquartile range] i.e. 1st – 3rd quartile.

[a] *p* Values were calculated using Independed Samples t-test or Mann-Whitney U test where appropriate. Bold = $p < 0.05$, italic = $p < 0.10$.

Slingerland-Boot R, Rooijakkers EF, Van Zanten AR

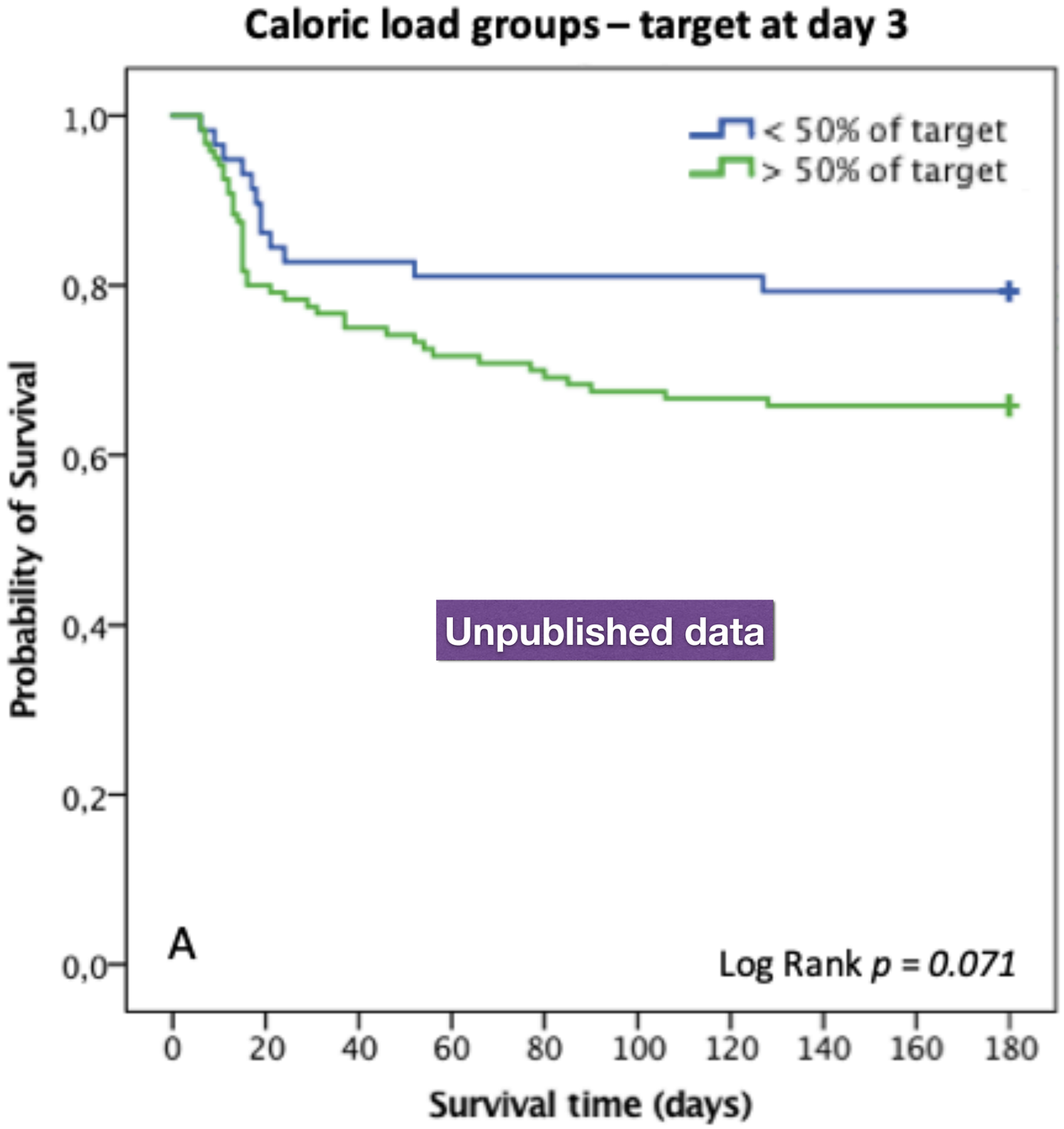
Variables	RFS patients	< 50% caloric target	> 50% caloric target	*p* Value [a]
Number of patients	178	58	120	
Mortality, N (%)				
ICU	26 (14.6%)	7 (12.1%)	19 (15.8%)	0.505
Hospital	38 (21.3%)	10 (17.2%)	28 (23.3%)	0.353
3 months	50 (28.1%)	11 (19%)	39 (32.5%)	*0.060*
6 months	53 (29.8%)	12 (20.7%)	41 (34.2%)	*0.065*
Length of stay, days				
ICU	14 [11-21]	13 [11-20]	14 [10-22]	0.928
Hospital	23 [17-35]	24 [17-34]	23 [17-36]	0.821
Duration of mechanical ventilation, days	10 [8-15]	10 [8-14]	10 [8-15]	0.969

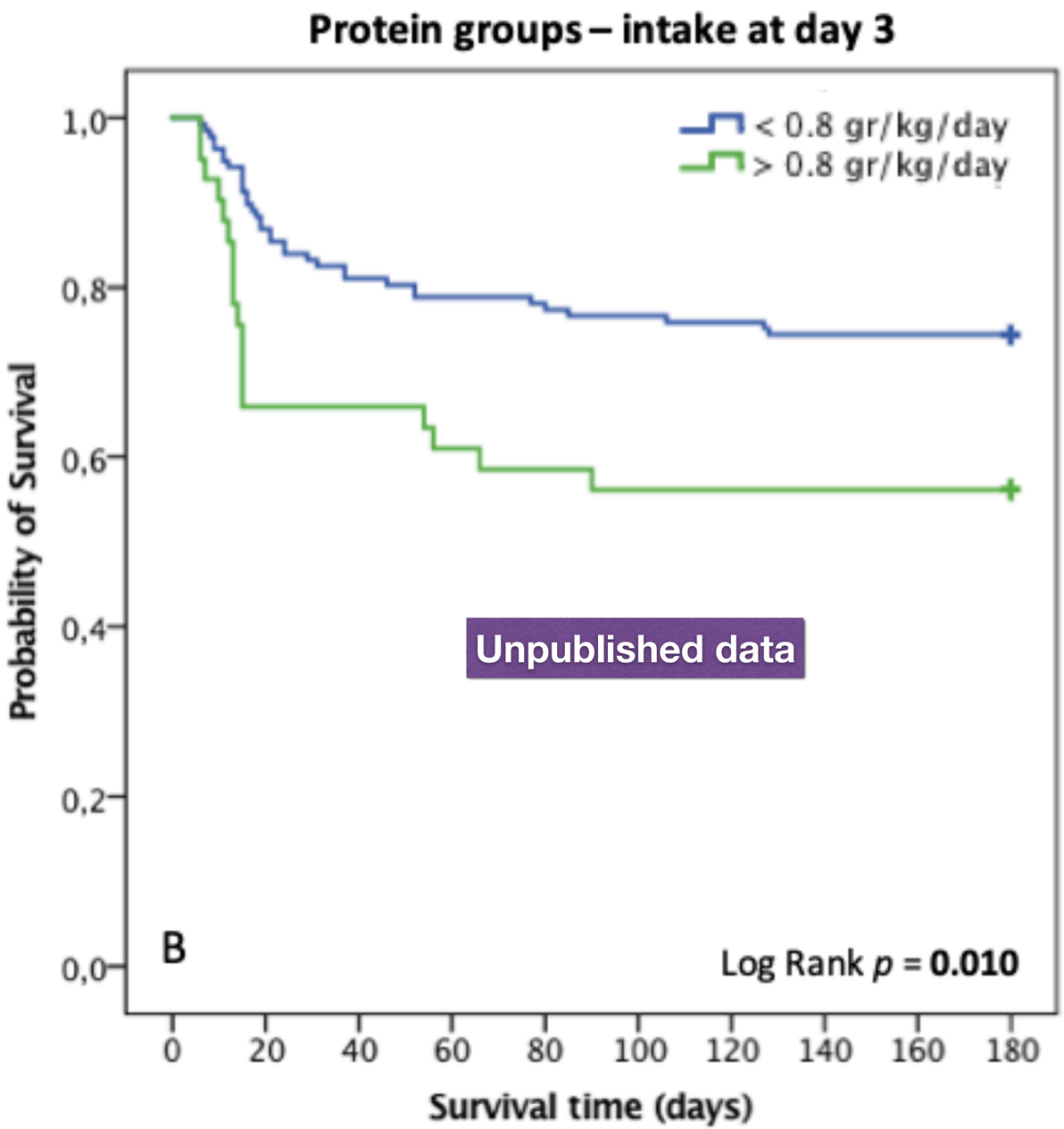
Unpublished data

RFS = Refeeding syndrome, < 50% caloric target = less than 50 percent of caloric target reached at day 3, > 50% caloric target = more than 50 percent of caloric target reached at day 3, N = number of patients, ICU = Intensive Care Unit. Values: N (%), median [interquartile range] i.e. 1st – 3rd quartile.

[a] *p* Values were calculated using Mann-Whitney U test or chi-square test where appropriate. Bold = $p < 0.05$, italic = $p < 0.10$.

Slingerland-Boot R, Rooijakkers EF, Van Zanten AR





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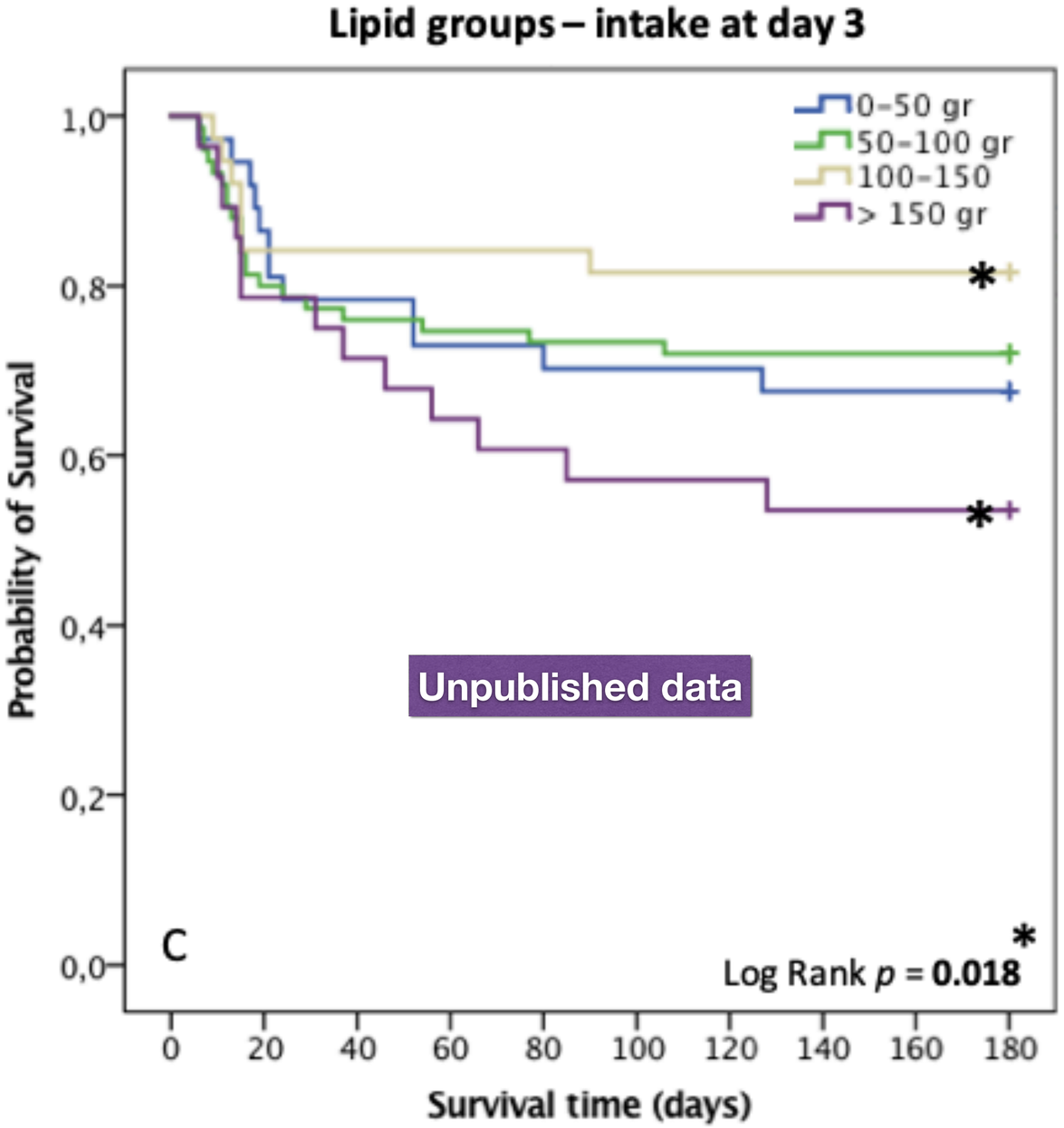

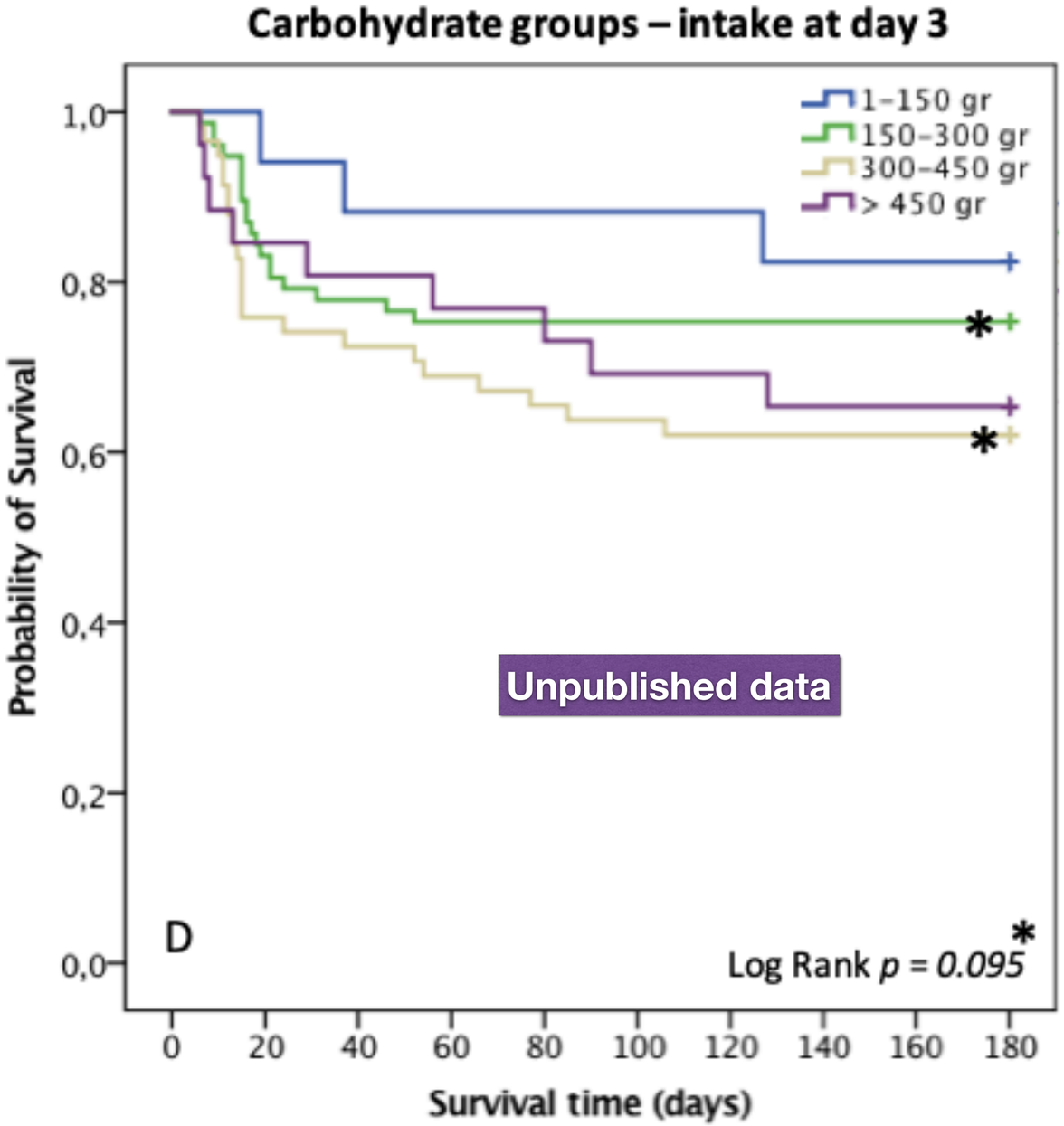

Slingerland-Boot R, Rooijakkers EF, Van Zanten AR

6-month mortality in RFS

Variables	Univariable COX regression		Multivariable COX regression	
	HR (95% CI) [a]	*p* Value	HR (95% CI) [a]	*p* Value
Caloric load < 50% of target	0.75 (0.50-1.03)	*0.077*	0.80 (0.50-1.26)	0.328
Protein load < 0.8 gr/kg/day	0.69 (0.52-0.92)	**0.012**	0.64 (0.44-0.93)	**0.019**
NUTRIC score	1.37 (1.16-1.62)	**0.000**	1.43 (1.20-1.70)	**0.000**
BMI	0.95 (0.89-1.00)	*0.055*	0.94 (0.89-0.99)	**0.037**
Admission types		*0.099*		**0.019**
Emergency surgery vs medical	0.52 (0.28-0.96)	**0.038**	0.44 (0.32-0.83)	**0.012**
Elective surgery vs medical	1.35 (0.82-2.24)	0.237	1.29 (0.77-2.18)	0.337
Carbohydrate load, vs group > 450 gr		0.235		0.851
0-150 gr	0.58 (0.24-1.39)	0.223	0.81 (0.30-2.16)	0.674
150-300 gr	0.89 (0.55-1.44)	0.643	1.01 (0.60-1.73)	0.945
300-450 gr	1.49 (0.94-2.38)	*0.092*	1.26 (0.75-2.13)	0.382
Lipid load, vs group > 150 gr		0.152		**0.009**
0-50 gr	1.07 (0.65-1.75)	0.800	3.37 (1.27-4.44)	**0.007**
50-100 gr	0.95 (0.63-1.45)	0.826	1.10 (0.70-1.75)	0.672
100-150 gr	0.59 (0.32-1.07)	*0.084*	0.35 (0.18-0.68)	**0.002**

Unpublished data

RFS = refeeding syndrome, caloric load < 50% of target = less than 50 percent of caloric target reached at day 3, protein load < 0.8 gr/kg/day = less than 0.8 gr per kg actual body weight per day reached at day 3, NUTRIC score = Nutrition Risk In Critically ill score, BMI = Body Mass Index.
[a] HR (95% CI) = Hazard ration with 95% confidence interval, vs = versus.
Bold = $p < 0.05$, italic = $p < 0.10$.

Slingerland-Boot R, Rooijakkers EF, Van Zanten AR

Conclusions preliminary data RFS study

Unpublished data

- **Univariate strong trend that high caloric loading in the early phase of RFS/RH reduces 6-months survival**
- **After adjustment for covariates this effect disappears**
- **High protein intake during RFS/RH is associated with higher mortality**
- **For lipids a U-shaped association is found. Both low and high are associated with harm**
- **No associations for carbohydrates is found although this is the suggested pathophysiology of RFS/RH**

Post-hoc RFS analysis from the Permit trial by Arabi and coworkers

Interpretation why the full feeding negative effect may not have been seen

Unpublished data

- **As no difference in protein intake was observed due to protein supplementation, this may have abolished the benefits of caloric restriction in the permissive underfeeding group with Refeeding Hypophosphatemia**

What we do?

- Measure serum phosphate daily for 3 days after ICU admission (we start EN within 6 hours after admission)
- In case normal on admission (>0.70 mmol/l) and drop below 0.65 mmol/l (delta >0.16 mmol/l), RFS protocol
- Back to 25% of energy target (<500 kcal/day)
- Supplement electrolytes
- Thiamine
- After 48 hours increase per day (25-50-75-100% target)
- No protein supplementation during this phase

What is in the guidelines?

Recommendation 55

Electrolytes (potassium, magnesium, phosphate) should be measured at least once daily for the first week.

Grade recommendation: GPP – strong consensus (92% agreement)

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)

Recommendation 57

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

Grade recommendation: B – strong consensus (100% agreement)

Caloric Restriction is essential in patients with Refeeding Hypophosphatemia and Refeeding Syndrome

Supplementation of Vitamin B1, Phosphate, Magnesium, Potassium and Insulin is not enough in ICU patients.

ESPEN ICU Nutrition guidelines for adults. Clin Nutr 2019

Conclusions

- Is refeeding hypophosphatemia rare?
  - NO, RH may be encountered frequently during critical illness among long stay ICU patients (1/3 meets criteria)
- Can we use risk factors to identify RH/RFS in the ICU?
  - NO, only difference in potassium and magnesium on admission (not clinically relevant)
  - NO, in ICU patients typical predictors fail to identify RFS
  - YES, Phosphate monitoring is mandatory during 72h after start feeding
- Is refeeding syndrome relevant for the critically ill patient?
  - Yes, new hypophosphatemia (<0.65 mmol/l) <72 hours after ICU admission/feeding warrants caloric restriction (< 500 kcal/day), and thiamine and electrolyte supplementation to improve survival
- Is refeeding syndrome increased mortality associated with carbohydrate intake in the ICU patient?
  - NO, in ICU patients high protein intake during RFS is associated with increased mortality, not carbohydrate intake. No protein supplementation during caloric restriction should be considered

Refeeding Syndrome in the ICU: New insights in pathophysiology, diagnosis and treatment

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Disclosures

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DANONE NUTRICIA

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Inclusion fees for patients in the MetaPlus trial published in JAMA, August 2014, from Nutricia were paid to the local ICU research foundation.

ICU Nutrition Academy in the Netherlands and website www.criticalcarenutrition.nl