Refeeding syndrome in the ICU, is it relevant?
Relevance in ICU remains unclear
What is Refeeding Syndrome?

• Starvation
  – ↓glucose levels within 24 – 72 hours
  – ↑glucagon + ↓insulin
    • Glycogenolysis → stores depleted in 72 hours max

Gluconeogenesis

Healthy volunteers
• Metabolic rate ↓25%
• Fat provides >90% of energy

Loss of body fat and protein
Depletion of potassium, phosphate, magnesium

Khan et al 2011
Koekkoek & Van Zanten 2018
Glucose

Insulin

PO₄

K

Mg

PO₄

Glucagon

Insulin

PO₄

K

Mg

PO₄

Glucose

Insulin

PO₄

K

Mg

PO₄

Cell

Serum

Boot et al 2018

Koekkoek & Van Zanten 2018
Glucose, Insulin, Resistance, PO₄, K, Mg, Na, ADP, ATP, Thiamine, Lactic Acidosis, Serum

Boot et al 2018
Koekkoek & Van Zanten 2018
What is refeeding syndrome?

Metabolic and electrolyte derangements

- **Hypophosphatemia**
- Hypomagnesaemia
- Hypokalemia
- Hypocalcaemia
- Vitamin deficiencies (thiamine)
- Glucose intolerance/insulin resistance
- Hypernatremia
- Fluid overload

Refeeding syndrome =
Serum PO$_4$ < 0.65mmol/l within 72 hours
Decrease > 0.16mmol/l from previous level
The question is...

- What is the incidence of refeeding syndrome in the ICU?

- Can patients at risk of refeeding syndrome be identified? And how?

- How should these patients be treated? And does it make a difference?
ICU Hypophosphatemia Incidence

Hypophosphatemia in critically ill patients

Satoshi Suzuki MD, PhD, Moritoki Egi MD, PhD, Antoine G. Schneider MD, Rinaldo Bellomo MD, Graeme K. Hart MD, Colin Hegarty BSc

- 2730 critically ill adult patients
- 10504 phosphate measurements
- Hyperphosphatemia – 45%
- Hypophosphatemia – 20%
- Hypophosphatemia
  • = general marker of illness severity
  • ≠ Independent predictor of ICU/hospital mortality

Suzuki et al 2013
Incidence of RFS in ICU

Olthof et al. 2017

Refeeding syndrome = Serum PO$_4$ < 0.65 mmol/l within 72 hours
Decrease > 0.16 mmol/l from previous level
Incidence of RFS in ICU

Refeeding syndrome = Serum PO₄<0.65mmol/l or decrease >0.16mmol/l from previous level after start of nutrition

Ralib & Mat Nor 2018
Incidence of RFS in ICU

- Retrospective medical record review
- 117 patients
- Hypophosphatemia <0.77mmol/L (Severe <0.32mmol/L)
- Refeeding recorded in 52%
  - Severe hypophosphatemia in 10%
Incidence of RFS in ICU

Clinical Research

Hypophosphatemia in Enterally Fed Patients in the Surgical Intensive Care Unit

Common but Unrelated to Timing of Initiation or Aggressiveness of Nutrition Delivery

Eva Fuentes MD, D. Dante Yeh MD, Sadeq A. Quraishi MD, MHA, MMS, Emily A. Johnson RN, BSN, CCRN, Haytham Kaafarani MD, MPH, ... See all authors

Retrospective review
213 patients started on EN
39% Developed Refeeding hypophosphatemia

Fuentes et al 2016
Identifying patients at risk
## Identifying patients at risk

**Table 2.** Criteria to identify high risk of developing refeeding problems among non-ICU patients according to NICE

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient has one or more of the following:</td>
</tr>
<tr>
<td>BMI less than 18.5 or 16.5 if a baseline BMI is unknown.</td>
</tr>
<tr>
<td>Unintentional weight loss greater than 10% in the last 3–6 months.</td>
</tr>
<tr>
<td>Little or no nutritional intake for more than 5 days.</td>
</tr>
<tr>
<td>Low levels of potassium or sodium prior to feeding.</td>
</tr>
<tr>
<td>Or patient has one or more of the following:</td>
</tr>
<tr>
<td>BMI less than 18.5 or 16.5 if a baseline BMI is unknown.</td>
</tr>
<tr>
<td>Unintentional weight loss greater than 10% in the last 3–6 months.</td>
</tr>
<tr>
<td>Little or no nutritional intake for more than 5 days.</td>
</tr>
<tr>
<td>A history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics.</td>
</tr>
</tbody>
</table>

— Koekkoek & Van Zanten 2018
Identifying patients at risk

• Prospective cohort study
• 243 patients started on nutrition support – ward and ICU
• Baseline low serum Mg ➔ independent predictor of RFS
  • Sensitivity 66.7%; Specificity >80%
Identifying patients at risk

But is it clinically relevant?

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 337)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>mean (SD)</td>
</tr>
<tr>
<td>Gender, female</td>
<td>N (%)</td>
</tr>
<tr>
<td>BMI on admission kg/m²</td>
<td>mean (SD)</td>
</tr>
<tr>
<td>BMI&lt;18.5 kg/m²</td>
<td>N (%)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>median [IQR]</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>median [IQR]</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>median [IQR]</td>
</tr>
<tr>
<td>Bilirubin (mmol/L)</td>
<td>median [IQR]</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>median [IQR]</td>
</tr>
</tbody>
</table>

Olthof et al 2017
Table 1. Identification of critically ill patients at risk for refeeding syndrome

Daily monitoring of serum phosphate and other electrolytes such as potassium, magnesium, especially during the first 72 h after the start of nutritional support, irrespective of the route of feeding used.

A decrease of serum phosphate levels of at least 0.16 mmol/l to below 0.65 mmol/l from normal levels on ICU admission within 72 h after the commencement of nutrition after excluding other causes of hypophosphatemia (refeeding hypophosphatemia) is suggestive for refeeding syndrome.

Among reasons not to classify patients as having refeeding hypophosphatemia or refeeding syndrome based on low serum phosphate levels are ongoing renal replacement therapy, recent parathyroidectomy or pharmacologic treatment for hyperphosphatemia.
Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study

Laura E. Olthof, W.A.C. Kristine Koekkoek, Coralien van Setten, Johannes C.N. Kars, Dick van Blokland, Arthur R.H. van Zanten

Department of Intensive Care Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, The Netherlands

Department of Internal Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, The Netherlands

Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, The Netherlands

Olthof et al 2017
The Evidence in Critical Illness

All ICU admissions between 01-01-2011 and 31-12-2015 (n = 2237)

Patients receiving invasive mechanical ventilation > 7 days (n = 546)

Not eligible (n=208)
- Multiple ICU admissions during hospital admission (n=25)
- Receiving renal replacement therapy (n=130)
- Hypophosphatemia on admission (n=39)
- OHCA receiving therapeutic hypothermia (n=14)

Eligible (n=338)

Excluded (n=1)
- Insufficient nutritional data

Enrolment (n=337)

Refeeding syndrome (n=124)
- Developed refeeding-induced hypophosphatemia
  - Low Caloric intake (n=35) <50% of caloric target day 3
  - High Caloric intake (n=89) <50% of caloric target day 3

No refeeding syndrome (n=213)
- Normal serum phosphate levels during refeeding period
  - Low Caloric intake (n=66) <50% of caloric target day 3
  - High Caloric intake (n=147) <50% of caloric target day 3

Olthof et al 2017
The Evidence in Critical Illness

A

B

p<0.001

p<0.001

Olthof et al 2017
The Evidence in Critical Illness

p < 0.001

P = 0.001

Olthof et al 2017
The Evidence in Critical Illness

Log rank RFS p = 0.018
Log rank no RFS p = 0.72

Olthof et al 2017
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 WJ Harrigan, for the Refeeding Syndrome Trial Investigators Group*
The Evidence in Critical Illness

Calorie restriction protocol:

- ↓ to 20kCal/h for 48 hours
- If PO₄ is normal increase to
  - 40kCal/hr for 24 hours
  - 60kCal/hr for 24 hours
  - 80% goal for 24 hours
  - 100% goal by day 4

Doig et al 2015
The Evidence in Critical Illness

**D** Lowest daily serum phosphates

**B** Intravenous phosphate replacement dose

- **Standard care (n=165)**
- **Caloric management (n=166)**
The Evidence in Critical Illness

![Graph showing highest daily blood glucose levels over time. The graph compares Standard care (n=165) and Caloric management (n=166). Significant differences are marked with asterisks (*).](image-url)

Doig et al 2015
The Evidence in Critical Illness

![Graph showing highest daily arterial lactate levels.](image)

Days in ICU after study enrolment

- Standard care (n=165)
- Caloric management (n=166)

Doig et al 2015
The Evidence in Critical Illness

A Overall survival time

- Standard care
- Caloric management

Survival (%)

P=0.002

Doig et al 2015
Why calorie restriction?

• Poorly understood

• Hypophosphatemia
  ➔ cellular dysfunction
  ➔ Independent risk factor – infection/sepsis/shock

• Insulin resistance
  ➔ Infection and sepsis risk

Olthof et al 2017
Management of RFS

### Table 2. Treatment strategy for critically ill patients with refeeding hypophosphatemia and refeeding syndrome

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte supplementation (phosphate, magnesium, potassium)</td>
</tr>
<tr>
<td>Glucose monitoring to prevent hypoglycemia and hyperglycemia</td>
</tr>
<tr>
<td>Intravenous insulin administration in case of hyperglycemia</td>
</tr>
<tr>
<td>Correction of fluid overload if necessary</td>
</tr>
<tr>
<td>Thiamine supplementation at a minimum dose of 100 mg daily, for at least 7-10 days</td>
</tr>
<tr>
<td>Restriction of total caloric intake to a maximum of 500 kcal/24 h during the first 48 h after the diagnosis of refeeding hypophosphatemia and refeeding syndrome</td>
</tr>
<tr>
<td>Consider the amount of nonnutritional calories from propofol, citrate (renal replacement therapy) and intravenous carbohydrate solutions as these may increase the total caloric load</td>
</tr>
<tr>
<td>Gradually advance feeding after 48 h of caloric restriction in daily steps of 25% of the target until the nutrition target is reached</td>
</tr>
</tbody>
</table>
Do we have any answers?

• What is the incidence of refeeding syndrome in the ICU?
  – RFS in ICU is fairly common – 37 – 52%

• Can patients at risk of refeeding syndrome be identified? And how?
  – No
  – Low baseline Mg and K - ? Clinical relevance
  – Monitor serum phosphate levels

• How should these patients be treated? And does it make a difference?
  – Yes, calorie restriction significantly improve outcome
  – 25% of requirements for 48hours
  – Increase if $PO_4$ normalize (50%, 75%, 100%)
  – Electrolyte and thiamine replacement