Refeeding syndrome – a practical approach

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&
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What will I cover?

• Definition, pathophysiology and consequences of RFS
• Who is at risk?
• Management and prevention
  – Available guidelines
  – Refeeding in anorexia nervosa
• PENG pocket guide to clinical nutrition 2018 recommendations
• Appraising the literature
Definition

• Metabolic and physiological problems of feeding malnourished patients

• Key factors involved
  – Glucose
  – Magnesium, Phosphate & Potassium
  – Vitamins (thiamine)
  – Fluid & sodium

• No internationally agreed definition making comparisons difficult
Starvation & Refeeding

Hypokalaemia
Hypomagnesaemia
Hypophosphataemia
Thiamine deficiency
Salt & water retention – oedema

Glycogen stores utilised

↓ Insulin production &
↑ Glucagon secretion

Gluconeogenesis =
Protein catabolism &
mobilisation of lipid

↑ Glucose uptake
↑ Uptake of
K⁺, Mg²⁺ & PO₄⁻
↑ Utilisation of
Thiamine

↑ Insulin secretion

Refeeding CHO main source of energy
(anabolism)

Protein, fat, mineral, electrolyte & vitamin
depletion – sodium & water intolerance

Refeeding syndrome

Adapted from Stanga et al (2008) EJCN, 62:687
Refeeding Syndrome

ECF

Na+/K+ Pump

ICF

Na+ → Mg²⁺ → Na+

K+ → K+

ATP

ADP

Krebs Cycle

ATP synthesis

PO₄⁻ & K⁺

Insulin

Glucose

Thiamine
## Consequences

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Cardiac</th>
<th>Respiratory</th>
<th>Neuro- muscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td>Altered myocardial function, Arrhythmia, congestive heart failure</td>
<td>Acute ventilatory failure</td>
<td>Lethargy, weakness, seizures, confusion, coma, paralysis, rhabdomyolysis</td>
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<tr>
<td>Potassium</td>
<td>Arrhythmia, cardiac arrest</td>
<td>Respiratory distress</td>
<td>Paralysis, weakness, rhabdomyolysis</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Arrhythmia, tachycardia</td>
<td>Respiratory depression</td>
<td>Ataxia, confusion, muscle tremors, weakness, tetany</td>
</tr>
<tr>
<td>Thiamine</td>
<td>Congestive heart failure &amp; lactic acidosis</td>
<td></td>
<td>Wernicke-Korsakoff syndrome, muscle weakness</td>
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</tbody>
</table>
# Who is at risk?

<table>
<thead>
<tr>
<th>Theme</th>
<th>Risk factor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease/clinical condition</strong></td>
<td>Anorexia nervosa, Crohn’s disease, small bowel obstruction, poorly controlled diabetes, pneumonia, dysphagia, complications post bariatric surgery, alcoholism and cancer</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td>Hypomagnesaemia - &lt;0.5mmol/L</td>
</tr>
<tr>
<td></td>
<td>- &lt;0.7mmol/L</td>
</tr>
<tr>
<td></td>
<td>Hypokalaemia - &lt;3.2mmol/L</td>
</tr>
<tr>
<td><strong>Nutritional support</strong></td>
<td>EN containing 34kcal/kg</td>
</tr>
<tr>
<td></td>
<td>PN containing 20kcal/kg</td>
</tr>
<tr>
<td></td>
<td>&lt;12mmol phosphate in first days PN</td>
</tr>
<tr>
<td></td>
<td>EN with a mean of 23kcal/kg</td>
</tr>
<tr>
<td></td>
<td>EN more than PN</td>
</tr>
<tr>
<td><strong>Starvation</strong></td>
<td>Prolonged fast - For 10 days</td>
</tr>
<tr>
<td></td>
<td>- For 7 days</td>
</tr>
<tr>
<td><strong>Malnutrition</strong></td>
<td>Weight loss - 5% in 1 month, 10% in 6 months</td>
</tr>
<tr>
<td></td>
<td>- &gt;15%</td>
</tr>
<tr>
<td></td>
<td>Low BMI - mean 12.3kg/m2</td>
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<tr>
<td></td>
<td>- mean 16.7kg/m2</td>
</tr>
<tr>
<td></td>
<td>- mean 16.2kg/m2</td>
</tr>
<tr>
<td></td>
<td>High nutrition risk score ≥3</td>
</tr>
</tbody>
</table>

Adapted from Fiedli et al. (2017) Nutrition, 35, p 151
Nutrition Support for Adults
Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition

D Grade evidence

METHODS, EVIDENCE & GUIDANCE

FEBRUARY 2006
Commissioned by the National Institute for Clinical Excellence
Patients at High Risk

- Patient has one or more of the following:
  - BMI <16kg/m²
  - Unintentional weight loss >15% over 3-6 months
  - Little or no nutritional intake for >10 days
  - Low levels of potassium, phosphate or magnesium prior to feeding

OR

- Patient has two or more of the following:
  - BMI less than 18.5kg/m²
  - Unintentional weight loss >10% over 3-6 months
  - Little or no nutritional intake for >5 days
  - A history of alcohol abuse or drugs including insulin, chemotherapy, antacids & diuretics
Patients at Extreme High Risk

- BMI <14kg/m²
- Negligible intake for more than 15 days

National Collaborating Centre for Acute Care, Feb 2006. Nutrition support in adults oral nutrition support, enteral tube feeding and parenteral nutrition
Identifying Risk – 2018 PENG recommendation

- Recommend using NICE (2006) guidelines as useful framework to identify RFS acknowledging its limitations

- Even when there appears to have been a sufficient level of oral intake to lower the risk of RFS, consideration should be given to the extent of any vomiting or malabsorption that may be present
Patients at High Risk

- Patient has one or more of the following:
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Additional considerations

- Due to homeostatic mechanisms it is common for serum concentrations of potassium, magnesium and phosphate to be within normal parameters prior to feeding.

- The presence of ketones in the urine may suggest a period of starvation which can provide an indication that RFS is more likely to occur.
Management/prevention of re-feeding syndrome
Nutrition Support for Adults
Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition

D Grade evidence
How to feed patients at risk (NICE 2006)

• High risk
  • *Consider* starting nutrition support at a maximum of 10kcal/kg increasing levels slowly to meet or exceed needs by 4 - 7 days
  • *Consider* restoring circulatory volume and monitoring fluid balance and overall clinical status closely

• Extreme high risk
  • *Consider* using only 5 kcal/kg/day and monitoring cardiac rhythm continually in these patients
How to feed patients at risk
(NICE 2006)

• *Consider* providing immediately before and during the first 10 days of feeding:
  — Oral thiamine 200-300 mg/day
  — Vitamin B co strong 1 or 2 tablets tds **OR**
  — Full dose intravenous vitamin B preparation if necessary
  — A balanced multivitamin/trace element supplement

• *Consider* providing oral, enteral or intravenous supplements of:
  — Potassium = **2 - 4mmol/kg/day**
  — Phosphate = **0.3 - 0.6mmol/kg/day**
  — Magnesium = IV 0.2 or oral 0.4 mmol/kg/day
    (unless pre-feeding plasma levels are high)
  — Pre feeding correction of low plasma levels unnecessary
What other guidelines exist in addition to NICE, 2006?
<table>
<thead>
<tr>
<th>Reference</th>
<th>Energy (macronutrient breakdown)</th>
<th>Daily electrolytes</th>
<th>Fluid</th>
<th>Micronutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solomen SM &amp; Kirby 1990</td>
<td>Week 1. <strong>20kcal/kg</strong></td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Dewar H &amp; Horvath R (2001) A pocket guide to clinical nutrition 2nd ed. BDA</td>
<td>Day 1. <strong>20kcal/kg</strong> Increase to full feeding during week one</td>
<td>Replenish as required</td>
<td>_</td>
<td>Thiamine IV <strong>2days</strong> → Oral 30 minutes before feeding Forceval daily</td>
</tr>
<tr>
<td>Fan et al Nutrition, 2004; 20: 346-350</td>
<td>Week 1. <strong>20kcal/kg</strong> (50% CHO:50% Fat)</td>
<td>Replenish as required</td>
<td>_</td>
<td>Supplement thiamine</td>
</tr>
<tr>
<td>Stanga et al Eur J Clin Nutr, 2008, 62:687</td>
<td>Day 1-3. 10kcal/kg and increase to 15kcal/kg (50-60% CHO:30-40% Fat) Day 4-6. 15-20kcal/kg</td>
<td>K 1-3mmol/kg Mg 0.3-0.4mmol/kg PO4 0.5-0.8mmol/kg Na &lt;1mmol/kg</td>
<td><strong>20-30ml/kg</strong></td>
<td>Thiamine 200-300mg daily IV/oral for <strong>3 days</strong> Vitamins 200% DRI Trace elements 10% DRI</td>
</tr>
<tr>
<td>Khan et al Gastro Res Pract, 2011 ii: 410971</td>
<td>Day 1. 10kcal/kg (50-60% CHO:30-40% Fat) Day 2-4. Increase by 5kcal/kg/day Day 5-7. 20-30kcal/day Day 8. 30kcal/day of full requirements</td>
<td>K: 1-3mmol/kg Mg 0.3-0.4mmol/kg PO4 0.5-0.8mmol/kg Na &lt;1mmol/kg</td>
<td><strong>20-30ml/kg</strong></td>
<td>Thiamine IV &amp; Vitamin B complex for <strong>3 days</strong> No Iron in week 1</td>
</tr>
</tbody>
</table>
Evidence in Anorexia Nervosa (AN)
<table>
<thead>
<tr>
<th>Study</th>
<th>Kcal</th>
<th>Electrolytes</th>
<th>Incid of RFS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golden et al (2013) J Adolesc Health. 53: p573</td>
<td>Compared &lt;1400kcal with &gt;1400 kcal/day 40-50%CHO</td>
<td>Administered if levels below normal range</td>
<td>Low PO4 26% (&gt;1400Kcal) &amp; 39% (&lt;1400Kcal)</td>
<td>Retrospective, 310 subjects Higher kcal group had significantly shorter LOS</td>
</tr>
<tr>
<td>Garber et al (2013) J Adolesc Health. 53: p579</td>
<td>Compared 1800kcal with 1100kcal / day</td>
<td>Electrolytes supplemented prophylactically</td>
<td>No symptomatic re-feeding but 45% low serum PO4</td>
<td>Retrospective, 56 subjects. Higher kcal resulted in faster wt gain 1800kcal group had higher baseline kcal intake</td>
</tr>
<tr>
<td>Madden et al (2015) J Eat Dis. 3:8</td>
<td>2400-3000kcal / day &lt;50%CHO</td>
<td>Prophylactic oral PO4</td>
<td>No biochemical or symptomatic re-feeding</td>
<td>Prospective cohort 78 subjects, combination of oral and NG intake. Mean Wt gain 2.8kg in 1 week.</td>
</tr>
<tr>
<td>Parker et al (2016) J Nutr Metab ID:5168978</td>
<td>&gt;2400kcal/d (58kcal/kg)</td>
<td>Prophylactic PO4</td>
<td>0% but 4%peripheral oedema, 1% low PO4, 7% low Mg, 2% low K</td>
<td>Retrospective, 162 subjects. 2.1kg wt gain/week.Avg 3 week admission</td>
</tr>
</tbody>
</table>
Some points to consider

- Lots of evidence but most is of weak quality with ++ limitations
- Much of the recent evidence is described in anorexia nervosa (AN)
- The management of refeeding is likely to change in different clinical situations
- Prior to 2006 a more generous provision of energy was recommended (20kcal/kg)
- Attitudes towards the NICE guidelines on RFS survey in UK:
  - 44% of doctors and 70% of dietitians followed the guidance
  - 39% believed them to be safe practice
  - 36% found them excessively cautious (De Silva et al, (2008) BMJ, 337, a680)
- Survey of dietetic practice:
  - 20kcal/kg was common increasing to full requirements over 3-4 days.
  - 75% of responders supplemented electrolytes reactively rather than prophylactically (Wagstaff (2011), J Hum Nutr Diet, 24, p.505–515)
### PENG recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a. Initiate nutrition support at 10-20kcal/kg</td>
<td>Likely safe if adequate electrolytes and micronutrients provided</td>
</tr>
<tr>
<td>1b. Higher energy intakes may be appropriate e.g. 20-40kcal/kg in AN or simple-uncomplicated starvation in specialised units</td>
<td>No evidence of RFS when higher intakes provided</td>
</tr>
<tr>
<td>2a. Where feeding is initiated at &lt;20kcal/kg and there is no evidence of RFS the feed should be increased aiming for 20kcal/kg within 48 hours</td>
<td>A high proportion of patients are categorised at risk of RFS but do not experience it. Under-feeding should be avoided to prevent exacerbating pre-existing malnutrition</td>
</tr>
<tr>
<td>2b. Where RFS is experienced a more cautious approach to increasing calorie provision should be adopted e.g. meeting or exceeding requirements by 4-7 days</td>
<td>Additional CHO may exacerbate RFS</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Rationale</td>
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</tr>
<tr>
<td>3a. Aim to provide approximately 40% of energy as carbohydrate</td>
<td>From what we understand of the pathophysiology CHO may be crucial to the development of RFS</td>
</tr>
<tr>
<td>3b. Avoid recommending fat free juice based oral nutritional supplements on the initiation of feeding</td>
<td>High CHO content</td>
</tr>
<tr>
<td>4a. Electrolytes should be provided from the onset of feeding</td>
<td>Prevention of RFS</td>
</tr>
<tr>
<td>4b. Dietitians should work as part of a MDT and discuss doses and routes with a pharmacist and doctor. Clinicians are encouraged to refer to local policies for the management of low electrolytes</td>
<td>All hospitals have different reference ranges as well as different electrolyte supplements on their formularies</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Rationale</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td>5a. Aim for fluid intake between 20-30ml/kg</td>
<td>Minimise the risk of fluid and sodium overload and refeeding oedema</td>
</tr>
<tr>
<td>5b. Aim for a sodium provision of &lt;1mmol/kg</td>
<td>Minimise the risk of fluid and sodium overload and refeeding oedema</td>
</tr>
<tr>
<td>6a. Thiamine should be provided from the onset of feeding however, there is limited evidence to make a specific recommendation</td>
<td>Increased demand for thiamine during refeeding and risk of deficiency</td>
</tr>
<tr>
<td>6b. Micronutrients should be provided from the onset of feeding however, there is limited evidence to make a specific recommendation</td>
<td>Likely to be deplete if malnourished and at risk of RFS</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Rationale</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>7. We recommend clinicians audit their practice regarding refeeding in their patient population</td>
<td>To inform practice and guidelines</td>
</tr>
</tbody>
</table>
Appraising the evidence in refeeding syndrome

- Consider the relevance of the studies to your clinical population
- Different criteria used for the identification and definition of RFS making direct comparison between studies difficult
- Different methods of nutrition support investigated
- Different management protocols of those deemed at risk e.g. whether prophylactic electrolyte replacement is administered
- Studies are often observational and retrospective
- Many small single centre reports
- The NICE guidelines on refeeding syndrome are based on D grade evidence and did not provide any references to support recommendations
Conclusion

• NICE guidelines for refeeding may be too cautious compared to previous guidelines & recent evidence

• There is a lack of robust evidence to support any guideline development

• New PENG guidelines provide a more pragmatic approach to management and focus on the available evidence, some of which requires local interpretation and application

• Likely to require different approaches/guidelines for patients at risk of re-feeding syndrome in different settings – consider literature relevant to your clinical area/population
Acknowledgements

Dr Alison Culkin – co-author of the refeeding chapter for the 2018 pocket guide

PENG Committee for reviewing and endorsing the recommendations made