



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

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

↑ Glucose uptake
↑ Uptake of
 K^+ , Mg^{2+} & PO_4^-
↑ Utilisation of
Thiamine

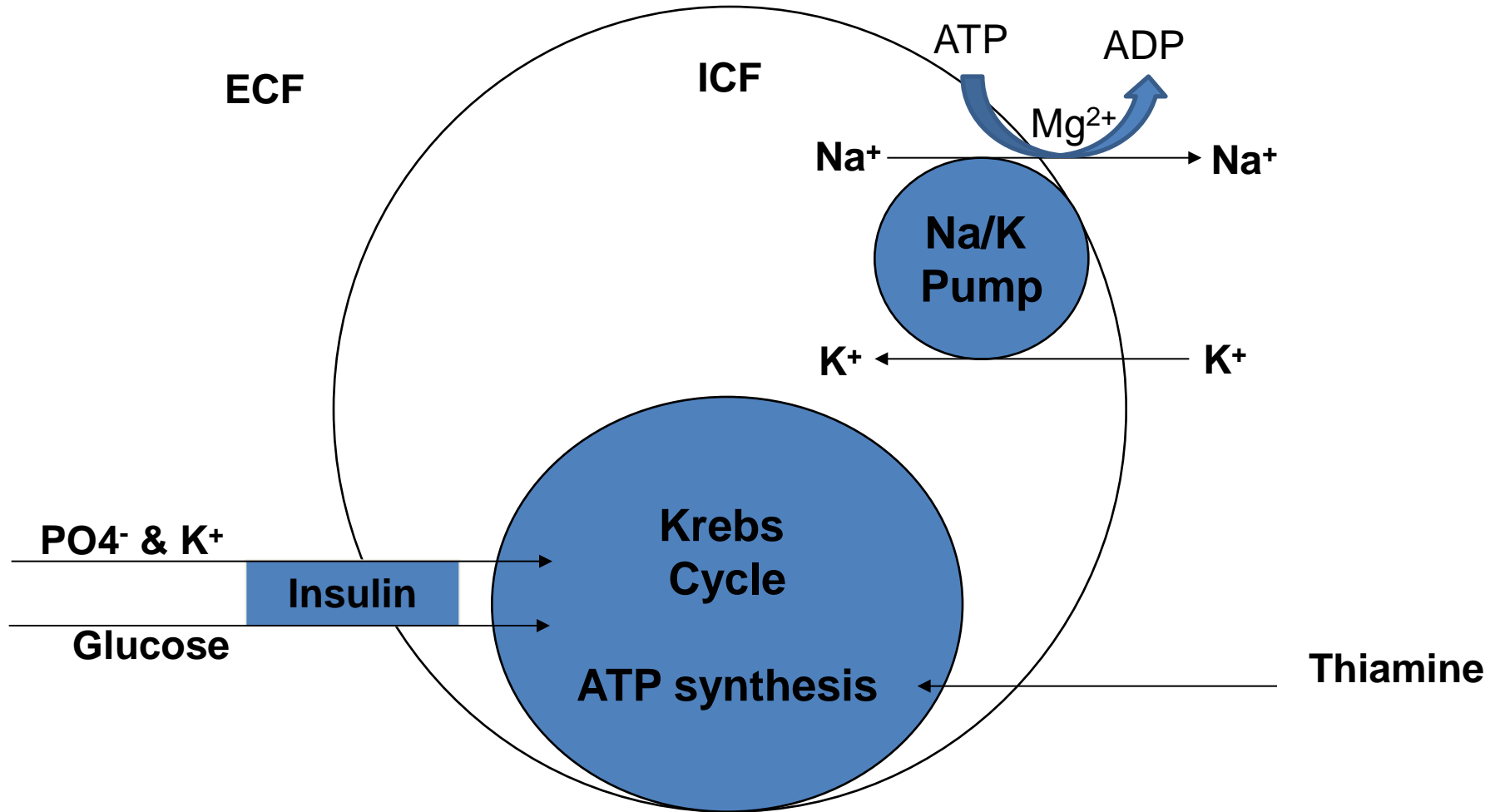
↑ Insulin
secretion

Refeeding
CHO main source of energy
(anabolism)

**Refeeding
syndrome**



Refeeding Syndrome





Consequences

	Cardiac	Respiratory	Neuro- muscular
Phosphate	Altered myocardial function, Arrhythmia, congestive heart failure	Acute ventilatory failure	Lethargy, weakness, seizures, confusion, coma, paralysis, rhabdomyolysis
Potassium	Arrhythmia, cardiac arrest	Respiratory distress	Paralysis, weakness, rhabdomyolysis
Magnesium	Arrhythmia, tachycardia	Respiratory depression	Ataxia, confusion, muscle tremors, weakness, tetany
Thiamine	Congestive heart failure & lactic acidosis		Wernicke-Korsakoff syndrome, muscle weakness



Who is at risk?

Theme	Risk factor(s)
Disease/clinical condition	Anorexia nervosa, Crohn's disease, small bowel obstruction, poorly controlled diabetes, pneumonia, dysphagia, complications post bariatric surgery, alcoholism and cancer
Biochemistry	Hypomagnesaemia - <0.5mmol/L - <0.7mmol/L Hypokalaemia - <3.2mmol/L
Nutritional support	EN containing 34kcal/kg PN containing 20kcal/kg <12mmol phosphate in first days PN EN with a mean of 23kcal/kg EN more than PN
Starvation	Prolonged fast - For 10 days - For 7 days
Malnutrition	Weight loss - 5% in 1 month, 10% in 6 months - >15% Low BMI - mean 12.3kg/m ² - mean 16.7kg/m ² - mean 16.2kg/m ² High nutrition risk score ≥3



*National Collaborating Centre
for Acute Care*

Nutrition Support for Adults Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition

METHODS, EVIDENCE & GUIDANCE

D Grade evidence

FEBRUARY 2006
Commissioned by the National Institute for
Clinical Excellence

Patients at High Risk

- Patient has one or more of the following:
 - BMI $<16\text{kg/m}^2$
 - 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/m^2
 - Unintentional weight loss $>10\%$ over 3-6 months
 - Little or no nutritional intake for >5 day
 - 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

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

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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



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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 0.4mmol/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?**

Reference	Energy (macronutrient breakdown)	Daily electrolytes	Fluid	Micronutrients
Solomen SM & Kirby 1990	Week 1. 20kcal/kg	–	–	–
Dewar H & Horvath R (2001) A pocket guide to clinical nutrition 2 nd ed. BDA	Day 1. 20kcal/kg Increase to full feeding during week one	Replenish as required	–	Thiamine IV 2days → Oral 30 minutes before feeding Forceval daily
Fan et al Nutrition, 2004; 20: 346-350	Week 1. 20kcal/kg (50% CHO:50% Fat)	Replenish as required		Supplement thiamine
Stanga et al Eur J Clin Nutr, 2008, 62:687	Day 1-3. 10kcal/kg and increase to 15kcal/kg (50-60% CHO:30-40% Fat) Day 4-6. 15-20kcal/kg	K 1-3mmol/kg Mg 0.3-0.4mmol/kg PO4 0.5-0.8mmol/kg Na <1mmol/kg	20-30ml/kg	Thiamine 200-300mg daily IV/oral for 3 days Vitamins 200% DRI Trace elements 10% DRI
Khan et al Gastro Res Pract, 2011 ii: 410971	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	K: 1-3mmol/kg Mg 0.3-0.4mmol/kg PO4 0.5-0.8mmol/kg Na <1mmol/kg	20-30ml/kg	Thiamine IV & Vitamin B complex for 3 days No Iron in week 1

Evidence in Anorexia Nervosa (AN)

Study	Kcal	Electrolytes	Incid of RFS	Comments
<i>Gentile et al (2010) Clin Nutr 29: p627</i>	42kcal/kg	Majority supplemented with prophylactic PO4 & K, rarely Mg.	No biochemical or symptomatic re-feeding	Retrospective cohort study of 33 subjects
<i>Golden et al (2013) J Adolesc Health. 53: p573</i>	Compared <1400kcal with >1400 kcal/day 40-50%CHO	Administered if levels below normal range	Low PO4 26% (>1400Kcal) & 39% (<1400Kcal)	Retrospective, 310 subjects Higher kcal group had significantly shorter LOS
<i>Garber et al (2013) J Adolesc Health. 53: p579</i>	Compared 1800kcal with 1100kcal / day	Electrolytes supplemented prophylactically	No symptomatic re-feeding but 45% low serum PO4	Retrospective, 56 subjects. Higher kcal resulted in faster wt gain 1800kcal group had higher baseline kcal intake
Madden et al (2015) J Eat Dis. 3:8	2400-3000kcal/ day <50%CHO	Prophylactic oral PO4	No biochemical or symptomatic re-feeding	Prospective cohort 78 subjects, combination of oral and NG intake. Mean Wt gain 2.8kg in 1 week.
Parker et al (2016) J Nutr Metab ID:5168978	>2400kcal/d (58kcal/kg)	Prophylactic PO4	0% but 4% peripheral oedema, 1% low PO4, 7% low Mg, 2% low K	Retrospective, 162 subjects. 2.1kg wt gain/week. Avg 3 week admission

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*)

Manging RFS in high and extremely high risk patients– 2018 PENG recommendation

Recommendation	Rationale
1a. Initiate nutrition support at 10-20kcal/kg	Likely safe if adequate electrolytes and micronutrients provided
1b. Higher energy intakes may be appropriate e.g. 20-40kcal/kg in AN or simple-uncomplicated starvation in specialised units	No evidence of RFS when higher intakes provided
2a. Where feeding is initiated at <20kcal/kg and there is no evidence of RFS the feed should be increased aiming for 20kcal/kg within 48 hours	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
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	Additional CHO may exacerbate RFS

Recommendation	Rationale
3a. Aim to provide approximately 40% of energy as carbohydrate	From what we understand of the pathophysiology CHO may be crucial to the development of RFS
3b. Avoid recommending fat free juice based oral nutritional supplements on the initiation of feeding	High CHO content
4a. Electrolytes should be provided from the onset of feeding	Prevention of RFS
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	All hospitals have different reference ranges as well as different electrolyte supplements on their formularies

Recommendation	Rationale
5a. Aim for fluid intake between 20-30ml/kg	Minimise the risk of fluid and sodium overload and refeeding oedema
5b. Aim for a sodium provision of <1mmol/kg	Minimise the risk of fluid and sodium overload and refeeding oedema
6a. Thiamine should be provided from the onset of feeding however, there is limited evidence to make a specific recommendation	Increased demand for thiamine during refeeding and risk of deficiency
6b. Micronutrients should be provided from the onset of feeding however, there is limited evidence to make a specific recommendation	Likely to be deplete if malnourished and at risk of RFS

Recommendation

7. We recommend clinicians audit their practice regarding refeeding in their patient population

Rationale

To inform practice and guidelines

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

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