NICE or not so NICE
Refeeding Guidelines

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Introduction

Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited

Roland L. Weinsier, M.D., Dr.P.H. and Carlos L. Krumdieck, M.D., Ph.D.

ABSTRACT  Although cachectic patients are relatively well adapted to their calorically deprived state, they are prone to acute metabolic imbalances when infused with hypertonic solutions of dextrose and amino acids. Of particular concern is hypophosphatemia and its associated disorders of cardiac, pulmonary, hematological, and neuromuscular functions. This report describes two chronically malnourished but stable patients who were given aggressive total parenteral nutrition support, which was rapidly followed by acute cardiopulmonary decompensation associated with severe hypophosphatemia and other metabolic abnormalities. Despite attempts at correction, progressive multiple systems failure led to death. In light of the high prevalence of hospital malnutrition and the ready availability of total parenteral nutrition, attention is brought to these examples of how overzealous nutrition repletion can paradoxically precipitate deterioration in clinical status.  Am. J. Clin. Nutr. 34: 393–399, 1981.

KEY WORDS  Total parenteral nutrition, hyperalimentation, hypophosphatemia, hospital malnutrition, protein-calorie malnutrition, marasmus

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
- Prevalence currently unknown
Starvation & Refeeding

Glycogen stores utilised

↓ Insulin production &
↑ Glucagon secretion

Gluconeogenesis = Protein catabolism & mobilisation of lipid

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

↑ Insulin secretion

Refeeding syndrome

CHO main source of energy (anabolism)

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

Refeeding syndrome

Hypokalemia
Hypomagnesaemia
Hypophosphataemia
Thiamine deficiency
Salt & water retention – oedema

Refeeding Syndrome

- Na/K Pump
- Na\(^+\) to Na\(^+\)
- K\(^+\) to K\(^+\)
- PO\(_4\)\(^-\) & K\(^+\)
- Insulin
- Glucose
- TCA Cycle
- ATP synthesis
- Thiamine & Mg\(^{2+}\)
## Consequences

<table>
<thead>
<tr>
<th></th>
<th>Cardiac</th>
<th>Respiratory</th>
<th>Neuro- muscular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phosphate</strong></td>
<td>Altered myocardial function, Arrhythmia, congestive heart failure</td>
<td>Acute ventilatory failure</td>
<td>Lethargy, weakness, seizures, confusion, coma, paralysis, rhabdomyolysis</td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td>Arrhythmia, cardiac arrest</td>
<td>Respiratory distress</td>
<td>Paralysis, weakness, rhabdomyolysis</td>
</tr>
<tr>
<td><strong>Magnesium</strong></td>
<td>Arrhythmia, tachycardia</td>
<td>Respiratory depression</td>
<td>Ataxia, confusion, muscle tremors, weakness, tetany</td>
</tr>
<tr>
<td><strong>Thiamine</strong></td>
<td>Congestive heart failure &amp; lactic acidosis</td>
<td></td>
<td>Wernicke-Korsakoff syndrome, muscle weakness</td>
</tr>
</tbody>
</table>
Nutrition support in adults
Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition
Patients at High Risk (NICE 2006)

- 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 day
  - A history of alcohol abuse or drugs including insulin, chemotherapy, antacids & diuretics

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

D Grade Evidence
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

**D Grade Evidence**
<table>
<thead>
<tr>
<th>Reference</th>
<th>Energy</th>
<th>Protein</th>
<th>Electrolytes</th>
<th>Fluid</th>
<th>Micro nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solomen &amp; Kirby (1990) JPEN, 14:90</td>
<td>20kcal/kg</td>
<td>1.2-1.5g</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Crook et al (2001) Nutrition. 7:632</td>
<td>20kcal/kg</td>
<td>1.2-1.5g</td>
<td>Replenish as required</td>
<td>_</td>
<td>Thiamine IV 48hrs → Oral</td>
</tr>
<tr>
<td>Kraft et al (2005) Nutr Clin Pract. 20:625</td>
<td>25% of requirements</td>
<td>_</td>
<td>10-15mmol of PO4/1000kcal Replenish as required</td>
<td>&lt;1L/d</td>
<td>Thiamine IV 50-100mg/d or 100mg PO 5-7d &amp; multivitamin</td>
</tr>
<tr>
<td>Stanga et al (2008) Eur J Clin Nutr. 62:687</td>
<td>10kcal/kg 50-60% CHO 30-40% Fat</td>
<td>10-20%</td>
<td>KCL: 1-3mmol/kg Mg 0.3-0.4mmol/kg PO4 0.5-0.8mmol/kg Na &lt;1mmol/kg</td>
<td>20-30ml/kg</td>
<td>100% Thiamine IV 200-300 for 72hrs</td>
</tr>
</tbody>
</table>
Attitudes to NICE Refeeding Guidelines

- Unpublished survey of HCP
- 44% of doctors followed the guidance vs. 70% of dietitians
- 39% thought guidance was safe practice
- 36% thought excessively cautious
- Obstacle to providing adequate nutrition
- Other never seen refeeding despite providing 100% requirement from day 1

Dietetic Practice in Refeeding

- Questionnaire including 3 case studies
- 30.8% response rate, 89.8% had read NICE
- 66.9% changed practice based on NICE
- 89.5% do not wait for normal biochemistry
- Feed increased over 3-4 days
- 75% supplement electrolytes reactively
- Current practice is inconsistent but 20kcal/kg common
- Common themes: lack of evidence, overcautious & exacerbate malnutrition vs. better safe than sorry
- Clinical Judgment
- Advice on supplementation confusing or difficult to follow and often impractical.

Wagstaff (2011) JHND 24:505

- Joint report – Royal College of Physicians & Royal College of Psychiatrists working group
- Recommendation 8
- The key tasks of the in patient team are to:
  - safely re-feed the patient
  - avoid re-feeding syndrome caused by too rapid re-feeding
  - avoid underfeeding syndrome caused by too cautious rates of re-feeding
Refeeding in Anorexia Nervosa

- 33 in-patients with anorexia nervosa
  - Mean BMI $11.3 \pm 0.7 \text{kg/m}^2$, REE $777 \pm 145 \text{kcal/d}$

Treatment:

- Oral/enteral thiamine & B vitamins bd before feeding
- IV 5-10% glucose $\sim 20-40 \text{ml/hr}$ (n=29)
- NG feeding over 24 hr (n=30), ONS (n=3)

Refeeding in Anorexia Nervosa

<table>
<thead>
<tr>
<th>Time</th>
<th>Day 0</th>
<th>7 days</th>
<th>15 days</th>
<th>30 days</th>
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</thead>
<tbody>
<tr>
<td>Measured kcal/expenditure – kcal/day</td>
<td>776 ± 145</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteral feeding regimen – kcal/day</td>
<td>806 ± 269</td>
<td>1002 ± 270</td>
<td>1133 ± 420</td>
<td>1154 ± 420</td>
</tr>
<tr>
<td>Oral diet – kcal/day</td>
<td>431 ± 331 (25)$^b$</td>
<td>707 ± 320</td>
<td>890 ± 314</td>
<td>1162 ± 387</td>
</tr>
<tr>
<td>Glucose$^c$ kcal/day – i.v.$^d$ infusion</td>
<td>171 ± 56 (29)</td>
<td>186 ± 91 (28)</td>
<td>189 ± 113 (21)</td>
<td>194 ± 88 (15)</td>
</tr>
<tr>
<td>Phosphate mEq/day – i.v./oral</td>
<td>39.9 ± 24.8 (26)</td>
<td>45.0 ± 32.0 (25)</td>
<td>46.5 ± 32.0 (23)</td>
<td>32.5 ± 26.9 (23)</td>
</tr>
<tr>
<td>Potassium mEq/day – i.v./oral</td>
<td>33.0 ± 19.2 (21)</td>
<td>29.9 ± 13.9 (16)</td>
<td>29.7 ± 20.9 (15)</td>
<td>20 ± 8.2 (16)</td>
</tr>
<tr>
<td>Body weight – kg</td>
<td>29.1 ± 3.2</td>
<td>30.3 ± 3.8</td>
<td>31.35 ± 2.8</td>
<td>32.3 ± 2.9</td>
</tr>
<tr>
<td>BMI$^f$ – kg/m$^2$</td>
<td>11.3 ± 0.7</td>
<td>11.8 ± 0.7</td>
<td>12.2 ± 0.9</td>
<td>12.6 ± 0.9</td>
</tr>
<tr>
<td>Δ Body weight$^g$ – kg</td>
<td>0</td>
<td>1.2 ± 1.3</td>
<td>2.3 ± 1.8</td>
<td>3.2 ± 2.2</td>
</tr>
</tbody>
</table>

Day 1

NG feeding & glucose & oral food = Total kcal day 1 => 40kcal/kg
Majority supplemented with IV/oral phosphate (n=26) & potassium (n=21) and occasionally magnesium (n=3)

Refeeding Audit

Aims

- Determine the overall & comparative incidence of refeeding hypophosphataemia (RH) between EN & PN
- Assessment of the number of patients progressing to RH in those deemed at risk according to NICE (2006)
- Determine mortality at one week of those with RH
- Assess sensitivity & specificity of NICE guidelines

Method

- Retrospective study using dietetic record cards
- Inclusion: All patients referred for EN or PN over a 12 month period
- Exclusion: Serum phosphate of <0.6mmol/L & ICU
- Refeeding hypophosphatemia: ↓ in serum phosphate to <0.6mmol/L during the first 7 days of feeding
Results – Enteral

- Significant association between being at risk of RH and developing RH ($p=0.02$)
- No difference in mortality between those deemed at risk of RH and developing RH compared to those who did not develop RH ($p=0.53$)
Results – Parenteral

- No significant associations between being at risk of RH and developing RH ($p=0.31$)
Results

- Death was more common in EN compared to PN ($p<0.001$)
- No association between developing RH and death in EN and/or PN ($p=0.73$)
- At risk EN patients more likely to develop RH than PN ($p=0.003$)
Specificity & Sensitivity

- Specificity measures the proportion of negatives which are correctly identified (i.e. the % of patients correctly identified as not experiencing RH)
- Sensitivity measures the proportion of actual positives which are correctly identified as such (i.e. the % of patients correctly identified as experiencing RH)
- Parenteral
  - Moderate specificity (0.76) & poor sensitivity (0.5)
- Enteral
  - Moderate specificity (0.73) & poor sensitivity (0.38)
Discussion

- A third of patients were at risk of RH using NICE criteria
- A quarter developed RH but more common in EN
- Possible causes include:
  - Inadequate phosphate in enteral feeds
  - Lack of prophylactic supplementation
  - Poor absorption in the gut
  - Incretin effect? ↑ Insulin secretion from enteral vs. parenteral delivery of glucose
  - Experienced Nutrition Team prescribing PN
- RH may be common but not association with mortality
Occurrence of Refeeding

- Prospective cohort study
- 243 patients starting EN or PN
- 133 at risk of refeeding
- Predictors of refeeding (sensitivity of 67%):
  - Poor intake for >10 days
  - Weight loss of >15%
  - Low serum magnesium
- No deaths attributable to refeeding.
- Rare survivable phenomena
- Starvation is the most reliable predictor

The Challenge

R C T
Buddha & Goldilocks

Thank you for your attention
Case Study

- Male age 27
- Crohn’s disease diagnosed 2000
- SB resection 2002 & 2009
- Previous EN via PEG
- Resistant to medical intervention
- BO x 2/day semi formed
- Ht 1.88, Wt = 49kg, O/E oedema ~6kg
- Est dry wt 43kg, est BMI=12.2kg/m²
- Usual wt 55kg 3/12 ago, % wt loss 21.8%
- TST <5th, MAMC <5th, Handgrip 21kg <85% normal
# Risk of Refeeding

**Patients with any one of the following:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;16kg/m²</td>
<td></td>
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<tr>
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<td></td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low levels of K, PO₄ or Mg before feeding</td>
<td></td>
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</table>

**Patients with 2 or more of the following:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;18.5kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unintentional weight loss &gt;10% in 3-6/12</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>History of alcohol, insulin, chemotherapy, antacids or diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>WCC</td>
<td>Na</td>
</tr>
<tr>
<td>--------</td>
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</tr>
<tr>
<td>19/9/12</td>
<td>4.2</td>
<td>137</td>
</tr>
<tr>
<td>20/9/12</td>
<td>3.7</td>
<td>137</td>
</tr>
</tbody>
</table>

Receiving IV fluids with electrolytes (40mmol Mg & 80mmol KCL)
IV Thiamine given before feeding as enteral route compromised
# Risk of Refeeding

Patients with any **one** of the following:

<table>
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<th>No</th>
</tr>
</thead>
<tbody>
<tr>
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<td>✓</td>
<td></td>
</tr>
<tr>
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<td>✓</td>
<td></td>
</tr>
<tr>
<td>Very little or no food for &gt; 10 days</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Low levels of K, PO4 or Mg before feeding</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Patients with **2 or more** of the following:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
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<td>✓</td>
<td></td>
</tr>
<tr>
<td>Unintentional weight loss &gt;10% in 3-6/12</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Very little or no food for &gt; 5 days</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>History of alcohol, insulin, chemotherapy, antacids or diuretics</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Calculated PN Requirements

- BMR = 1233kcal + stress 0% (apyrexic & CRP 59) + activity 20% = 247kcal = Total = 1480kcal
- N\textsubscript{2} = 0.3g/kg = 12.9g/day
- Fluid = 35ml/kg = 1505ml
- GOR = 991kcal
- Sodium 1-1.5mmol/kg = 43-65mmol
- Potassium 1-1.5mmol/kg = 43-65mmol
- Calcium 0.1-0.15mmol/kg = 4.3-6.5mmol
- Magnesium 0.1-0.2mmol/kg = 4.3-8.6mmol
- Phosphate 0.5-0.7mmol/kg = 21.5-30mmol
# Requirements

<table>
<thead>
<tr>
<th></th>
<th>Calculated requirements</th>
<th>NICE</th>
<th>Prescribed</th>
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</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>1480</td>
<td>215</td>
<td>1400</td>
</tr>
<tr>
<td>Kcal/kg</td>
<td>?</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>Glucose (kcal)</td>
<td>991</td>
<td>?</td>
<td>400</td>
</tr>
<tr>
<td>Lipid (kcal)</td>
<td>?</td>
<td>?</td>
<td>1000</td>
</tr>
<tr>
<td>Nitrogen (g)</td>
<td>12.9</td>
<td>6.5</td>
<td>9</td>
</tr>
<tr>
<td>K (mmol)</td>
<td>43-65</td>
<td>86-172</td>
<td>100</td>
</tr>
<tr>
<td>Ca (mmol)</td>
<td>4.3-6.5</td>
<td>?</td>
<td>6</td>
</tr>
<tr>
<td>PO4 (mmol)</td>
<td>21.5-30</td>
<td>12.9-25.8</td>
<td>30</td>
</tr>
<tr>
<td>Mg (mmol)</td>
<td>4.3-8.6</td>
<td>4.3-8.6</td>
<td>30</td>
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</table>
# PN & Biochemistry

<table>
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<tr>
<th>Date</th>
<th>N2</th>
<th>Glucose</th>
<th>Lipid</th>
<th>Na</th>
<th>K</th>
<th>Mg</th>
<th>Ca</th>
<th>PO4</th>
<th>Volume</th>
<th>Rate</th>
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<tr>
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<td>9</td>
<td>400</td>
<td>1000</td>
<td>60</td>
<td>100</td>
<td>30</td>
<td>6</td>
<td>30</td>
<td>1500</td>
<td>24</td>
</tr>
<tr>
<td>24/9/12</td>
<td>9</td>
<td>800</td>
<td>571</td>
<td>60</td>
<td>100</td>
<td>30</td>
<td>6</td>
<td>30</td>
<td>1500</td>
<td>24</td>
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<tr>
<td>27/9/12</td>
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<td>1000</td>
<td>571</td>
<td>60</td>
<td>80</td>
<td>30</td>
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<table>
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<tr>
<th>Date</th>
<th>WCC</th>
<th>Na</th>
<th>K</th>
<th>Cr</th>
<th>Urea</th>
<th>CRP</th>
<th>ALT</th>
<th>AP</th>
<th>Bili</th>
<th>Alb</th>
<th>Ca</th>
<th>Mg</th>
<th>PO4</th>
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<tbody>
<tr>
<td>19/9/12</td>
<td>4.2</td>
<td>137</td>
<td>3.3</td>
<td>41</td>
<td>2.7</td>
<td>59</td>
<td>18</td>
<td>148</td>
<td>4</td>
<td>7</td>
<td>1.85</td>
<td>&lt;0.27</td>
<td>0.87</td>
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<td>20/9/12</td>
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<td>137</td>
<td>2.6</td>
<td>41</td>
<td>2.3</td>
<td></td>
<td>22</td>
<td>174</td>
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<td>7</td>
<td>1.80</td>
<td>0.43</td>
<td>0.86</td>
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<tr>
<td>21/9/12</td>
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<td>135</td>
<td>4.2</td>
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<td>24</td>
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<td>2.14</td>
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<td>104</td>
<td>16</td>
<td>309</td>
<td>7</td>
<td>8</td>
<td></td>
<td>0.54</td>
<td>1.14</td>
</tr>
</tbody>
</table>
Outcome

- At extreme high risk of refeeding according to NICE but did not refeed
- 50:50 mix of lipid:glucose
- Electrolytes improved before feeding
- BG 4.2-5.9mmol/L
- Biochemical vs. symptomatic refeeding
- Recommendation: Kcal/kg → Glucose kcal/kg