Local Guideline

REFEEDING SYNDROME: CLINICAL GUIDELINES FOR THE MANAGEMENT OF REFEEDING SYNDROME (EXCLUDING CHILDREN AND ADOLESCENTS WITH EATING DISORDERS)

Sites where Local Guideline and Procedure applies	JHCH / PICU
This Local Guideline applies to:	
Adults	No
Children up to 16 years	Yes
Neonates – less than 29 days	No
Target audience	Paediatric Medical Staff, Dietetics, Pharmacy, and Nursing
Description	This guideline provides information for all medical, nursing, pharmacy, and dietetics staff for the management of refeeding syndrome in paediatrics

Go to Guideline

National Standards	1, 5
Keywords	Refeeding, syndrome, refeeding syndrome, dietetics, children, paediatrics, JHCH
Document registration number	JHCH 16.5
Replaces existing document?	No

Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- NSW Health Directive PD2017_032_PCP_2_Clinical_Procedure_Safety.pdf
- NSW Health Directive PD2017_013 Infection Prevention and Control Policy .pdf
- NSW Health Policy IB2020_010 Consent to Medical and Health Care Treatment Manual .pdf

Position responsible for the Local Guideline and authorised by:	JHCH Clinical Quality and Patient Care Committee
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This document reflects what is currently regarded as safe and appropriate practice. The guideline section does not replace the need for the application of clinical judgment in respect to each individual patient but the procedure/s require mandatory compliance. If staff believe that the procedure/s should

not apply in a particular clinical situation they must seek advice from their unit manager/delegate and document the variance in the patient's health record.

PURPOSE AND RISKS

This guideline has been developed to guide clinicians in the safe management of refeeding syndrome in the paediatric population (excluding eating disorders). This guideline does not replace the need for the application of clinical judgment in respect to each individual patient. In oncology and endocrine cases, this guideline may not be applicable – consult with specialist.

RISKS: The greatest risk of refeeding syndrome is in the first week of refeeding. Note that "normal" feeding of a child at risk of refeeding syndrome can result in clinical consequences such as hypophosphatemia, hypomagnesaemia, and hypokalemia. In some cases potentially leading to cardiac failure, fluid overload, arrhythmia and death.

This risk is mitigated by gradual reintroduction of food or feeds, as outlined in this refeeding syndrome guideline.

Risk Category: Clinical Care & Patient Safety

GLOSSARY

Acronym or Term	Definition
Arrhythmia	Irregularity or loss of rhythm, especially of the heart
Ataxia	Defective muscular coordination that manifests when voluntary muscular movements are attempted
BMI	Body Mass Index a measurement of body size calculated by dividing actual body weight (Kg) by height-squared (m^2)
Catabolism	The destructive phase of metabolism. Catabolism includes all the processes in which complex substances are converted into simpler ones, usually with the release of energy
Confabulation	A behavioural reaction to memory loss in which the patient fills in memory gaps with inappropriate words or fabricated ideas, often in great detail.
Glycolysis	The series of reactions that convert a molecule of glucose into two molecules of pyruvic acid
Haemolytic anaemia	Condition where there is not enough red blood cells in the blood due to the breaking down of red blood cells
Hypokalemia	An abnormally low concentration of potassium in the blood
Hypomagnesaemia	An abnormally low concentration of magnesium in the blood

Hypophosphatemia	An abnormally low concentration of phosphate in the blood
Korsakoff's syndrome	Brain disorder due to thiamine deficiency.
Nasogastric tube (NGT)	A medical process involving the insertion of a plastic tube through the nose, past the throat, and down into the stomach for medications or feeding
Nystagmus	Involuntary back and forwards movement of the eyes
QTc interval	On an electrocardiogram, the duration of the QT interval is corrected for the patient's heart rate
Syncope	Transient and sudden loss of consciousness, accompanied by the inability to maintain an upright posture
Wernicke's encephalopathy	Brain disorder due to thiamine deficiency
Z-score	BMI-for-age Z -score is a quantitative measure of the deviation of a specific BMI value from the mean of that population

GUIDELINE

SCOPE

This guideline provides information for all medical, nursing, pharmacy, and dietetics staff for the management of refeeding syndrome in paediatrics at JHCH. This document does not include the management of patients with Eating Disorders. Refer to section 8.2 of the document HNELHD Eating Disorders Service Plan Child and Adolescent Inpatient Model of Care, included as Appendix 6. This document is current at time of publication and subject to change. Please contact Dr Julie Adamson (speed dial 67040) for most recent documents. Whilst this document is aimed at guiding clinicians, clinical judgement needs to be exercised in all medical conditions.

AIMS

1. Identify patients at risk of refeeding syndrome
2. Minimise metabolic complications by close monitoring and early supplementation
3. Early aggressive management of electrolyte disturbances
4. Safely initiate nutrition support
5. Achieve metabolic and medical stability
6. Promote weight gain

DEFINITION

Refeeding syndrome is characterised by severe metabolic complications that may occur during the implementation of nutritional support (parenteral, enteral or oral) in a malnourished patient. The metabolic derangements may include but are not limited to, severe hypophosphatemia, depletion of potassium and magnesium, fluid and glucose intolerance, and vitamin deficiencies such as thiamine.

IDENTIFY PATIENTS AT RISK

Patients at risk of refeeding syndrome are those with one or more of the following:

- Acute weight loss of >15% in the past 3 months
- BMI less than 14 or < 5th Centile (or - 2 z-score)
- Patients underfed or not fed for at least 7 – 10 days
- Anorexia Nervosa Appendix 6.
- Prolonged or severe vomiting and/or diarrhoea for >5 days
- Conditions involving severe malabsorption, severe metabolic stress

BASELINE CLINICAL ASSESSMENT

- Accurate weight and weight history plotted on age and gender specific growth charts
- Accurate height/length plotted on age and gender specific growth charts
- BMI plotted on age and sex specific growth charts – some medical conditions and <2 years of age BMI is not an appropriate form of assessment
- Assess subcutaneous fat, muscle stores, skin integrity, nails, mucosae, cornea and conjunctivae, teeth and gums. A Dietitian may also perform a Subjective Global Nutritional Assessment (SGNA).
- Cardiovascular assessment including pulse rate, respiratory rate, blood glucose level, fluid balance and urinalysis, ECG, signs of oedema, temperature, orthostatic BP. Recorded on Standard Patient Observation Chart (SPOC).
- Check gastrointestinal symptoms such as abdominal pain, vomiting, diarrhoea.

BASELINE INVESTIGATIONS

- Urinalysis and electrocardiogram (ECG)
- Full Blood Count (FBC), folate, ferritin
- Sodium, Potassium, Creatinine, Bicarbonate, Chloride, Albumin (EUC)
- Calcium, Magnesium, Phosphate (CMP)
- Liver Function Tests (LFTs), Thyroid Stimulating Hormone (TSH)

BASELINE SUPPLEMENTATION

Provide baseline supplementation with thiamine, phosphate and a multivitamin and mineral medication BEFORE feeding commences. Ideally, supplementation should be started 24 to 48 hours PRIOR to feeding or as soon as possible. If oral supplementation is not possible then seek specialist advice.

Nutrient	Duration	Age	Dosage
Thiamine Presentation: 100mg tablet (Disperse/dissolve tablets in water to facilitate dosing in children)	Supplement for a minimum of 7 days. If not achieved full feeds within 7 days, continue supplementation until receiving 100% of estimated energy requirements. IV replacement – Seek specialist or pharmacy advice	<4 years	Enteral: 1-2 mg/kg MAX 50 mg per day
		>4 years	Enteral: 1-2 mg/kg MAX 100 mg per day
Multivitamin and mineral Presentation: Various oral and liquid forms – discuss with pharmacy	Supplement for a minimum of 7 days. If not achieved full feeds within 7 days, continue supplementation until receiving 100% of estimated energy requirements. IV replacement – Seek specialist or pharmacy advice	0-1 years	E.g. Pentavite infant multivitamin 0.45 mL daily
		1-12 years	1 x multivitamin (chewable tablet) or liquid multivitamin with Iron daily as directed on packaging
		>12 years	1x multivitamin and mineral tablet daily
Phosphate Presentation: 500mg effervescent tablet (Phosphate Phebra) contains 16.1mmol phosphate.	Supplement for 7 days and continue to supplement until levels within reference range. IV replacement – Seek specialist or pharmacy advice	1-8 years	250mg BD
		9-18 years	500mg BD

EARLY MANAGEMENT OF ELECTROLYTE DISTURBANCES

It is recommended that the following supplements be commenced if serum levels are low at baseline or begin to fall substantially within age specific ranges when refeeding. Consult with the specialist prior to commencing.

Potassium: JHCH Guideline Intravenous Potassium Chloride - Paediatrics. The document provides advice for intravenous and oral supplementation.

Magnesium: 1 month – 18 years;

- Initially 2.5 – 5 mg/kg (0.1- 0.2 mmol/kg) three times a day (TDS);
- Increase to 10-20 mg/kg (0.4- 0.8 mmol/kg) up to 4 times daily (QID) if required.

See Appendix 3: RDI reference ranges for potassium and magnesium

REHYDRATION

- Administration of oral or IV fluids may be required in the first 24 – 48 hours of admission. The signs of wasting are similar to dehydration and there is a tendency to overestimate dehydration.
- Suitable oral drinks are water, rehydration solutions, unflavoured milk and diluted juice. Limit high carbohydrate fluids such as soft drink, juice, cordials.
- IV fluids are only indicated in severe cases of circulatory compromise
- Hypoglycaemia should be corrected via continuous administration of oral rehydration solution (eg gastrolyte, hydralyte) via nasogastric tube.

NUTRITION

ORAL INTAKE

- Avoid large quantities of food at a meal and encourage six small meals a day, breakfast, morning tea, lunch, afternoon tea, dinner, supper
- Avoid food and fluids containing a large about of carbohydrate (soft drink, juice, lollies, chocolate, jelly, desserts)
- Oral intake should be maintained at the same volume as the past 48 hours until initial dietitian review and formulation of a meal/feeding plan

ENTERAL NUTRITION

- Feeding will usually require a nasogastric tube (NGT) over the first week. Malnourished children are often weak, quickly become exhausted and have poor appetites, so are unable to take required volume orally
- NGT **continuous** feeding is the safest delivery method to meet **Estimated Energy Requirements (EER).**
- Refeeding needs to be gradual and closely monitored, and must increase in controlled phases
- Refeeding rates should not be lower than intake prior to admission

ENTERAL FEEDING SOLUTIONS

- Infants should continue to breastfeed. Allow oral breastfeeds and slowly increase any supplemental feeds if required (e.g. expressed breast milk [EBM] or infant formula) and monitor electrolytes closely. It is recommended that full strength infant formula (0.7 kcal/mL or 20 kcal/30mL) are used during the refeeding phase for infants who are not breastfed (e.g. Aptamil Gold 1).
- Children 1-9 years or 8-20 kg: It is recommended that standard paediatric feeds which provide 1 kcal/mL are used during the refeeding phase (e.g. Pediasure + Fibre)
- Children > 10 years or > 20 kg: It is recommended that standard Adolescent feeds which provide 1 kcal/mL are used during the re-feeding phase (e.g. Nutrison Multifibre). Higher 1.5 kcal/mL feeds should be used with caution due to a higher carbohydrate load.

GRADING UP FEEDS:

AT ANY TIME **do not increase feed rate** if electrolytes (potassium, magnesium, phosphate) are below reference ranges. Supplement with appropriate electrolytes, and don't increase feed rate for 24 hours.

- **Day 1 commence refeeding at a maximum of 50% of EER via continuous feeding**
- **Day 2 if biochemistry stable increase nutrition to 75% of EER via continuous feeding**
- **Day 3 if biochemistry stable increase nutrition to 100% of EER via continuous feeding**
- From day 5 can progress to overnight feeds and bolus in the day if electrolytes stable and tolerating continuous feeds
- From day 7, if the risks of refeeding have passed, progress to bolus feeding or increase formula strength as required

Contact a Dietitian ASAP. If a dietitian is not available, use the following guide.

Use the table below to provide the starting dose of formula. Values based on the 50th percentile weight for each age group commencing at 50% of the estimated energy requirements. **Additional fluid for hydration will be required until full feed rate is achieved.**

Age	Commencement (ml/kg/d)	Daily Increments (ml/kg/d)	Average weight
1 – 12 months	70 mL/kg of EBM or standard infant formula	35 mL/kg	4 – 9.5 kg
1 – 3 years	45 mL/kg of Pediasure with Fibre	20 mL/kg	9.5 – 15 kg
4 – 7 years	30 mL/kg of Pediasure with Fibre	15 mL/kg	16 – 25 kg
8 – 10 years	25 mL/kg of Pediasure with Fibre	13 mL/kg	26 – 35 kg
11 – 15 years	20 mL/kg of Nutrison MultiFibre	10 mL/kg	36 – 55 kg
15+ years	15 mL/kg of Nutrison MultiFibre	7 mL/kg	>56 kg

PARENTERAL NUTRITION

Contact the Paediatric Gastroenterology team for specific advice. See JHCH TPN Guideline. The enteral route is preferred where possible as parenteral nutrition may cause complications such as liver damage and infection risk in some patients.

Parenteral nutrition should be graded up gradually over 7 days, in a similar way to enteral feeds. Also, children on parenteral nutrition need to follow the same Refeeding Guideline for initiation of feeding i.e. require baseline bloods and assessments, replacement of phosphate, potassium or magnesium if values are low, and commencement of prophylactic thiamine, phosphate, and multivitamin and mineral supplements.

MONITORING

AT ANY TIME **do not increase feed rate** if electrolytes (potassium, magnesium, phosphate) are below reference ranges. Supplement with appropriate electrolytes, and don't increase feed rate for 24 hours.

Test	Day 1-5	Day 5 onwards	Responsibility
Serum Electrolytes – EUC + CMP	**Daily**	**Every 3 days**	**Medical**
Urinalysis and fluid balance	Daily	Daily	Medical
SPOC (temp / pulse / BP)	Q4-6h	Daily	Nursing
Cardiac and respiratory function	Q4-6h	Daily	Medical
Blood glucose	Q4-6h	Daily	Nursing
Weight	Twice weekly	Twice weekly	Nursing
Caloric intake – nursing to document in fluid balance chart, dietitian to assess	Daily	Daily	Nursing and dietitian

ROLES AND RESPONSIBILITIES

Note: the below table is the minimum requirement for tests and observations. Decisions to alter the frequency of observations MUST be made by the treating consultant of documented on the SPOC in the altered calling criteria section on page 1.

- Abnormalities usually occur within the first 4 days of refeeding. Refeeding can occur up to 10 – 14 days post initiation of feeding, so it is important to continue to repeat electrolytes once stable.
- Consider measuring urine osmolality, electrolytes, pH, glucose, and protein in the first 5-10 days in patients with serum or clinical signs of refeeding syndrome.

IMPLEMENTATION AND MONITORING COMPLIANCE

The level of implementation, monitoring or compliance and audit will be based on the risk rating of the document. Owners/developers must detail how:

1. The document will be communicated and implemented; via email to all JHCH staff via HNELHD-CYPFCommunication@health.nsw.gov.au, as well as to key staff including medical staff and NUM's of H1, J1, J2, and PICU, Director of Pharmacy and Director of Nutrition and Dietetics.
2. Resources, education or training will be provided including in-service to the relevant wards, pharmacy, and medical staff.

3. The document will be monitored for effectiveness and compliance by completing annual retrospective file audits for patients admitted to JHCH identified as at risk of refeeding syndrome
4. The guideline will be audited. Not all guidelines require auditing, documentation of risk assessment and decision to audit or not must be retained by the author. A clinical audit template can be found at: http://intranet.hne.health.nsw.gov.au/__data/assets/word_doc/0014/133142/Clinical_Audit_Tool.docx Further advice on clinical audit can be found at: http://intranet.hne.health.nsw.gov.au/cg/clinical_audit

APPENDICES

Appendix 1 Background
Appendix 2 Conditions to consider when identifying Refeeding Syndrome
Appendix 3: RDI reference ranges for Potassium and Magnesium
Appendix 3 Complications of refeeding syndrome
Appendix 4 Flow Chart for Clinical Management

REFERENCES

ESPGHAN Committee on Nutrition. Practical approach to paediatric enteral nutrition: A comment by the ESPGHAN Committee on Nutrition. *Journal of the Pediatric Gastroenterology and Nutrition.* 2010, 51(1):110-112

Fuentebella J, Kerner JA. Refeeding Syndrome. *Pediatric Clinics of North America.* 2009, 56:1201-1210

Great Ormond Street Hospital (2017). Refeeding Guideline

Children's Health Queensland Hospital and Health Service (2019). Management of Re-Feeding syndrome in 0-16 years.

John Hunter Children's Hospital (2010). Prevention and treatment of refeeding syndrome

Hofer M, Pozzi A, Joray M, Ott R, Hahni F, Leuenberger M, Van Kanel R, Stanga Z. Safe refeeding management of anorexia nervosa inpatients: an evidenced-based protocol. *Nutrition.* 2014, 30:S24-530

O'Connor G, Nicholls D, Hudson L, Singhal A. Refeeding Low weight Hospitalized adolescents with anorexia nervosa: a multicentre randomized controlled trial. *Nutrition in Clinical Practice.* 2016, 31(5):681-689

Sydney Children's Hospital (2013). Refeeding syndrome: prevention and management

National Health and Medical Research Council (2017). Nutrient Reference Values. https://www.nrv.gov.au/

ESPGHAN. Guidelines on Paediatric Parenteral Nutrition 2005 41:S1-87

Australian Medicines Handbook: Children's Dosing companion 2019.

Westmead Meds4Kids Dosing Guide. http://webapps.schn.health.nsw.gov.au/meds4kids/browse/M accessed 26/5/20

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APPENDIX 1: BACKGROUND

Refeeding syndrome describes the various metabolic complications that can occur during the implementation of nutritional support (parenteral, enteral or oral) in a malnourished patient. During starvation, the body alters metabolic pathways, organ function and hormone regulation to compensate for the lack of energy. The body goes into a state of catabolism, shifting from carbohydrate to fat and protein catabolism to provide glucose and ketones for energy.

Sudden reversal of catabolism through nutritional support which is mainly due to excessive carbohydrate load, leads to a rapid shift from fat to carbohydrate metabolism. This results in a surge of insulin and rapid shift of glucose, thiamine, phosphate, magnesium, potassium, and water into cells. This often results in a fall of serum electrolyte concentrations. Insulin also effects the kidneys by causing sodium and fluid retention and expansion of the extracellular fluid volume. The clinical consequence of hypophosphatemia, hypokalemia and hypomagnesaemia include haemolytic anaemia, muscle weakness and impaired cardiac function, which can lead to cardiac failure, fluid overload, arrhythmia and death. For most children and adolescents, the most significant finding is a fall in serum phosphate. Refeeding syndrome can occur up to 2 weeks after initiating feeding, so close monitoring is required for this period.

Thiamine is the principal vitamin deficiency and is one of the contributing factors of sudden death in refeeding syndrome. Thiamine is a necessary component in glycolysis and a cofactor in many enzyme reactions. When carbohydrates are reintroduced intracellular thiamine uptake is increased. Depleted stores can result in Wernicke's encephalopathy (delirium, oculomotor paresis, nystagmus and ataxia) or Korsakoff's syndrome (anterograde and retrograde memory loss accompanied sometimes by confabulation).

APPENDIX 2: CONDITIONS TO CONSIDER WHEN IDENTIFYING REFEEDING SYNDROME

- Patients with kwashiorkor or marasmus
- Patients with neurological conditions such as cerebral palsy (not all patients will be at risk)
- Chronic alcohol abuse should be considered, but unlikely in the paediatric population
- Inflammatory bowel disease, gut infection, coeliac disease, pancreatitis
- Infection or immune deficiency e.g. HIV, occult UTI
- Malignancy
- Thyrotoxicosis, hypoadrenalism, hypopituitarism
- Renal failure, renal tubular disorders, metabolic disorders
- Collagen vascular diseases, e.g. lupus
- Poisoning, Munchausen by Proxy Syndrome (MBS)

APPENDIX 3: RECOMMENDED DAILY INTAKE (RDI) REFERENCE RANGES FOR POTASSIUM AND MAGNESIUM

<table>
<tr><td rowspan="10">Potassium</td><td rowspan="10">Supplement to RDI levels
Check the amount of potassium already received in multivitamin, enteral or parenteral replacement

IV replacement – Seek specialist or pharmacy advice</td><td colspan="2">Age and gender</td><td>Potassium mmol/d (AI)</td></tr>
<tr><td rowspan="2">Infants</td><td>0-6m</td><td>10</td></tr>
<tr><td>7-12m</td><td>18</td></tr>
<tr><td rowspan="2">Children</td><td>1-3y</td><td>50</td></tr>
<tr><td>4-8y</td><td>60</td></tr>
<tr><td rowspan="2">Boys</td><td>9-13y</td><td>76</td></tr>
<tr><td>14-18y</td><td>92</td></tr>
<tr><td rowspan="2">Girls</td><td>9-13y</td><td>64</td></tr>
<tr><td>14-18y</td><td>66</td></tr>
<tr><td rowspan="10">Magnesium</td><td rowspan="10">Supplement to RDI levels
Check the amount of magnesium already received in multivitamin, enteral or parenteral replacement

IV replacement – Seek specialist or pharmacy advice</td><td colspan="2">Age and gender</td><td>Magnesium mg/d (AI)</td></tr>
<tr><td rowspan="2">Infants</td><td>0-6m</td><td>30</td></tr>
<tr><td>7-12m</td><td>75</td></tr>
<tr><td rowspan="2">Children</td><td>1-3y</td><td>80</td></tr>
<tr><td>4-8y</td><td>130</td></tr>
<tr><td rowspan="2">Boys</td><td>9-13y</td><td>240</td></tr>
<tr><td>14-18y</td><td>410</td></tr>
<tr><td rowspan="2">Girls</td><td>9-13y</td><td>240</td></tr>
<tr><td>14-18y</td><td>360</td></tr>
</table>

APPENDIX 4: COMPLICATIONS OF REFEEDING SYNDROME

Hypophosphatemia	Hypokalemia	Hypomagnesemia	Thiamine Deficiency	Sodium Retention	Hyperglycaemia
Cardiac	Cardiac	Cardiac	Encephalopathy	Fluid Overload	Cardiac
Hypotension	Arrythmias	Arrythmias			Hypotension
Decreased stroke volume	Respiratory Failure	Neurologic Weakness	Lactic Acidosis Death	Pulmonary Oedema Cardiac compromise	Respiratory Hypercapnea Failure
Respiratory	Neurologic	Tremor			Other
Impaired diaphragm contractility	Weakness Paralysis	Tetany Seizures Altered mental status			Ketoacidosis Coma Dehydration Impaired immune function
Dyspnoea	Gastrointestinal	Coma			
Respiratory failure	Nausea Vomiting	Gastrointestinal			
Neurologic	Constipation	Nausea			
Parasthesia	Muscular	Vomiting			
Weakness	Rhabdomyolysis	Diarrhoea			
Confusion	Muscle necrosis	Other			
Disorientation	Refractory	Refractory hypokalaemia and hypocalcaemia Death			
Lethargy	Other				
Areflexic paralysis	Death				
Seizures					
Coma					
Hematologic					
Leukocyte dysfunction					
Haemolysis					
Thrombocytopenia					
Other					

APPENDIX 5: FLOW CHART FOR CLINICAL MANAGEMENT