PEDIATRIC NEWBORN MEDICINE CLINICAL PRACTICE GUIDELINES

Neonatal Refeeding-like Syndrome

Clinical Practice Guideline: Neonatal Refeeding-like Syndrome

Points of emphasis/Primary changes in practice:

1. No NICU policy on Neonatal Refeeding-like Syndrome exists.

2. We created a new policy to provide guidance about best practices for prevention and treatment of this condition.

3. The overall goal is for the multidisciplinary NICU clinical team to systematically identify at risk patients and intervene early to minimize the occurrence of severe hypophosphatemia

Rationale for change: Creation of new policy.

Questions? Please contact: Neonatal Clinical Pharmacist and Clinical Nutrition Working Group

Clinical Guideline Name	Neonatal Refeeding-like Syndrome
CWN Clinical Practice Manual Policy Number	
Implementation Date	
Due for CPC Review	
Contact Person	Neonatal Clinical Pharmacist and Clinical Nutrition Working Group
Approved By	NICU Clinical Nutrition Working Group 12/6/17 Neonatal Pharmacy Committee __1/2018_____ Dept of Pediatric Newborn Medicine Clinical Practice Council _4/2018___

I. Purpose

The purpose of this clinical practice guideline is to ensure that infants at risk of Neonatal Refeeding-like syndrome (1) are consistently identified, (2) receive consistent preventive interventions and (3) receive appropriate treatment if Neonatal Refeeding-like Syndrome occurs.

II. Scope

This guideline applies to infants in the neonatal intensive care unit (NICU), with emphasis on very-low-birth-weight (VLBW) infants receiving parenteral nutrition support. The scope of this guideline includes the identification, evaluation, monitoring, prevention, treatment and related care of infants who are being evaluated for Neonatal Refeeding-like Syndrome in the NICU.

III. Guidelines

Background: Refeeding Syndrome (RS) is characterized by a combination of fluid and electrolyte disorders that can occur in both children and adults when enteral or parenteral nutrition is initiated after a period of starvation or malnutrition (Pulcini 2016, Skipper 2012, Boateng 2010, Mehanna 2008, Kraft 2005). Signs and symptoms range from mild to severe and include hypophosphatemia, hypokalemia, hypomagnesaemia, hyperglycemia, vitamin and mineral deficiencies (most notably thiamine) and sodium/fluid retention.

Pathophysiology: During prolonged periods of starvation, insulin secretion is suppressed and the body uses endogenous stores of glycogen, amino acids, and fat for energy. Upon reintroduction of a carbohydrate source, insulin secretion increases and there is a shift back to glucose as the predominant fuel source. This shift leads to an increase in the production of phosphorylated intermediates of glycolysis. The high demand for phosphorus in this anabolic state combined with low total body stores (despite normal serum levels) and the action of insulin to shift phosphorus into the intracellular space together ultimately lead to the hallmark

sign of RS: hypophosphatemia (Kraft 2005, Boateng 2010). Other manifestations of refeeding syndrome include hypokalemia and hypomagnesemia (also due to insulin effects to shift K and Mg intracellularly); sodium retention and fluid overload (likely due to decreased renal excretion of sodium and water as a result of hyperinsulinemia) and thiamine deficiency (a cofactor required for carbohydrate metabolism with available stores being quickly depleted) (Boateng 2010, Kraft 2005).

See **Appendix 1** for select complications of RS and associated electrolyte dyscrasias [based on adult and pediatric literature (Boateng 2010, Kraft 2005, Pulcini 2016)].

Risk Factors & Etiology of Neonatal Refeeding-like Syndrome

Although most reports of RS involve pediatric and adult populations, recent literature highlights a syndrome in neonates characterized by similar metabolic alterations (Bonsante 2013, Brener 2015, Moltu 2013, Senterre 2015). As early and higher doses of parenteral amino acids have become standard of care in the recent years (Kleinman 2014), hypophosphatemia and other electrolyte and mineral abnormalities may occur in the absence of adequate electrolyte and mineral provision in the first days of life (Bonsante 2013, Brener 2015, Senterre 2015). This is likely due to earlier achievement of an anabolic state at the cellular level, which promotes phosphorus and potassium uptake with concurrent calcium mobilization from the bone. Bonsante and colleagues have proposed an algorithm to ensure provision of adequate phosphorous and appropriate calcium doses alongside early amino acid delivery (Bonsante 2013). Adjustments to parenteral calcium and phosphorus ratios, specifically ≤1 mmol:mmol , have also been proposed to minimize hypercalcemia and hypophosphatemia seen with higher early doses of amino acid delivery (2-3.5 g/kg/day) (Senterre 2015, Mulla 2017). Individualized ratios may be warranted beyond the first day of birth in response to close monitoring of serum electrolytes (Boubred 2015).

A higher incidence of "Refeeding-like" syndrome has been reported in small-for-gestational age (SGA, <10%ile) and growth-restricted infants (Ross 2013, Boubred 2015, Moltu 2013, Rouba 2016, Mulla 2017) as compared with normally-grown infants. While IUGR mimics a state of malnourishment during the gestational period, metabolic pathways and alterations likely differ slightly from pediatric or adult states of starvation. The most common cause of IUGR is placental insufficiency, which results in a chronic malnourished state for the fetus, including reductions in muscle mass for body weight, glycogen stores in the liver and skeletal muscle, and adipose tissue (Hay 2001). Additionally, active transfer of potassium and phosphorus across the placenta may also be limited (Boubred 2015). IUGR infants born *preterm* also have reductions in muscle weight, glycogen stores and adipose tissue as well as bone mineralization and calcium and phosphorous stores due to their shortened gestation.

Timeline
Electrolyte disorders generally occur in neonates within 2-5 days after nutrition support begins (Boubred 2015, Ross 2013, Moltu 2012). Based on the pediatric literature RS may take up to 7-10 days to appear (Pulcini 2016), although this later onset is not consistent with our clinical experience.

Incidence and Clinical Data
The overall incidence of a Neonatal Refeeding-like syndrome among neonates is unknown and likely varies due to nutritional and clinical management. However, the incidence of hypophosphatemia due to a 'Refeeding-like syndrome' appears to be highest among IUGR compared with appropriately grown VLBW infants (approximately 40% vs. 9%) (Ross 2013, Boubred 2015). Ross and colleagues also reported higher incidence of hypophosphatemia in the setting of maternal preeclampsia, regardless of IUGR status at birth.

See **Appendix 2** for a review of Neonatal Refeeding-like Syndrome as reported in the literature. Studies and case reports of Neonatal Refeeding-like Syndrome vary widely by population, standards of nutrition support, definition of electrolyte abnormalities and treatment and management strategies. For example, definitions of hypophosphatemia ranged from ≤2.5-4.95 mg/dL; severe hypophosphatemia ranged from ≤1-2.8 mg/dL and hypokalemia ranged from ≤3-3.6 mg/dL. Early amino acid delivery ranged from ≤1.5-3.5 g/kg/day; and initiation of parenteral phosphorus and potassium delivery ranged from day of birth to several days of life.
Many above listed complications of RS are commonly seen in VLBW infants during the first few days of life. Thus, clinical manifestations of Neonatal Refeeding-like syndrome may be difficult to distinguish from complications of preterm birth.

The impact of RS-associated electrolyte abnormalities on clinical outcomes in preterm neonates is unclear. In one study, hypophosphatemia was associated with higher risks of BPD (OR: 2.38; 95% CI: 1.73, 3.28; p<0.0001), the need for mechanical ventilation ≥3 days (OR: 1.76, 95% CI: 1.1, 2.70, p=0.0096), and patent ductus arteriosus (OR: 1.68; 95% CI: 1.24, 2.27; p=0.0004), after controlling for birth gestational age, weight and IUGR (Ross 2013). However, hypophosphatemia does not appear to be associated with an increased risk for late onset sepsis (Ross 2013, Brener 2015).

How to balance of risks of RS-associated electrolyte abnormalities with benefits of enhanced nutritional support must also be considered. An illustrative example is a randomized trial of an enhanced nutrition regimen consisting of higher parenteral amino acid and higher/different lipid emulsions from day of birth for VLBW infants. Lower mean phosphorous (despite higher phosphorous delivery) and potassium levels during the first week of life were found in the intervention group. However, clinically significant benefits of the intervention included shorter time to weight loss nadir (2.5 vs. 3.9 days, p=0.01) and shorter time to regain birth weight (7.1 vs. 9.7 days, p=0.02).

Based on the current evidence and literature available, careful monitoring and adjustment of early amino acid and micronutrient delivery is warranted in the VLBW population to decrease risk of developing Neonatal Refeeding-like syndrome and possible associated adverse outcomes. Growth restricted infants or those born with maternal pre-eclampsia/placental insufficiency are at highest risk.

Prevention & Treatment

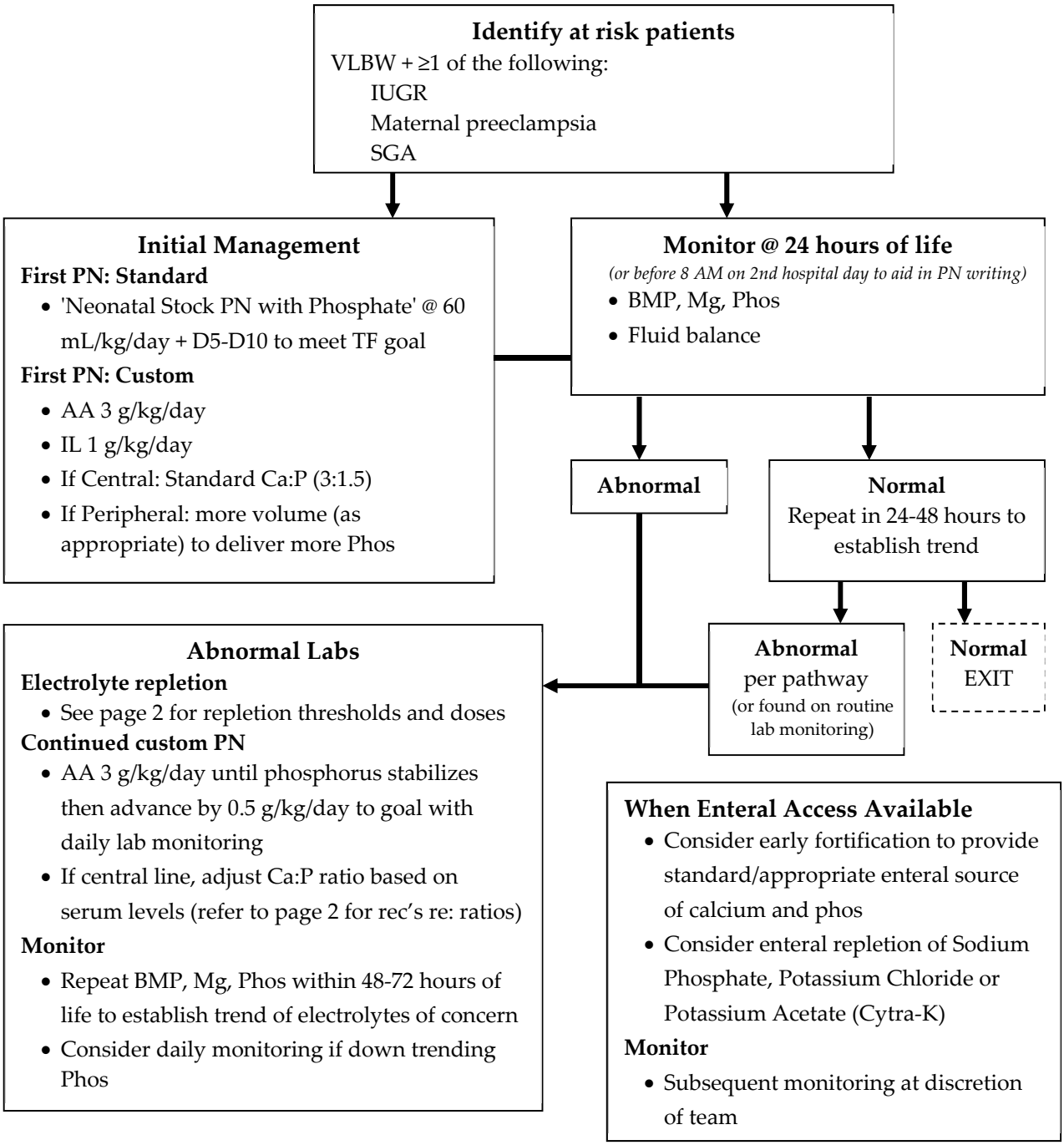
Limited and varied evidence exists describing Neonatal Refeeding-like syndrome and regarding optimal intervention and monitoring strategies, including normal electrolyte serum concentrations and electrolyte repletion dosing regimens. Earlier and adequate provision of phosphorous and potassium and adjusted calcium and phosphorus ratios in parenteral nutrition support may limit electrolyte abnormalities and associated complications (Ross 2013, Boubred 2015, Jamin 2010, Senterre 2015, Brener 2015). One expert group proposes that the safest means of electrolyte repletion is enteral therapy (Gaasbeek 2005). Enteral supplementation can be achieved by routine fortification of preterm milk or use of preterm formula, and via use of enteral supplementation outside of routine feeds.

General principles: Identify patients at risk for Neonatal Refeeding-like Syndrome (see Risk Factors section), monitor electrolytes closely, be cautious with parenteral nutrition advancements, institute nutrition interventions before considering IV electrolyte repletion, initiate enteral feeds as soon as possible with consideration of early fortification and/or consider enteral repletion of phosphorous and potassium based on risk versus benefit of individual patient.

BWH NICU Therapeutic Algorithm for At-Risk Patients:

First Line: Neonatal Stock PN with Phosphate at birth
Second Line: Custom PN adjustments to amino acids and Calcium:Phosphorus (Ca:P) ratio
Third Line: IV electrolyte repletion
If Enteral Access: Consideration of early fortification and/or electrolyte repletion

Prevention &Treatment Flow Chart



Assessment and Monitoring

- Perinatal history (for history of maternal preeclampsia and IUGR).
- Birth weight assessment for VLBW status and size-for-gestational age categorization.
- Laboratory tests:
  - Chemistries including phosphorus, calcium, potassium and magnesium.
  - Blood glucose level
- Fluid status

Classification of levels

Symptoms of hypophosphatemia among adult patients are usually not seen until serum levels fall below 1 mg/dL (Boateng 2010). It is unknown at which level symptoms appear in neonates. However, reference norms for infants are known to be higher than those in adults (Custer 2009).

BWH NICU Classifications of Electrolyte Abnormalities

Electrolyte Abnormality	Level/Severity
Hypophosphatemia	Mild: 2.5 – 4 mg/dL
	Moderate: 1.5 – 2.5 mg/dL
	Severe: < 1.5 mg/dL
Hypokalemia	Mild: 2.5 – 3.1 mmol/L
	Moderate/Severe: < 2.5 mmol/L
Hypomagnesemia	< 1.5 mg/dL

Electrolyte Replacement

Electrolyte Abnormality	Level/Severity	Intravenous Intervention	Enteral Intervention
Hypophosphatemia	Mild: 2.5 – 4 mg/dL	Adjustments to PN: -Amino acid (AA) restriction to 3 g/kg/day, check full BMP, Mg, Phos prior to any advance -Adjust Calcium to Phosphorus ratio (Ca: P) <u>If central access:</u> AND <100 mL/kg/day: 4:2 (Avoid with PN volume >100 mL/kg/day) AND elevated serum Calcium: 3:2, AND elevated serum Calcium on 3:2 previously: 2:2 <u>If peripheral access:</u> Low threshold to optimize PN volume to provide more Ca/Phos vs. restrict AA to <3 g/kg/day	Sodium phosphate: 0.5 mmol/kg PO daily; may increase up to 2 mmol/kg/day
	Moderate: 1.5 – 2.5 mg/dL	-Step 1: PN adjustments as above -Step 2: If at risk/clinical suspicion of evolving Neonatal Refeeding-like Syndrome and consecutive phosphorus levels decreasing, may consider IV sodium or potassium phosphate as below	
	Severe: < 1.5 mg/dL	-Sodium phosphate: 0.25 mmol/kg IV x 1 or -Potassium phosphate**: 0.18 mmol/kg IV x 1†	
Hypokalemia	Mild: 2.5 – 3.1 mmol/L	Adjustments to PN as able	Potassium Chloride or Cytra-K: 1 mEq/kg PO Q12H; may increase as tolerated
	Moderate/Severe: < 2.5 mmol/L	Potassium chloride: 0.5–1 mEq/kg IV x 1†	
Hypomagnesemia	< 1.5 mg/dL	Magnesium sulfate: 0.4 mEq/kg IV x 1	n/a

*At risk if VLBW + ≥ 1 of the following: IUGR, maternal preeclampsia, SGA.

** IV potassium phosphate contains aluminum; use only in the setting where sodium phosphate is undesirable based on laboratory results. See BWH NICU DAG page for more details.

† Use discretion with potassium repletion in setting of renal impairment

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Appendix 1: Select complications of RS and associated electrolyte dyscrasias

Based on adult and pediatric literature (Boateng 2010, Kraft 2005, Pulcini 2016)

Body System	Manifestations	Associated electrolyte dyscrasia(s)
Cardiac	Arrhythmias, hypertension, congestive heart failure, sudden death	Hypophosphatemia; Hypokalemia; Hypomagnesemia; sodium retention
Gastrointestinal	Abdominal pain, constipation, vomiting, anorexia	Hypokalemia; Hypomagnesemia
Musculoskeletal	Weakness, myalgias, rhabdomyolysis, osteomalacia, weakness	Hypokalemia; Hypomagnesemia
Respiratory	Dyspnea, respiratory failure, ventilator dependency, diaphragm/intercostal muscle weakness, pulmonary edema	Hypophosphatemia; Hypokalemia
Neurologic	Weakness, parasthesias, tremors, ataxia, delirium, acute encephalopathy, coma	Hypophosphatemia; Hypomagnesemia
Metabolic	Metabolic alkalosis, metabolic acidosis, respiratory alkalosis, hyperglycemia	
Hematologic	Infections, thrombocytopenia, hemolysis, anemia	Hypophosphatemia
Others	Acute tubular necrosis, Wernicke's encephalopathy, lactic acidosis, liver failure, fluid overload	Vitamin/Thiamine deficiency; sodium retention

Appendix 2: Review of references related to Neonatal Refeeding-like Syndrome

Reference	Population	Electrolyte dyscrasia definitions	Significant/Notable Outcomes
Ichikawa 2012	58 ELBW infants 22-29 weeks 2009-2011	Hypophosphatemia: ≤2.5 mg/dL Hypercalcemia: ≥11 mg/dL	Parenteral nutrition in first 7 days after birth among SGA/ELBW infants was correlated with hypophosphatemia and hypercalcemia
Mizumoto 2012 **case study*	Severely IUGR infant Published 2012	Hypophosphatemia: <2.5 mg/dL Severe: <1 mg/dL Hypokalemia: <3.6 mmol/L	Case of a severely IUGR infant born to a mother with maternal preeclampsia. Overall clinical deterioration found in setting of profound hypophosphatemia and hypokalemia requiring rapid IV replacement.
Bonsante 2013	154 infants <33 weeks GA 2006-2007	Hypophosphatemia: <3.1 mg/dL Hypercalcemia: >11.2 mg/dL	-Calcium-phosphorus homeostasis is influenced by early AA intake -"PI-ReFeeding" syndrome defined -Tool to calculate optimal phosphate intake provided
Moltu 2013	50 VLBW infants 2010	Hypophosphatemia: 4.3 mg/dL Marked hypophos.: 2.8 mg/dL Hypokalemia: <3.5 mmol/L	-Hypophosphatemia, hypokalemia and hypercalcemia common in VLBW fed 'enhanced' nutrition support -Infants fed 'enhanced' support also had more sepsis
Ross 2013	2253 VLBW infants 2001-2010	Hypophosphatemia: <4 mg/dL Severe: <2.5 mg/dL Hyperglycemia: >180 mg/dL	-Hypophosphatemia and severe hypophosphatemia more common in IUGR infants -Preeclampsia was independently associated with hypophosphatemia regardless of IUGR status -Hypophosphatemia significantly positively associated with BPD, PDA and likelihood of requiring mechanical ventilation for ≥3 days
Boubred 2015	48 ELGAN infants 2011-2012	Hypophosphatemia: <4.95 mg/dL Severe: <2.79 mg/dL Hypokalemia: <3 mmol/L	-SGA ELGAN infants at significantly higher risk of hypophosphatemia and hypokalemia
Brener 2015	61 infants <1250g at birth 2012-2014	Hypophosphatemia: <4 mg/dL Mild/Moderate: 2-4 mg/dL Severe: <2 mg/dL	-Prevalence of hypophosphatemia in infants <1250g at birth is high and deserves future research -Higher incidence among IUGR
Senterre 2015	102 infants <1250g at birth 2006-2007	Hypophosphatemia: 4.95 mg/dL Hypokalemia: <3 mmol/L Hypercalcemia: >11.2 mg/dL Hyponatremia: <130 mmol/L	-Increasing early protein and energy increases phosphorus requirements with an altered Ca:P ratio of ≤1.0 (mmol/mmol) as well as potassium and sodium requirements to avoid development of a refeeding-like syndrome.
Rouba 2016 **case study*	Severely IUGR infant Published 2016	Graphs of labs given, but norms not defined	Case of a severely IUGR infant found to have persistent hypophosphatemia, hypokalemia and hypomagnesemia requiring IV potassium replacement as well as phosphorus and magnesium supplementation without full resolution until IV thiamine infusion was provided
Mulla 2017	100 preterm infants <37 weeks at birth 2013-2014	Hypophosphatemia: 4.6 mg/dL Hypokalemia: <3.5 mmol/L Hypercalcemia: > 12 mg/dL	Two different epochs studied with differing Ca:P ratio in setting of higher concentrations of amino acids. An equimolar ratio appears preferable to the prior standard ratio of ≥1.3:1