Metabolic Bone Disease of Prematurity - NICU

Guideline Responsibilities and Authorisation

Department Responsible for Guideline	Newborn Intensive Care Unit (NICU)
Document Facilitator Name	Marisa Pacella
Document Facilitator Title	Neonatologist
Document Owner Name	Jutta van den Boom
Document Owner Title	Head of Department
Target Audience	Medical Officer, Nurse Practitioner or Clinical Nurse Specialist working in NICU
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Guideline Review History

Version	Updated by	Date Updated	Summary of Changes
1	Marisa Pacella	July 2022	New guideline - use of PTH, ALP threshold 500

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Contents

1 Overview

1.1 Purpose

- To optimize bone growth in premature (<32 week) or very low birth weight (<1500g) infants in the Neonatal Intensive Care Unit (NICU)

For routine vitamin supplementation (Vitamin A, D, iron, folate), please refer to Vitamin and Mineral, and Enteral Supplementation in NICU protocol (Ref 1526)

1.2 Scope

Medical Officer, Nurse Practitioner or Clinical Nurse Specialist working in NICU.

1.3 Patient / client group

Infants in NICU.

1.4 Definitions and acronyms

ALP	Alkaline phosphatase
EBM	Expressed breastmilk
HMF	Human milk fortifier
MBD	Metabolic bone disease
PTF	Preterm formula
PTH	Parathyroid hormone
RDI	Recommended daily intake
VLBW	Very Low Birth Weight

2 Background

2.1 Premature/VLBW bone formation

All premature and VLBW infants are at risk of Metabolic Bone Disease (MBD) of prematurity. This was previously referred to as osteopenia of prematurity. Because many premature infants have elements of osteopenia and of osteomalacia, MBD is the more accepted term.

In utero, the majority of mineral deposition occurs during the third trimester. Premature babies are born early and need either human milk fortifier, parenteral nutrition, or oral supplementation in order to acquire sufficient calcium and phosphate. The recommended calcium intake is 150 to 220 mg/kg per day [3.7 to 5.5 mmol/kg/day] and phosphorus 75 to 140 mg/kg per day [2.4 to 4.5 mmol/kg/day] to provide a calcium-to-phosphorous ratio less than 2:1. A calcium-to-phosphorous ratio of 1.5 to 1.7:1 ratio may be optimal for

preterm infants. Exceeding a calcium intake of 5 mmol/kg/day may be associated with nephrocalcinosis.

In addition to prematurity and growth restriction, NICU babies may be at risk of MBD due to:

- Maternal vitamin D deficiency
- Paucity of movement, due to prolonged sedation or neuromuscular disorder
- Intestinal disorders (NEC, gastroschisis, spontaneous intestinal perforation)
- Delayed enteral feeding
- Unfortified enteral feeding
- Malabsorption, i.e. conjugated hyperbilirubinemia
- Chronic lung disease
- Medications such as diuretics and corticosteroids
- Primary disorders of phosphate or calcium regulation such as parathyroid disorders or renal failure

2.2 Diagnosis

The aim is to diagnose MBD before radiographic evidence of bone disease (e.g. thinning, rickets, or fractured bone) becomes apparent. Serum phosphate and serum calcium levels are NOT accurate measures of MBD. This is because of compensatory mechanisms which trigger renal retention and osteoclastic bone break down.

Elevated alkaline phosphatase (ALP) in combination with low serum phosphate is the most sensitive and specific indication of inadequate phosphate intake and MBD. ALP levels of up to 400 may be normal in the rapidly growing premature infant. ALP is not specific only to bone and may be raised due to liver disease. ALP may be decreased due to corticosteroid use, zinc deficiency, copper overload, or hypothyroidism.

Inadequate calcium intake may lead to a secondary hyperparathyroidism. These infants will have a high PTH in order to drive calcium out of the bone and normalize serum calcium levels. Therefore, phosphate supplementation alone may not be sufficient for preterm bone growth.

Finally, vitamin D deficiency is common in the general population. Preterm infants will not have the same vitamin D stores as a term infant. While normal vitamin D levels for premature infants are unknown, they may be extrapolated from adult data. We are recommending the measurement of vitamin D levels for specific at-risk groups (conjugated hyperbilirubinemia, known/suspected maternal vitamin deficiency, severe MBD based on x-ray findings of rickets or very elevated ALP).

3 Clinical Management

3.1 Fortify EBM

For infants born <32/40 or <1800g, **HMF** should be started as soon as the infant is tolerating 8 mL Q2 hourly of EBM (or using 25ml within 4h). HMF is necessary to meet the recommended daily intake of nutrients (see Appendix A). PTF is an alternative to HMF if EBM is not available.

3.2 Blood tests

At 3 weeks postnatal age (Day 21), check serum ALP, Phosphate, Calcium, PTH. (All bloods can be done on a single Red tube). See Treatment table below.

- If all levels are normal, check every 2-4 weeks until discharge.
- If levels are abnormal, check every 1-2 weeks to monitor for response to treatment.

3.3 Handle with care

Post a bedside sign to remind the team that baby has “Fragile Bones”. This is especially important if the infant has known fractures or severe MBD (i.e. ALP>800).

3.4 Treatment

Lab	Treatment threshold	Initial dose	Reminders	Ongoing management	Discontinuation
ALP	ALP >500u/L or Phosphate < 1.5 mmol/L	Phosphate solution (0.5mmol/mL) 1 mmol/kg/day divided 2-4 doses/day	Separate calcium and phosphate supplements at different feeding times by at least 2 hours	Recheck every 1-2 weeks If ALP is improving, continue same dose. If ALP isn't improving, increase to 2 mmol/kg/day. Check PTH.	Discontinue when ALP < 400 If ALP >500 on discharge, will require community monitoring.
PTH	PTH > 10 pmol/L	Calcium 1mmol/mL solution (effervescent tabs 500 or 1000 mg) **(NOTE: section 29)** 1 mmol/kg/day	Separate calcium and phosphate supplements at different feeding times by at least 2 hours	Recheck every 1-2 weeks	Discontinue when PTH<10
Vitamin D	Birthweight <1000g Vitamin D level < 50 nmol/L Vitamin D level <30	Cholecalciferol 2 drops +1 drop above daily dose +3 drops above daily dose	Check vit D level *only* if: -x-ray shows rickets or fractures. -ALP>800 and/or not improving with phosphate -conjugated bilirubinaemia.	Recheck in 4 weeks Return to 1 drop/day when >1000g and when level >50 nmol/L. Do not recheck levels once they have normalized.	1 drop daily until first birthday

Table 1: Laboratory results and treatment indications

4 Outpatient Management

4.1 Prescribing

Ensure that local pharmacy can manufacture desired solution prior to discharge, or ask whānau/family to obtain medicines from Pharmacy on Meade. Continue phosphate at home if ALP >500. Continue calcium if PTH >10 pmol/L.

4.2 Home blood tests

Recheck ALP, PTH, Phosphate, Ca levels every two weeks ONLY IF going home on one or both medications. Recheck vitamin D levels monthly if meeting criteria (Table 1). Homecare nursing team will discuss with primary neonatologist regarding titration of supplements.

5 Audit

5.1 Indicators

- Datix submitted for any skeletal fractures

6 Evidence base

6.1 Bibliography

- https://www.starship.org.nz/guidelines/osteopenia-of-prematurity
- Australasian Neonatal Medicine Formulary (ANMF): Colecalciferol, Phosphorus, and Calcium - Oral
- Matejek T et al. Parathyroid hormone – reference values and association with other bone metabolism markers in very low birth weight infants. J Mat-Fet and Neonatal Med. 2019.
- Moreira A et al. Parathyroid hormone as a marker for metabolic bone disease of prematurity. J Perinatology, 2014.
- Chinoy A et al. Current status in therapeutic interventions of neonatal bone mineral metabolic disorders. Semi Fet and Neo Med, 2020 Vol 25(1).

6.2 Associated Te Whatu Ora Waikato Documents

- Calcium oral for neonates drug guideline (Ref. 2903)
- Phosphate oral for neonates drug guideline (6370)
- Fluid orders for neonates guideline on refeeding syndrome (5439)
- Enteral Feeding: Standardisation of Feeding in Neonatal Intensive Care Unit guideline (6172) HMF

Appendix A – Nutritional Content

Nutritional Content (Ref: Starship)

Key Nutrients	Units	EBM at 180 ml/kg/d	Fortified EBM at 180ml/kg/d	RDI per kg/d	Suggested supplement to provide equivalent to fortified EBM 180ml/kg/d
Vitamin D	IU	2.9	257	400 - 700	1 or 2 drops/kg/d (routine dose) + 1 drop/kg/d
Calcium	mmol	1.6	5.0	3 - 5.5	2.6 mmol/kg/d
Phosphorus	mmol	0.4	2.9	2.3 - 3.7	2.6 mmol/kg/d