Metabolic Bone Disease in Preterm Infants on the Neonatal Unit - Full Clinical Guideline

Reference no.:NIC ME 08

1. Introduction

Preterm babies are at an increased risk of inadequate bone mineralisation owing to their premature delivery, and challenges in optimising nutrition in the early weeks of life. This can be associated with an on going risk of morbidity both in the acute setting, and in growth an development on discharged from the neonatal unit.

2. Aim and Purpose

For medical staff to be able to optimise the detection and management of metabolic bone disease in preterm babies, to prevent later complications.

3. Definitions, Keywords

Metabolic Bone Diesease (MBD), Osteopenia, Prematurity, Preterm Infants, NICU, Neonatal Unit

4. Basis for Guideline and Current Recommendations

Background

In-utero mineral accretion is at its most rapid in the last trimester of pregnancy. Prematurity will interrupt this critical period of growth. Preterm infants are therefore at risk of inadequate bone mineralisation if dietary intake of calcium, phosphate, magnesium, and Vitamin D is insufficient. Metabolic bone disease occurs when the demand for minerals to facilitate bone mineralisation outstrips supply[1,2].

In practice calcium and magnesium deficiency is rare and current vitamin supplements give adequate Vitamin D. Traditionally it was thought that when mineral intake was low, phosphate deficiency was most likely to arise first. Emerging evidence suggests however, that calcium is highly likely to be as important in normal bone mineralisation in preterm infants as phosphate, and indeed that excessive phosphate supplementation without sufficient calcium intake can lead to secondary hyperparathyroidism. It is widely accepted that absorption of calcium in the neonate is far less than that of phosphorus (50-60% in the former as compared to 80-90% in the latter)[2.]

Applicable Patient Group

Babies born at 33 weeks gestation or less, who are now 4 weeks and older, and who are meeting their nutritional requirements with enteral feeds, or parenteral nutrition.
Exclude: acutely unwell babies, babies <4weeks old, babies with known inadequate nutrition.

Identified antenatal, and postnatal risk factors[1]:

- < 30 weeks of gestation
- Weight < 1500gms

- Reduced active movements
- Placental insufficiency
- Prolonged TPN
- Breast fed babies (without any supplementation)
- Prolonged use of Medications – diuretics, steroids ,bicarbonate
- Cholestatic jaundice
- Short gut syndrome (malabsorption of Vitamin D and calcium)

Prevention

Prevention of MBD is best achieved through matching calcium and phosphate delivery to that which would be expected in utero in the preterm infant[1]. The primary considerations in this regard are therefore:

1. Adequate delivery of calcium and phosphate enterally (see nutritional values of milks in appendices), or parenterally[3]:
   - ESPGHAN[4] advises a calcium:phosphate ratio of 1.2-1.6:1 which is achieved with EBM, fortified EBM, and all term and preterm formulas used in the neonatal unit. As such it is feasible to use the enteral feeding route when clinically safe and effective to do so, with age and gestation appropriate vitamin and mineral supplementation (see local guideline 'Enteral feeding in preterm and growth restricted infants' reference no. NIC FF 12/July 22/v005)
   - The latest NICE Guidelines[5] recommend preterm babies parenterally receive:
     - Calcium and phosphate up to 1 mmol/kg/day in the first 48 hours
     - Maintenance dosage of calcium and phosphate of 2 mmol/kg/day after 48 hours
     - A resulting calcium:phosphate ratio of between 0.75:1 and 1:1 (mmol:mmol) for preterm babies on neonatal parenteral nutrition

2 Adequate provision of vitamin D
   - Included as standard for babies on parenteral nutrition
   - Supplemented as needed in babies who are fully enterally fed (see local guideline 'Enteral feeding in preterm and growth restricted infants' reference no. NIC FF 12/July 22/v005)

3 Facilitating detection of early biochemical abnormalities and appropriate monitoring for early intervention
   - Weekly monitoring of serum ALP in babies >4 weeks of age and <33 weeks gestation at delivery

Biochemical Features

- ↑ Alkaline phosphatase (>1200 IU)
- Hypophosphatemia (<1.2mmol/L)
- Abnormal Ca: PO4 ratio in urine. This should be <1 after 3 weeks of age (Both measured in mmols/L)

Clinical Features

Metabolic bone disease presents between 6-12 weeks of age. Babies may remain asymptomatic for weeks. Symptoms include poor weight gain, respiratory difficulty Some

show evidence of severe demineralisation. Features include:

- Radiological features, e.g. fractures, rickets, osteoporosis. Peak time for these changes are 36-40 weeks after conception
- Skeletal deformity, e.g. rib cage softening, craniotabes, reduced growth velocity

Investigations

- Weekly ALP, calcium (serum calcium may remain normal until late) and phosphate on babies at risk
- Weekly urine calcium and phosphate
- Consider measurement of vit D and parathyroid hormone (PTH) (low urinary calcium and raised parathyroid hormone suggest calcium deficiency)

Actioning Results

An ALP >500 in a baby >4weeks of age should prompt further investigation for a possible cause, as well as regular monitoring.

See figure 1 for the pathway or investigating such results and managing babies accordingly.

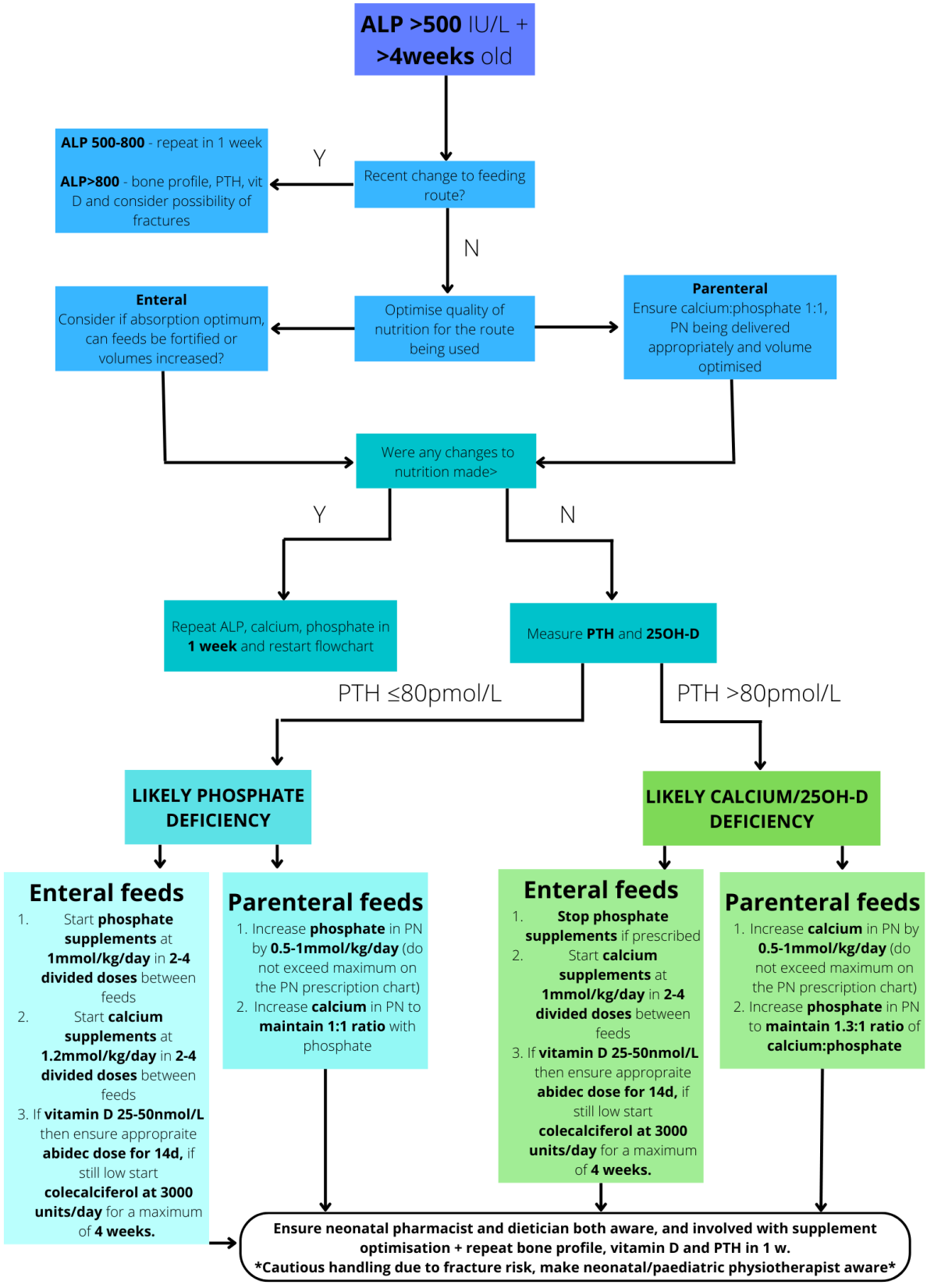

Figure 1: flowchart for the assessment and management of babies with an ALP >500 IU/L.

Troubleshooting

If ALP rising despite normal phosphate and PTH consider:

- Timing of blood test from last feed
- Alternative causes for a raised ALP (fracture, liver dysfunction)

Discuss babies with bloods which are unresponsive to treatment, or who have overt bone disease on x-ray with a paediatric endocrinologist.

Discuss babies with renal disease who required additional calcium of phosphate supplementation with a paediatric nephrologist.

Moving Forward

Calcium and Phosphate

If changes to a prescription have been made, allow **2 weeks** to see their full effect before making further alterations, unless clinically indicated otherwise. When adjusting doses thereafter aim to **increase and decrease in increments of 0.5mmol/kg/day**. Any baby requiring more than 2.5mmol/kg/day of calcium or phosphate should be discussed with a neonatal consultant, and likely a paediatric endocrinologist.

Vitamin D

Treatment at 3000 units should only routinely be used for 4 weeks due to a theoretical risk of subsequent hypercalcaemia. This dose should be sufficient to treat most babies on enteral feeds, and if longer is required this should be discussed with a neonatal pharmacist or consultant.

If a child is on PN with a low vitamin D, then ensure the full volume of prescribed PN is being delivered, and if not tolerating standard volumes of 120ml/kg/day arrange bespoke PN to meet nutritional need at a lower volume. If optimising PN delivery fails to improve the vitamin D then discuss with a neonatal consultant.

Discharge Planning

Follow up babies who remain on supplements at discharge, or those not on treatment who have residual bone profile abnormalities at discharge.

Arrange a bone profile, PTH and ALP to be taken in 4 weeks, and follow up with the named consultant in 6-8 weeks. Those who are on supplementation at discharge should be discussed with a paediatric radiologist to screen for radiological evidence of osteopenia if not already done.

Clearly tell parents to stop giving the 3000 units vitamin D 4 weeks after it was commenced if being given as a TTO.

Future Audit Points

- Number of babies (for whom it is clinically appropriate) reliably getting a weekly bone profile checked
- Age in weeks at which MBD is diagnosed, and the number of babies discharged from the neonatal unit on supplements or treatment dose vitamin D
- Duration of time spent on supplements when MBD detected and managed as per new recommendations compared to previous
- Number of babies with MBD associated fractures

5. References

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3 - British Association of Perinatal Medicine (BAPM) (2016). The Provision of Parenteral Nutrition within Neonatal Services -A Framework for Practice. Available at: https://www.bapm.org/resources/42-the-provision-of-parenteral-nutrition-within- neonatal-services-a-framework-for-practice-2016
4 - Mihatsch, W., Fewtrell, M., Goulet, O. et al. (2018). ESPHAGN/ESPEN/ESPR/CSPEN guideline on pediatric PN: Calcium, Phosphate and Magnesium. Clinical Nutrition. 37. 2360-2364.
5 - National Institute for Health and Care Excellence (2020). Neonatal Parenteral Nutrition (NICE Guideline NG154). Available at: https://www.nice.org.uk/guidance/ng154.

6. Documentation Controls

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7. Appendices

Appendix A: calcium and phosphate content of frequently used feeds in neonates

Feed type	Calcium mmol/kg	Phosphate mmol/kg	Ratio Ca:P mmol/kg
EBM* at 100ml/kg	0.6	0.5	1.2:1
EBM* at 150ml/kg	0.9	0.75	1.2:1
EBM* at 165ml/kg	0.99	0.83	1.2:1
Fortified EBM* at 100ml/kg	2.3	1.7	1.35:1
Fortified EBM* at 150ml/kg	3.4	2.6	1.35:1
Fortified EBM* at 165ml/kg	3.8	2.8	1.35:1
Cow and Gate Nutriprem 1® at 100ml/kg	2.5	2.1	1.2:1
Cow and Gate Nutriprem 1® at 150ml/kg	3.75	3.15	1.2:1
Cow and Gate Nutriprem 1® at 165ml/kg	4.13	3.47	1.2:1
Cow and Gate Nutriprem 2® at 100ml/kg	2.1	1.5	1.4:1
Cow and Gate Nutriprem 2® at 150ml/kg	3.15	2.25	1.4:1
Cow and Gate Nutriprem 2® at 165ml/kg	3.47	2.48	1.4:1
SMA Gold Prem 1® at 100ml/kg	2.9	2.5	1.2:1
SMA Gold Prem 1® at 150ml/kg	4.35	3.75	1.2:1
SMA Gold Prem 1® at 165ml/kg	4.79	4.13	1.2:1

Appendix B: Ratio of calcium:phosphate when supplements added to milk.
Note feed volumes have little effect on ratios of calcium and phosphate delivered

Feed type	Calcium mmol/kg	Phosphate mmol/kg	Ratio Ca:P mmol/kg	Ratio when 1mmol/kg/day Phosphate and 1.2mmol/kg/day Calcium
EBM* at 100ml/kg	0.6	0.5	1.2:1	1.2:1
EBM* at 165ml/kg	0.99	0.83	1.2:1	1.2:1
Fortified EBM* at 100ml/kg	2.3	1.7	1.35:1	1.3:1
Fortified EBM* at 165ml/kg	3.8	2.8	1.35:1	1.31:1
Cow and Gate Nutriprem 1® at 100ml/kg	2.5	2.1	1.2:1	1.2:1
Cow and Gate	4.13		1.2:1	1.2:1

Nutriprem 1® at 165ml/kg		3.47		
Cow and Gate Nutriprem 2® at 100ml/kg	2.1	1.5	1.4:1	1.32:1
Cow and Gate Nutriprem 2® at 165ml/kg	3.47	2.48	1.4:1	1.34:1
SMA Gold Prem 1® at 100ml/kg	2.9	2.5	1.2:1	1.17:1
SMA Gold Prem 1® at 165ml/kg	4.79	4.13	1.2:1	1.17:1