Metabolic Bone Disease of Prematurity - Guideline for Prevention and Treatment

University Hospitals of Leicester NHS Trust

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Contents

1. Introduction and Who Guideline applies to

This guideline is for all medical and nursing staff involved in the care of preterm and other at risk babies on the neonatal units at UHL.

Aim

- To provide guidance on identifying and assessing babies at risk of metabolic bone disease of prematurity.
- To recommend supplementation and feeding regimes for babies to optimise Calcium and phosphate intake.
- To outline ongoing monitoring after supplementation is started both for inpatients and babies after discharge.

Background

Pathogenesis

Metabolic bone disease of prematurity (MBD) results in skeletal demineralisation and fragility of the bones. It is commonly seen in very low birth weight babies. Although there are many contributing factors to the development of MBD the main pathogenic

mechanism is the reduced transplacental transfer of calcium and phosphate which occurs predominantly in the third trimester. During the last trimester of fetal life calcium accretes at a rate of 100-130mg/kg body weight/day and phosphate at a rate of 60-70 mg/kg body weight/day. These requirements are very difficult to meet ex utero. Calcium phosphate homeostasis is summarised in the figure below.

2. Guideline Standards and Procedures

2.1 At risk groups

Babies most at risk of developing MBD include those born <28 weeks or weighing <1500g, babies receiving Parenteral Nutrition for 4 weeks or more, babies treated with diuretics or steroids.

2.2 Prevention by screening

It is recognised the best management of MBD hinges around prevention by screening at risk babies and amending their nutritional intake. The development of radiological changes such as osteopaenia, rickets and fractures are late signs and prior to this elevated alkaline phosphatase often with deranged calcium and phosphate levels can be seen. MBD typically develops between 3 and 12 weeks of age with a peak at 4 to 8 weeks. Phosphate is predominantly an intracellular ion. While a robust mechanism exists for maintaining serum calcium within the normal range, such a mechanism does not exist for phosphate.

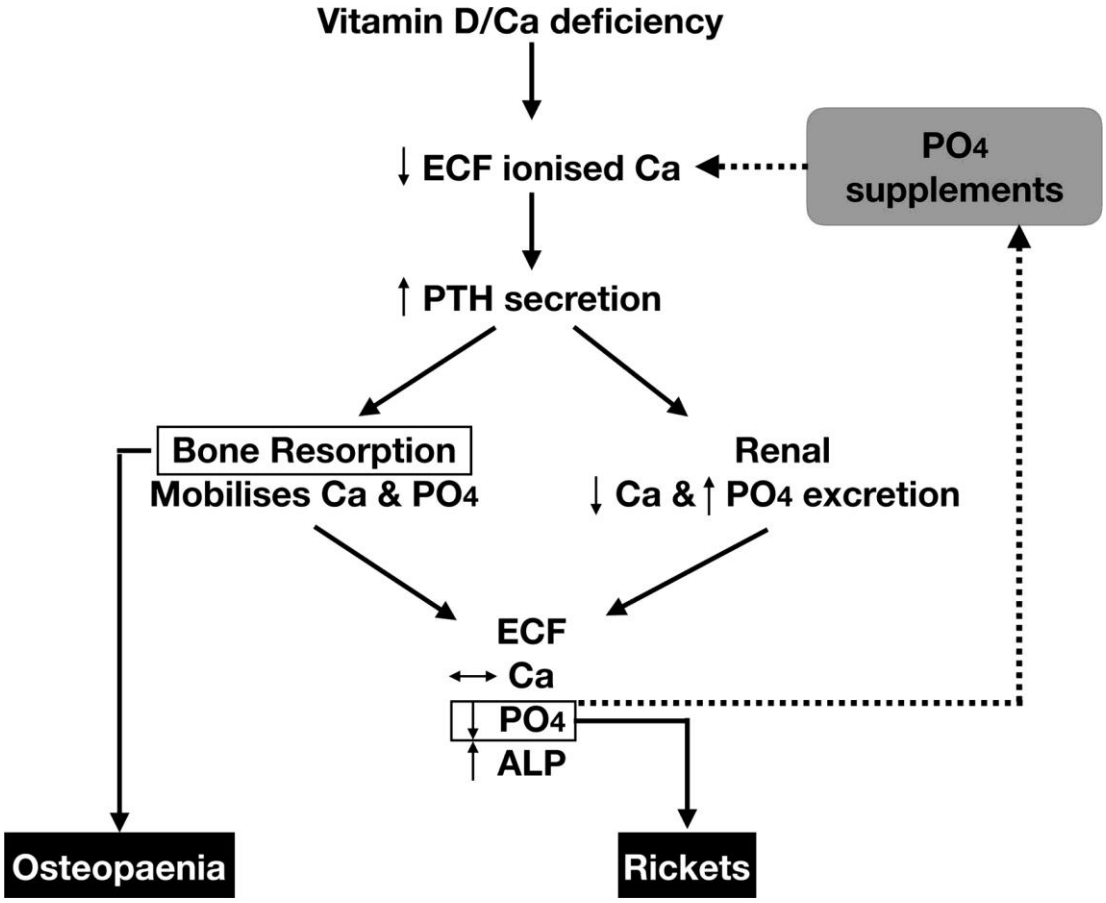
2.3 Rationale for not giving routine phosphate supplementation

Parathyroid Hormone (PTH) facilitates conversion of 25-hydroxy-vitamin D to 1,25-dihydroxy-vitamin D (the active metabolite of vitamin D), which helps in calcium and phosphate absorption from the diet. In a state of vitamin D deficiency and/or inadequate dietary absorption/intake of calcium (calcipaenia), PTH mobilises calcium and phosphate from the bones and actively excretes phosphate in the urine. Paradoxically therefore in mild to moderate calcipaenia, serum calcium concentration is maintained, while that of phosphate is reduced. The increased bone turnover from the resorptive action of PTH on bones leads to elevated Alkaline Phosphatase (ALP). Treatment with phosphate supplements without concurrent calcium supplementation to address the calcipaenia results in secondary hyperparathyroidism and worsening of bone demineralisation. By simply providing adequate calcium supplementation, the secondary hyperparathyroidism often resolves.

2.4 Principles of Treatment

In the calcipaenic state, treatment with high dose calcium +/- vitamin D supplementation provides additional calcium for bone mineralisation and increases serum ionised calcium which reduces PTH concentration, thereby reversing hypophosphataemia as well as bone resorption. Treatment with oral phosphate alone causes a further reduction of ionised calcium as it will bind to ionised calcium to form a calcium-phosphate product. This then triggers a further elevation of PTH, thereby increasing the risk of metabolic bone disease further.

Flowchart of Calcium/ Phosphate homeostasis



Chinoy A, Mughal MZ, Padidela R. Metabolic bone disease of prematurity: causes, recognition, prevention, treatment and long-term consequences. Arch Dis Child Fetal Neonatal Ed. 2019 Sep;104(5):F560-F566. doi: 10.1136/archdischild-2018-316330. Epub 2019 May 11. PMID: 31079069.

Chinoy recommends that the terms “osteopenia” or “rickets” should be avoided in isolation as they often coexist and therefore the term metabolic bone disease of prematurity refers to a condition where both may be present.

Summary – MBD Flow Chart

* PTH should be checked 2 weeks after 2nd course of dexamethasone is completed irrespective of alk phos levels

MBD screening for high risk group

- < 28/40 GA OR birth weight <1.5 kg
- Diuretics for >2 weeks,
- 2 Postnatal steroid courses (dexamethasone)*
- PN > 4 weeks

Weekly bone profile (Alk phos, PO4 and Ca) from 4 weeks until cga 35 weeks or discharge home (whichever is later)

Alk Phos > 700 or PO4 < 1.8 on 2 consecutive occasions (recheck within 48 hours)

- Check PTH
- Optimise feeds and ensure all Expressed Breast Milk (EBM) is fortified
- Use preterm formula if no EBM – Nutriprem 1 if < 1.8Kg, Nutriprem 2 for >1.8Kg
- Ensure baby is on Dalivit or other suitable vitamin

PTH >10 pmol/L ➔ Secondary hyperparathyroidism; Suggests either Ca or vit D deficiency

- Stop any PO4 supplements
- Start Calcium supplements if orally fed 0.5mmol/kg/day** in 2 – 4 divided doses (do not give at same time as milk feed or PO4 supplement)
- Review Ca:PO4 ratio is < 1.4:1 in feeds/TPN

PTH >7 but <10 may indicate developing 2º hyperparathyroidism – repeat after 2 weeks if alkaline phosphatase continues to rise

Recheck Alk phos, Ca, PO4, PTH in 1 to 2 weeks and measure vitamin D levels

PTH ≤ 10 pmol/L ➔ Suggests PO4 deficiency

- Consider PO4 supplements at 1mmol/kg/day*** in 2 divided doses (do not give at the same time as Calcium)
- If giving PO4, also start Calcium supplements at 1.2mmol/kg/day in 2 divided doses between feeds (do not give with PO4 supplements or a milk feed)

  The higher dose of Calcium is used in these babies to ensure the Ca:PO4 ratio is maintained.

  **1mmol Ca^{++} = 40mg Ca^{++}

  *** 1mmol PO_4 = 94mg PO_4

Recheck Alk Phos, Ca and PO4 levels in 1-2 weeks and recheck PTH if not improving

Vitamin D deficiency (<50nmol/L) – give supplements for 4 or 6 weeks

- 25-50 nmol/L - Colecalciferol 600 IU/day for 4 weeks in addition to Dalivit
- < 25 nmol/L – Cholecalciferol 2600 IU/day for 6 weeks in addition to Dalivit

- Weekly bone profile with PTH every 2 weeks while on supplements
- If Serum levels remain deranged:
  - Increment calcium dose to 1.2 mmol/kg/day Higher doses of calcium may be required if PTH and alkaline phosphatase remain high. If ongoing concerns check urine Ca:PO_4
  - where phosphate is used, increment doses by 1 mmol/kg/day and ensure Ca dose adjusted to maintain molar ratio (see below and appendix).

Secondary hyperparathyroidism

- Halve doses of supplements once PTH < 7
- Stop once parameters normal for 2 weeks

PO4 Deficiency

- Stop supplements once Alk Phos and PO4 levels normal and continue weekly screening

- Oral calcium:phosphate must stay in molar ratio of 1.2:1 to 1.3 :1 (see appendix)
- Check bloods 2 weeks after stopping if inpatient, or 2-4 weeks if outpatient (book with Homecare team)
- If babies are discharged on supplements, bone profile & PTH should be checked 4 - 6 weeks after discharge

2.5 Prevention of MBD

Nutrition

Fortified Expressed Breast Milk (EBM) and preterm formulas are designed to provide adequate calcium and phosphate for preterm infants. Fortified EBM and preterm formulas provide:

- Calcium 120-200 mg/kg/day
- Phosphate 70-115 mg/kg/day

Babies in the at risk groups should ideally be continued on either fortified EBM until fully breast fed or on preterm formula until 4 weeks after monitoring is completed.

- Parenteral nutrition
- NICE Guidance (NG154) recommends calcium to phosphate ratio in the range of 0.75:1 to 1:1 is maintained where possible.
  Calcium 1.5-3.5 mmol/kg/day
  Phosphate 1.5- 3.5 mmol/kg/day
- At risk babies should have dietetic and pharmacy review of their "off the shelf" TPN to ensure it meets requirements for prevention of MBD.

Vitamin D

- Included in Vitlipid portion of TPN
- Dalivit supplement for babies on enteral feeds
  - **Dose 0.6 ml once daily (0.3ml OD if on Nutriprem)**

2.6 Monitoring for evolving MBD

Babies at increased risk of developing MBD fall into any of the categories below. Assessment and evaluation of alkaline phosphatase and phosphate levels is more difficult before 4 weeks of age especially in babies still on PN. Babies at risk of MBD should be screening weekly for the biochemical markers of evolving MBD with bone profile until 35 weeks of postnatal age or discharge home (whichever is soonest).

- Born before 28 weeks
- Birth weight <1.5 kg
- Diuretic use >2 weeks duration
- Completed 2 courses of postnatal dexamethasone*
- On full PN for > 4 weeks

***If babies are on postnatal steroids they may have an artificially low ALP. Therefore babies who receive 2 full courses of dexamethasone should have PTH checked 2 weeks after completing the course of dexamethasone irrespective of Alkaline phosphate levels.**

Deranged Calcium/phosphate homeostasis is defined as:

- PO_4 <1.8 on 2 consecutive occasions (re-check within 48 hours)

  AND/OR

- Elevated alkaline phosphatase (ALP) >700

If deranged Ca/PO_4 homeostasis is seen, PTH and then vit D levels should be checked (see flow chart).

- Normal range for babies of PTH is 1-7 pmol/L. Using a level of 10 pmol/L is a pragmatic approach to screening for MBD.
- 25 hydroxy vitamin D should be 50 to 120 nmol/L, If levels < 50 nmol/l, additional supplementation is required and can be given for a 4 week period. Dose can be altered based on monitoring with an aim to keep vitamin D levels within the normal range.

2.7 Management of evolving MBD based on biochemical abnormalities

If MBD is suspected *(↑ALP, ↓phosphate, normal or ↑PTH, ↓vit D)* the likely underlying cause of MBD can be determined based upon the results of the initial screening investigations and treatment can be tailored accordingly. Once mineral supplementation is started, monitoring and therapeutic goals can be individualised to the underlying deficiency and specific treatment. Please refer to flow chart/text below

- **Make sure breast milk fortifier is used for maternal or donor milk and vitamins prescribed appropriately**

- **Review contributing medications to see if any can be discontinued.**
  a) Diuretics
  b) Steroids
  c) Caffeine

- **Commence Ca and PO_4 supplementation as appropriate (see flow chart)**
  a) If on TPN discuss with pharmacy to ensure maximum supplementation of calcium balanced with phosphate is prescribed.

  b) If enterally fed, these oral supplements require prescribing carefully depending on timing of feeds.
    i. Calcium 0.5 mmol/kg/day in 2 divided doses (i.e. 0.25 mmol/kg bd see appendix 1 for prescribing details)
    ii. Doses can be increased in weekly increments as required if no response seen.

<u>Ensure the molar ratio of Ca;PO_4 is maintained if PO4 supplementation also used</u>.
These further increments are to be to be titrated according to serum levels. If serum levels are difficult to manage consider using urine Ca:PO_4 calculation as an additional guide

c) **Calcium and phosphate must be given separately in different feeds to avoid precipitation**.

d) **Calcium should not be given at the same time as a milk feed**

e) High serum calcium poses a risk for nephrocalcinosis, but in the presence of normal or elevated PTH, the risk is negligible as PTH

facilitates active tubular reabsorption of calcium from the glomerular filtrate. Where PTH becomes very supressed (levels <1pmol/L) after treatment, urine calcium:creatinine ratio can identify hypercalciuria and consideration can be given to screening for nephrocalcinosis.

- **If vitamin D insufficiency, serum levels 25 - 50 nmol/L**
    - Ensure baby on dalivit
        - 0.6ml dalivit provides 400IU of vitamin D
    - Start additional cholecalciferol (vitamin D) at a dose of 600 IU/day for a minimum of 4 weeks

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- If vitamin D deficiency with serum levels < 25nmol/L
    - Ensure baby on dalivit
        - 0.6ml dalivit provides 400IU of vitamin D
    - Give additional 2600 units cholecalciferol per day for 4 weeks

After 4 weeks stop additional vitamin D and continue dalivit. No need to repeat levels

- **Doses of calcium, Phosphate and vitamin D are amended based upon:**
    - Weekly bone profile
    - 2 weekly PTH
    - Urinary Ca:PO_4 ratio may be helpful in complicated cases.

- **Doses of vitamin D are determined by the initial measurement**
    - Vit D levels do not need repeating if the baby has additional vitamin D supplementation for 4 weeks after low levels

- Treatment aims to normalise:
    - Serum PO_4
    - Alk Phos
    - PTH
    - Vit D levels

- Weaning supplementation
    - See MBD Flow chart in section 7.0
    - In secondary hyperparathyroidism - halve supplementation once PTH < 7 pmol/L and stop once parameters have been normal for 2 weeks
    - Recheck bone profile and PTH 2 weeks after stopping treatment (2-4 weeks if outpatient).
    - In phosphate deficiency – stop calcium and phosphate supplements once alk phos and PO4 are normal and continue weekly screening

2.8 Fractures noted as an incidental finding on X-ray

- Immobilise limb and provide analgesia
- Measure the baby's biochemistry (Ca/PO_4/ALP/PTH/vit D)

- Contact
    - Orthopaedics regarding care of fracture site

- Consider if referral to Endocrine team is required (see section below)
- Treat as with supplementation as indicated by bone profile

2.9 Referral to Endocrine team in UHL

This should be done in cases where there is:

- X-ray suggestive of alternative cause for metabolic bone disease e.g. x-linked hypophosphotasia
- Bone disease or blood results not responding to treatment pathways above
- Recurrent fractures associated with no/minimal trauma and/or evidence of vertebral fracture

When referring a patient to the endocrine team the referrer will need access to, and comprehension of the following:

- Biochemistry, including bone profile, vitamin D and PTH, Urine for calcium:creatinine ratio
- Trends in biochemistry and any changes in relation to mineral supplementation
- Medications
- Growth charts
- Current clinical condition
- Level of activity
- Results of any imaging
- Current feeds, total calcium and phosphate intake and calculated calcium to phosphate as a molar ratio (enteral or parenteral)

2.10 Post discharge

Bone mineralisation improves rapidly in the first few months of life. Preterm discharge formula and Dalivit 0.6ml od contains adequate levels of supplementation for the majority of Very Low Birthweight (VLBW) babies. Babies requiring ongoing supplements after discharge should be prescribed twice daily Calcium and/or twice daily phosphate to make dosing easy for parents.

For babies in at risk groups on formula feeds, consider continuing preterm formula to term even if catch up weight gain is achieved. Where weight has not reached birth centile it may be appropriate to be continued to 3-6 months corrected age.

Post discharge bloods are required at 4 - 6 weeks post discharge on babies who meet the following criteria:

- Discharged on calcium or phosphate supplements
- Exclusively breast fed babies with VLBW (<1.5Kg) (this is required regardless of postnatal growth but is not needed if baby is mixed feeds or receiving fortifier at this time)

The supplements should be stopped if biochemical markers normalised. If ongoing supplementation is required further monitoring will be required

3. Education and Training

None

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Compliance with guidance	Audit	Neonatal audit lead	6-12 months	Neonatal audit group

5. Supporting References

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Enteral Nutrient Supply for Preterm Infants: Commentary from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010; 50(1): 85-91

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6. Key Words

Calcipaenia, Calcium, Expressed breast milk, Fractures, Osteopaenia, Parathyroid Hormone, Phosphate, Rickets,Vitamin D

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS			
Guideline Lead (Name and Title) Jo Preece – Neonatal Consultant			**Executive Lead** Chief medical officer
Details of Changes made during review:			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
June 2023	**1**	**Neonatal Guidelines group Neonatal Governance group**	**New document**
November 2024	**2**	**Neonatal Guidelines group Neonatal Governance group**	**No change Review in 12 months**

Appendix 1- Oral Calcium supplements

In hospital

Sandocal 1000 (effervescent table) CALVIVE

Sandocal contain 25mmol (1000mg) of Calcium per tablet (a combination of Calcium lactate gluconate and Calcium Carbonate).

Directions: Measure out 20mls of sterile water and add 1 dispersible tablet (25mmol). This provides 1mmol/mL or 40 mg/ml (as 1 tablet displaces 5mL)

Doses must not be given at the same time as milk and also not with the Phosphate supplement. Calcium and phosphate supplements should be separated by at least 2 hours.

Draw up required amount and discard remaining solution.

At discharge

Calcium syrups are no longer available show parents should be taught how to make up the right dose using dispersible tablets.

Appendix 2 Calcium : Phosphate ratio

Calcium: Phosphate can be given as a molar or mg:mg value.

Molar ratio	**Enteral 1.2:1 to 1.3:1**
mg:mg	**Enteral 1.5:1 to 1.7:1**

This is because:

1mmol of calcium is 40 mg
1mmol of phosphate is 31 mg

Calcium and Phosphate content of Milks used

Feed content per **150 ml**	Calcium		Phosphorous		**Ca:Po4 mmol: mmol**	**Ca:PO4 mg:mg**
	mmol	**mg**	**mmol**	**mg**		
Preterm EBM[a]	0.9	37.5	0.7	22	1.3:1	1.7:1
EBM[b]	1.3	51	0.7	22.5	1.8:1	2.3:1
Fortified EBM (1 sachet Nutriprem HMF per 25ml)	3.9	155	2.6	79	1.5:1	2:1
Nutriprem 1	3.8	151.5	3	94.5	1.3:1	1.6:1
Nutriprem 2	3.2	124.5	2.3	72	1.4:1	1.7:1
ESPGHAN 2022 (/kg/day)	3 - 5	117 - 194.5	2.2-3.7	69 - 116	1.35:1	1.7:1

[a] Koletzko b et al. Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, World Rev Nutr Diet, Karger 2014 vol 110: 304-305
[b] McCance and Widdowson. The Composition of Foods Seventh Summary Edition

Note; All combinations of EBM with fortifier give a calcium phosphate mg;mg ratio of 1.5:1 to 1.7:1 (equivalent to a molar ratio of 1.2:1 to 1.3:1)