**Northwest London**

**NETWORK CLINICAL GUIDELINE**

# Prevention and Management of Metabolic Bone Disease of Prematurity and Vitamin D deficiency in Northwest London Neonatal Network neonatal units

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| Related documents | Initiating and advancing enteral feeding and preterm nutritional supplementation |

## RATIONALE AND SCOPE

The aim of this document is to provide a consistent clinical approach to prevention, diagnosis and management of metabolic bone disease in preterm infants and Vitamin D deficiency across the North West London Perinatal Network based on latest national and international guidance and evidence.

## DEFINITIONS AND ABBREVIATIONS

| | |
|---|---|
| MBDP | Metabolic bone disease of prematurity |
| ALP | Alkaline phosphatase |
| Ca | Calcium |
| ECF | Extracellular fluid |
| PTH | Parathyroid hormone |
| PO4 | Phosphate |
| MEBM | Mother's expressed breastmilk |
| DEBM | Donor expressed breastmilk |
| FS BMF | Full strength breast milk fortifier (Cow and Gate) |
| HS BMF | Half strength breast milk fortifier (Cow and Gate) |
| NP1 | Nutriprem 1 (Cow and Gate) |
| NP2 | Nutriprem 2 (Cow and Gate) |

## FULL GUIDELINE

### 1.1 Metabolic bone disease

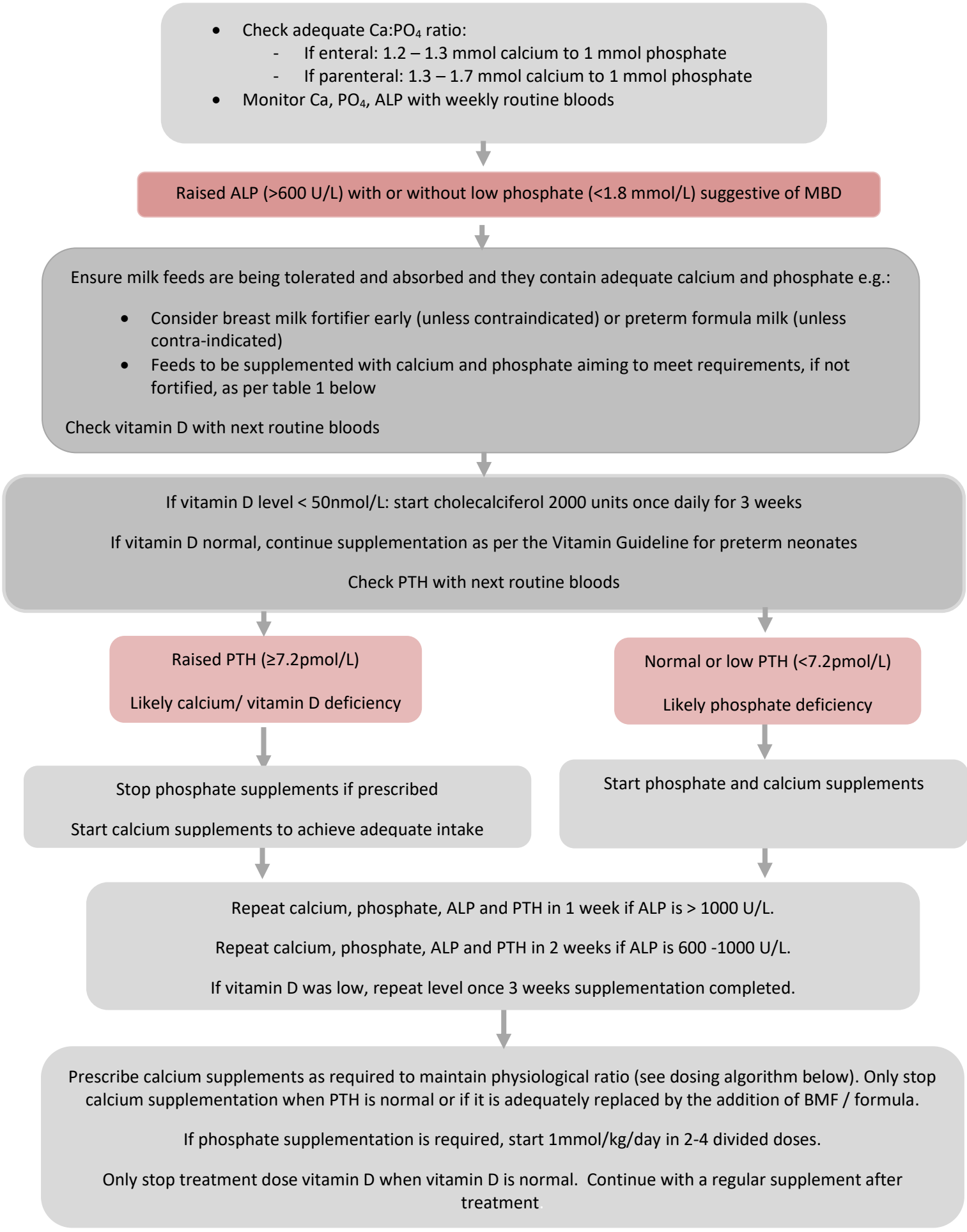
Preterm infants are at significant risk of metabolic bone disease because skeletal growth and bone mineralisation take place mostly during the third trimester of pregnancy (specifically 32-36 weeks gestation). Metabolic bone disease of prematurity (MBD) is essentially a substrate deficiency disease arising from inadequate calcium and phosphate supplementation.

MBD is often asymptomatic in the early stages and diagnosed based on biochemical changes noted in routine bloods. A combination of high ALP, low phosphate and elevated parathyroid hormone (PTH) is highly sensitive and specific for a diagnosis of MBD.

This under mineralisation of the bone can range from mild to severe and can be associated with osteopenia, fragility fractures and rickets in its most severe form (1). This can be asymptomatic until late in the disease when an infant may develop fractures of the bones due to fragility.

Therefore, preterm infants require adequate calcium and phosphate in an appropriate ratio in their diet and appropriate monitoring to identify the biochemical markers of MBD. Vitamin D is also essential for the absorption of calcium and phosphate from the intestine to enable bone mineralisation.

**1.2 Summary - for all high-risk infants (see table 4), follow this guidance after establishing enteral feeding:**



**Dosing algorithm for infants requiring phosphate supplementation**

The recommended nutrient intakes for calcium and phosphate, as per ESPGHAN 2022, are as follows:

- Calcium: 3 – 5 mmol/kg/day

- Phosphate: 2.2 – 3.7 mmol/kg/day

Additional calcium and phosphate supplementation whilst keeping an optimal calcium : phosphate molar ratio may be required to meet the recommended nutrient intakes for calcium and phosphate, using Table 2 below as a starting point.

**Table 1.** Whilst the starting dose of phosphate can be standard at 1mmol/kg/day, the dose of calcium will depend on the feed type and volume.

| **Treatment of MBD** | **mmol** |
|---|---|
| | Calcium: Phosphate |
| **PN** | 1.3:1 to 1.7:1 |
| **Enteral** | 1.2:1 to 1.3:1 |

**Table 2.** The following table details the calcium dose required, for every 1mmol of phosphate, for feeds commonly used:

| Enteral feed at 150mL/kg/day | Additional phosphate dose mmol/kg/day | Additional calcium dose mmol/kg/day | Total phosphate (inc.feed) mmol/kg/day | Total calcium (inc. feed) mmol/kg/day | Ratio $Ca:PO_4$ mmol |
|---|---|---|---|---|---|
| EBM | 1 | 1 | 1.7 | 2.3 | 1.3:1 |
| EBM + FS BMF | 1 | 0.8 | 3.6 | 4.7 | 1.3:1 |
| Nutriprem 1 | 1 | 1.2 | 4 | 5 | 1.25:1 |
| Nutriprem 2 | 1 | 1 | 3.3 | 4.3 | 1.3:1 |

Please note that simultaneous administration of calcium and phosphate supplements with feeds will result in precipitation and poor absorption. Calcium and phosphate should therefore be administered at a separate time with or before feeds.

**Table 3.** The following table details the provision of calcium and phosphate from feeds commonly used:

| **Milk** | **Volume (mL/kg/day)** | **Calcium (mmol/kg/day)** | **Phosphate (mmol/kg/day)** | **$Ca:PO_4$ ratio (mmol)** |
|---|---|---|---|---|
| Mature MEBM | 180 | 1.5 | 0.9 | 1.7 : 1 |
| DEBM | 180 | 1.5 | 0.9 | 1.7 : 1 |
| Mature MEBM + FS BMF | 160 | 4.2 | 2.8 | 1.5 : 1 |
| DEBM + FS BMF | 160 | 4.2 | 2.8 | 1.5 : 1 |
| NP1 | 160 | 4 | 3.3 | 1.2 : 1 |
| NP2 | 160 | 3.5 | 2.5 | 1.4 : 1 |
| Similac High Energy* | 130 | 2.6 | 1.8 | 1.4 : 1 |
| Infatrini Peptisorb* | 130 | 2.6 | 1.7 | 1.5 : 1 |

** not for use in infants < 2kg weight*

### 1.3 Risk factors[1]

- Recommendations suggest that all infants less than <30 weeks gestation or with a birth weight of less than 1000g are at high-risk of MBD, although all infants with a birth weight less than 1500g should be screened for MBD.

- Infants with intrauterine growth restriction (<2nd centile) are at significant risk of developing metabolic bone disease because of placental insufficiency resulting in inadequate transport of minerals in utero.

- Medications such as glucocorticoids, antacids, methylxanthines and diuretic therapy as well as postnatal immobilisation lead to increased bone resorption.

- Parenteral nutrition for > 2 weeks is a risk factor for metabolic bone disease as the risk of calcium and phosphate precipitation limits the content of these minerals in parenteral nutrition.

**Table 4: Risk factors for metabolic bone disease and their underlying causative mechanisms[1]**

| Risk factor | Underlying mechanism(s) |
|---|---|
| Prematurity | Loss of maximal in utero mineralisation. |
| Loss of maternal oestrogen | Increased osteoclast formation and bone resorption. |
| Intrauterine growth restriction | Associated with placental insufficiency resulting in reduced active placental transport of minerals in utero. |
| Reduced physical activity | Increased bone resorption from reduced mechanical stimulation and deformation. |
| Parenteral nutrition | Limitations in calcium and phosphate content due to precipitation. |
| Glucocorticoids | Reduce gut absorption of minerals.<br>Direct effect on bone (increased bone resorption and reduced bone formation). |
| Antacids | Reduced gut absorption of calcium (neutralisation of stomach acid). |
| Loop diuretics | Increased renal calcium loss (inhibition of calcium reabsorption). |
| Chronic lung disease/ bronchopulmonary dysplasia | Higher energy requirements compromising mineral supply to the bones.<br>Increased use of glucocorticoids and loop diuretics. |
| Necrotising enterocolitis | Prolonged periods of parenteral nutrition.<br>Poor gut function and therefore poor mineral absorption. |
| Excessive phosphate supplementation | Imbalance in calcium to phosphate ratio resulting in secondary hyperparathyroidism and bone resorption. |

### 1.4 Diagnosis

MBD is often asymptomatic in the early stages and diagnosed based on biochemical changes noted in routine bloods. **A combination of high ALP, low phosphate and elevated parathyroid hormone (PTH) is highly sensitive and specific for a diagnosis of MBD.**

**Calcium:**

- The assessment of serum calcium levels is not a reliable screening tool because newborns can maintain normal calcium values despite a bone calcium loss.
- Serum calcium levels may also be affected by other disorders such as phosphate depletion and hypophosphatasemia.

**Phosphate:**

- Hypophosphatemia is the earliest marker of disrupted mineral metabolism, occurring 7–14 days after birth.
- Serum phosphate levels lower than 1.8 mmol/L in newborns suggest the depletion of the mineral content and indicate a greater risk for MBD development.

**Alkaline phosphatase (ALP) measures the rate of bone function activity** (modelling and remodelling):

- ALP is a bone turnover marker which physiologically increases over the first 3 weeks of life and reaches a peak at 6–12 weeks of age.
- A rising ALP >600 U/L is an early sign of MBD.
- There is no cut-off value for marker of MBD. High ALP >800 U/L often is considered a marker for MBD.
- It is normal for a preterm infant's ALP to rise initially to 2-3 times an adult value (e.g. 250-375 IU/L) by 2-3 weeks of age but should fall. ALP >1200 IU/L in the neonatal period is associated with long-term linear growth deficit (Lucas 1989).

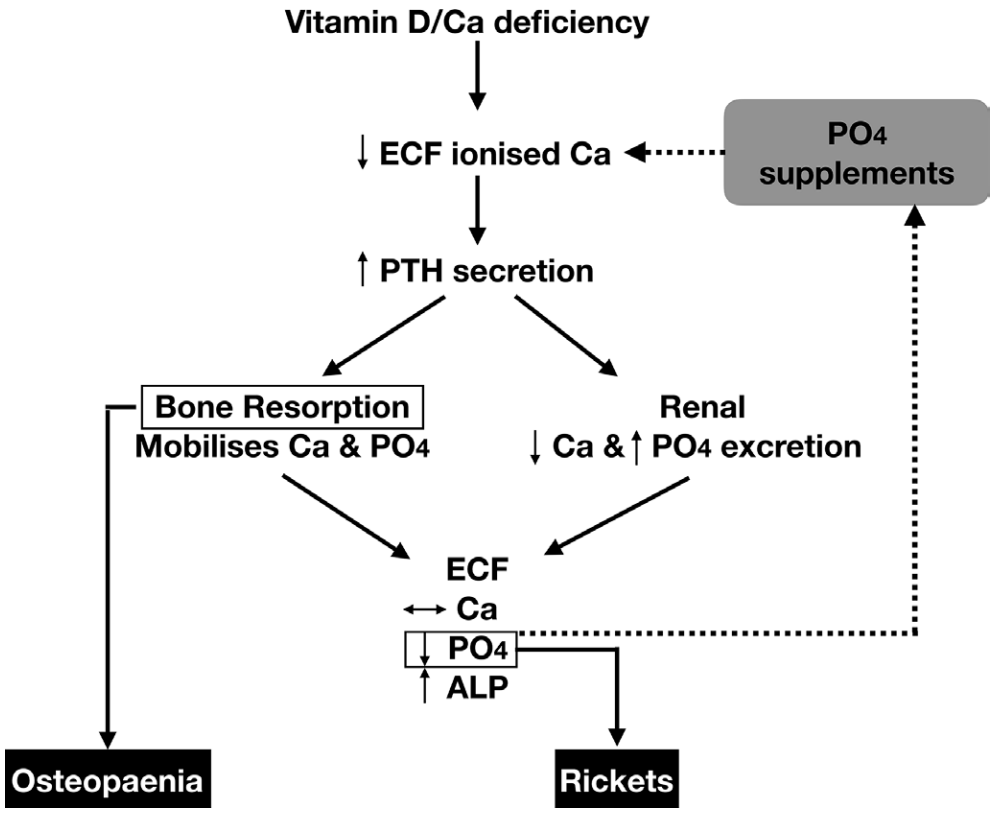
**Parathyroid hormone (PTH):**

- PTH is secreted in response to low serum calcium levels and stimulates bone resorption, so PTH levels are a measure of bone turnover
- Routine supplementation of oral phosphates in high risk neonates could lead to secondary hyperparathyroidism, and thus worsen MBD (Figure 1). It also increases the calcium turnover and results in calcium depletion.
- Therefore in cases of suspected MBD with elevated ALP and low phosphate, PTH measurement will help in establishing if there is underlying calcium or phosphate deficiency and will guide which minerals need to be supplemented.
    - In the case of calcium or vitamin D deficiency, the PTH will be raised
    - In the case of a phosphate deficiency the PTH will be low or normal.
- PTH level takes an average turnaround of 3 working days. Normal levels: 1.6 – 7.2 pmol/L (reference range on Cerner).

**X-ray changes:**

- Bone mineralization must be reduced by 20–40% to be identifiable on X-ray and usually it occurs later in life.
- Radiological features include osteopenia (a 'washed out' appearance and thin cortices on radiographs) and eventually pathological fractures if left untreated. Rickets is uncommon these days.
- Babies should be examined carefully to check for fractures and bony deformities. Often fractures are picked up incidentally on X-Rays.
- Fractures are often in the ribs and long bones and may manifest with pain on handling with swelling and tenderness at the fracture site. Fractures in the wrists and knees occur due to intravenous cannulation in high risk patients.

Figure 1: Pathophysiology of calcipaenic metabolic bone disease of prematurity, demonstrating how resultant hyperparathyroidism leads to bone resorption, hypophosphataemia and rickets, as well as how treatment with phosphate supplements alone without adequate calcium intake further drives this secondary hyperparathyroidism (dotted arrows)[2].



### 1.5 Prevention

- Once feeds are established, regular weekly review of bone biochemistry as below in section 1.6
- Consider routine multicomponent fortification of breast milk (unless contraindicated)
- If no fortification is used, ensure feeds are supplemented with calcium and phosphate adequately as per table 1 above to meet nutritional requirements as per table 2
- Consider using preterm formulas when needed if not contra-indicated

### 1.6. Management

- Aim for a corrected calcium level of 2.2 - 2.7mmol/L with a phosphate level of 1.3 - 2.4 mmol/L, with Ca>$PO_4$.
- Treatment of metabolic bone disease with oral supplements should ensure enteral calcium to phosphate intake ratio at 1.2 – 1.3 mmol: 1 mmol basis. Higher concentrations of phosphate will bind to the serum ionised calcium and worsen the secondary hyperparathyroidism and further potentiate urinary phosphate loss.
- If both calcium and phosphate supplements are prescribed to an infant – ensure that they are <u>not</u> given together as they precipitate in feeds.
- Aim to normalise biochemistry by 34 weeks gestation.
- If needs longer supplementation, check biochemistry in 1-2 weeks after stopping.
- If needs to continue supplements after discharge - TTO for 4 weeks and arrange blood test 1-2 weeks after stopping supplements.

**Calcium supplementation**

- Recommended starting dose: 0.25 mmol/kg every 6 hours orally. Increase doses according to repeat blood tests, if needed.
    - For phosphate deficiency: aim to keep optimal Ca:$PO_4$ ratio from milk /PN and supplements (see table 2).
- 1 mmol of calcium provides 40 mg of calcium.

**Phosphate supplementation**

- Recommended starting dose: 0.5 mmol/kg every 12 hours po (see table 2).
- 1 mmol of phosphate provides 95mg of phosphate (potassium dihydrogen phosphate preparation).

**Vitamin D supplementation:**

- Vitamin D is required for the absorption of calcium and phosphate from the intestine and reabsorption of calcium in the kidney to enable bone mineralisation.
- If taking levels for vitamin D these should be taken at a different time to giving doses of vitamin D.

**Dose for preterm infants**

- All preterm infants, irrespective of the type of feed, should receive 400-700 IU/kg/day with a maximum of 1000 IU per day of vitamin D daily.
- Vitamin D levels should be maintained above 50nmol/L.
- If adequate vitamin D levels cannot be maintained with oral vitamin D because of poor absorption or reduced oral intake, vitamin D as ergocalciferol or colecalciferol can be given as an IM injection.

- There is no evidence that Alfacalcidol or calcitriol have advantage over vitamin D in treating or preventing MBD.
- However, neonates with significant liver impairment should be prescribed the active form Alfacalcidol (hydroxychole-calciferol).
- See doses for vitamin D deficiency below (2.3)

**Dose for term infants**

- Public Health England advice states that all infants and children should have a preventive daily dose of at least 400 IU per day of vitamin D.
- Additional Vitamin D supplementation is only needed in confirmed cases of deficiency/insufficiency. See doses for vitamin D deficiency below (2.3)

### 2.1 Definition of Vitamin D deficiency

Vitamin D status is defined on the basis of serum 25-hydroxyvitamin D (25-OH-D) levels, as this is the major circulating form of vitamin D and reflects both endogenous synthesis and dietary intake. Vitamin D is critical for infant bone mineralisation.

Newborn babies whose mothers did not take regular vitamin D supplements during pregnancy and / or whilst breastfeeding are at an increased risk of vitamin D deficiency, particularly those from high risk ethnic groups (African-Caribbean and South Asian).

The British Paediatric and Adolescent Bone Group (BPABG)[3] and RCPCH[4] recommend the following thresholds:

| | |
|---|---|
| Deficiency | < 25 nmol/L |
| Insufficiency | 25 – 50 nmol/L |
| Sufficiency | > 50 nmol/L |

### 2.2 Risk factors for vitamin D deficiency:

- Metabolic bone disease (as defined above)
- Symptomatic hypocalcaemia – low total serum or ionised calcium in the presence of seizures, tetany, arrhythmia, or cardiac failure.
- Persistent asymptomatic hypocalcaemia that is not otherwise explained (e.g. by a hypoxic insult, unwell preterm, sepsis, maternal diabetes or preeclampsia).
- Fracture
- GI malabsorption (e.g. short bowel syndrome)
- Chronic liver disease or cholestasis which is not resolving after 3 weeks
- Chronic renal failure
- Infant's mother did not take vitamin D during pregnancy
- Infant's mother is vitamin D deficient herself (non-Caucasian women are a high-risk group)

### 2.3 Management of Vitamin D Deficiency / Insufficiency in Neonates

The two major forms of vitamin D are vitamin D3 (colecalciferol) and vitamin D2 (ergocalciferol). Neonates needing vitamin D supplementation should be prescribed colecalciferol unless otherwise indicated.

Neonates with levels of vitamin D < 50nmol/L should be treated with **colecalciferol 2,000 units once a day for 3 weeks and to continue with a regular maintenance supplement after treatment if their level normalised.**

Other prescribed multivitamin supplements containing vitamin D (such as Abidec or Dalivit) should be continued whilst the treatment course is given.

Neonates with significant liver impairment should be prescribed the active form alfacalcidol (hydroxycolecalciferol). Additional monitoring will be required as per specialist advice.

The vitamin D level should be re-tested one week after the end of the treatment course. Discuss the management with the consultant / pharmacist if vitamin D levels remain <50 nmol/L following completion of the course of treatment and consider giving another 3 week treatment course.

If adequate vitamin D levels cannot be maintained with oral vitamin D because of poor absorption or reduced oral intake, vitamin D as ergocalciferol or colecalciferol can be give as an IM injection. Please seek specialist advice in this instance.

### 2.4 Who to refer to paediatric endocrinology follow up

- All infants and children with hypocalcaemia (see relevant guideline)
- Patients with renal / hepatic impairment
- Children with radiological abnormalities or orthopaedic deformities of rickets.
- Children who have been treated for rickets should be followed-up in the paediatric endocrine clinic and have calcium, parathyroid hormone (PTH), alkaline phosphatase (ALP) and vitamin D checked at the end of treatment.
- If the diagnosis is not certain or there appear to be no risk factors.

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