MCN for Neonatology

West of Scotland

Neonatal Guideline

Metabolic Bone Disease of Prematurity (MBDP)

Guideline for Investigation & Management

Introduction
This guideline is applicable to all medical staff, ANNPs or extended role practitioners working in neonatal units in the West of Scotland. Reference should also be made to the separate *WoS guideline for enteral feeding of the preterm baby* as well as the WoS Drug Monographs for any medications mentioned in the document.

This guideline is based on contemporaneous published work acknowledging the importance of considering both calcium and phosphate as potential causative deficiencies. It also gives weight to optimising nutritional vitamin D in these babies. The treatment algorithm outlines the use of parathyroid hormone measurement in guiding individual management plans.

Contents

Background

Advances in the nutritional care of preterm babies have been associated with a declining incidence of osteopenia in preterm infants. However osteopenia remains a significant problem for extremely preterm and very low-birth weight (VLBW) babies, particularly those who have chronic illness and multiple risk factors. Even with good nutrition and early phosphate, calcium and vitamin D supplementation, it is very difficult to achieve the specific and very high requirements of a preterm baby 1-3. Infants with osteopenia have bones that are fragile and at risk of fracture even with normal handling. Term corrected age is the highest risk time for an occult fracture to occur1, 2. It is estimated that 2%1, 2 of all preterm babies have fractures secondary to osteopenia. However, this number increases with decreasing birth weight and gestation, with an estimated 10-30%1,3 of VLBW (1000-1500g) babies being affected and up to 70% of extremely LBW 1(<1000g) babies being affected.

Recent findings suggest that, despite large differences in neonatal mineral intake, no effect of neonatal nutrition on bone mass or bone turnover is detectable in early adult life4. However, greater exposure to human milk in the neonatal period, despite its very low mineral content, is associated with higher peak bone mass4. Studies in healthy term infants suggest that suboptimal maternal vitamin D status during pregnancy has adverse effects on offspring bone health in infancy and later childhood5; however, effects in infants born preterm have not been investigated. The role and optimal dose of vitamin D for later bone health in preterm infants still requires further research [4,6].

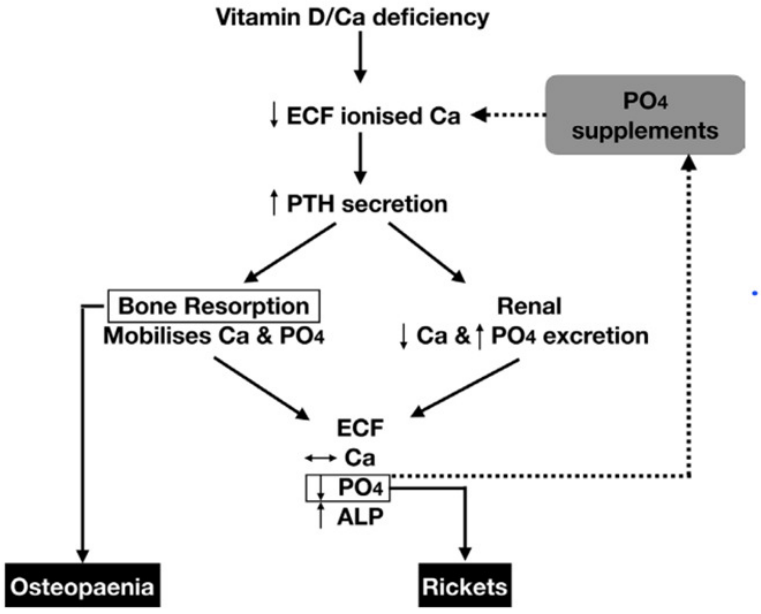
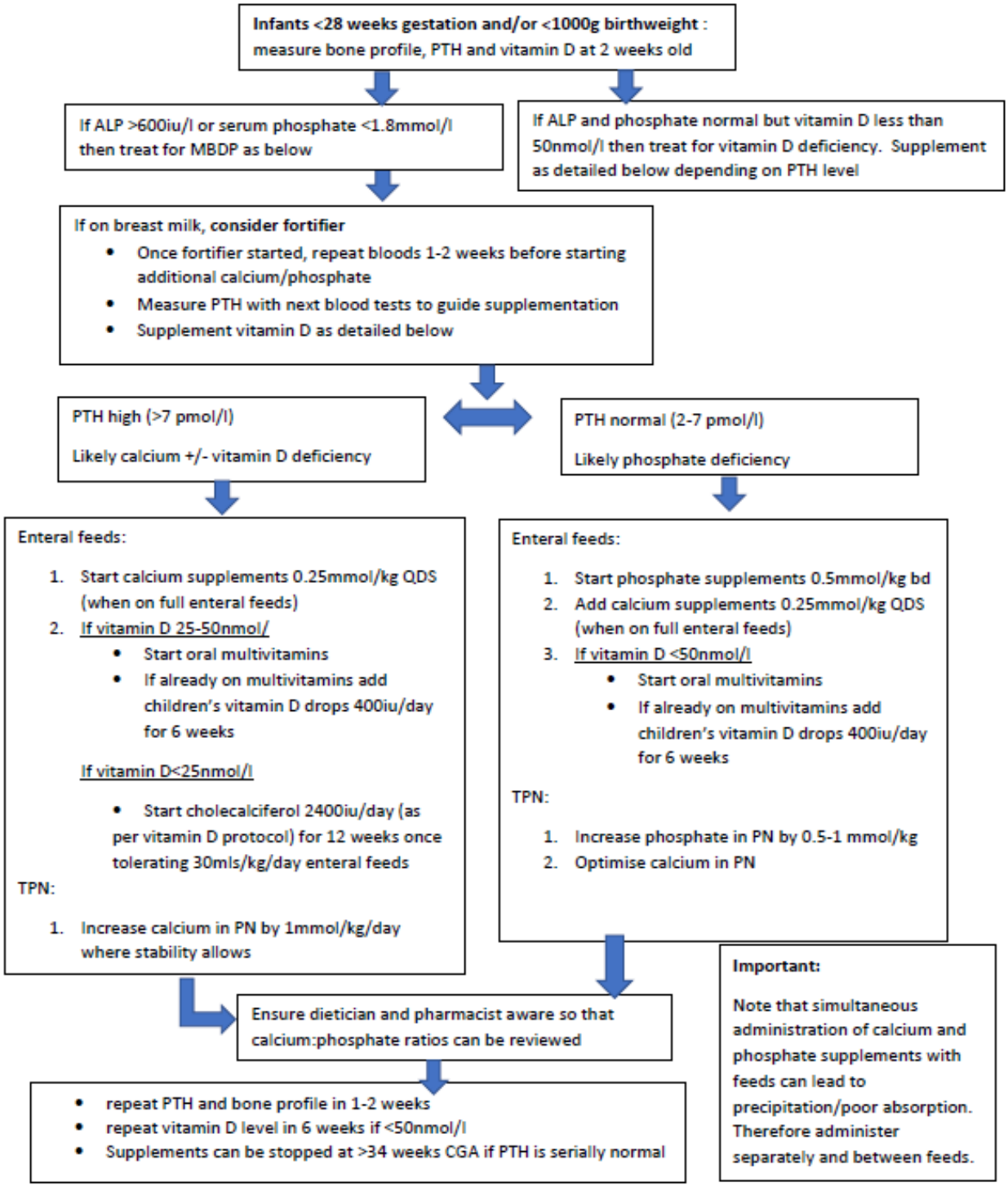
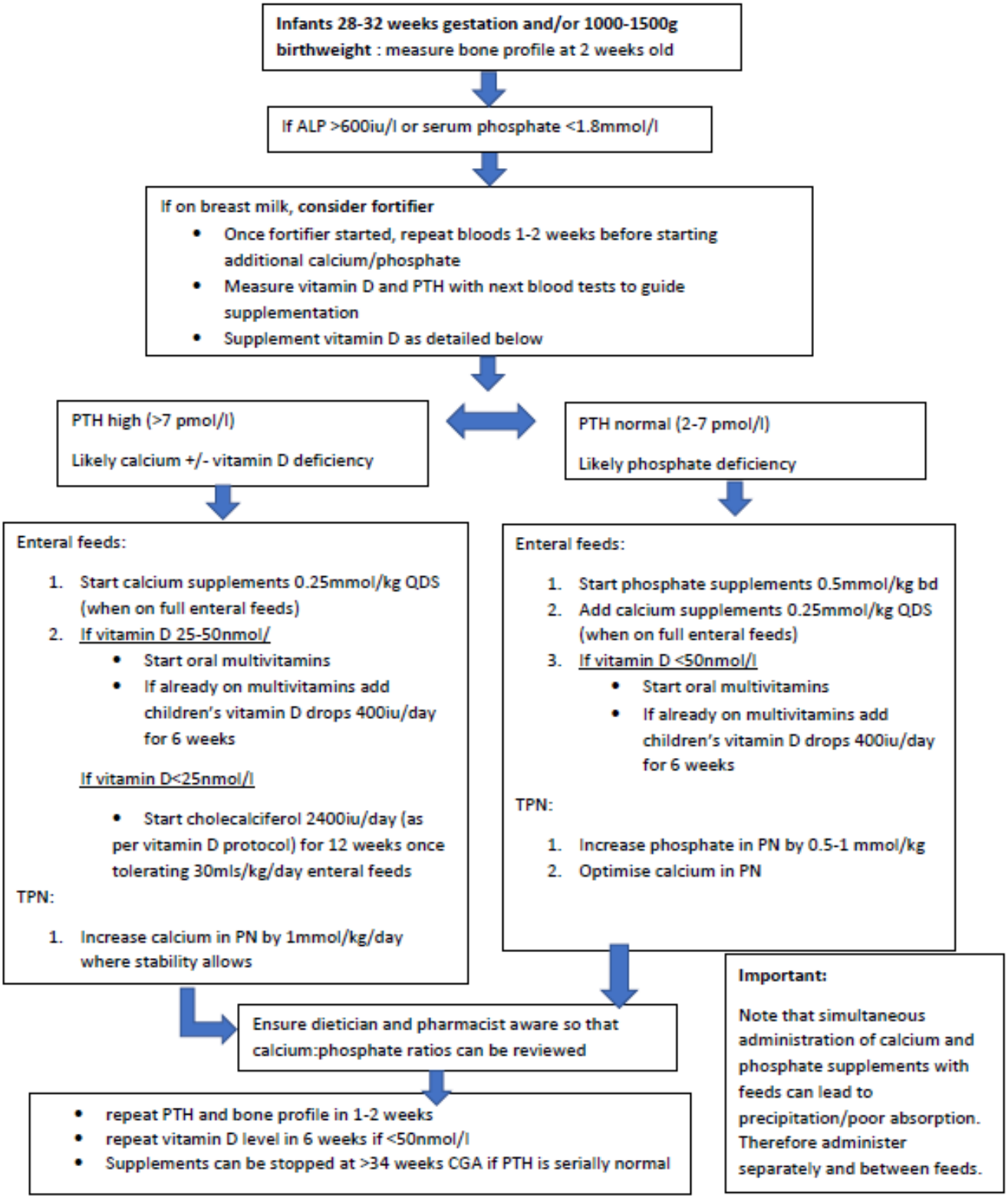


Figure 2 Pathophysiology of calcipaenic metabolic bone disease of prematurity, demonstrating how resultant hyperparathyroidism leads to bone resorption, hypophosphataemia and rickets, as well as how treatment with phosphate supplements alone further drives this secondary hyperparathyroidism (dotted arrows). ALP, alkaline phosphatase; Ca, calcium; ECF, extracellular fluid; PTH, parathyroid hormone; PO_4, phosphate.

Management of Babies <28 weeks Gestation and/or <1000g at birth



Management of Babies born at 28 – 32 weeks Gestation and/or 1000 – 1500g at Birth



Risk Factors [6,7]

- <30 weeks gestation, <1000g birthweight, male gender
- Delayed establishment of full enteral feeds, fluid restriction
- Prolonged intravenous nutrition (>3 weeks)
- Enteral feeds with low mineral content or bioavailability (unfortified EBM, term formula)
- Chronic use of medications that increase mineral excretion: diuretics, dexamethasone, sodium bicarbonate
- Lack of mechanical stimulation e.g. sedation and paralysis
- Phosphorus deficiency
- Vitamin D deficiency
- Calcium deficiency
- Cholestatic jaundice
- Short gut syndrome (malabsorption of vitamin D and calcium)
- Chronic lung disease
- Necrotising enterocolitis

Clinical Presentation

Osteopenia of prematurity presents between 4 and 12 weeks of age but may remain asymptomatic for weeks until overt rickets or fractures develop6. Symptoms may include poor weight gain, faltering growth, and respiratory difficulties or failure to wean off ventilatory support due to excessive chest wall compliance. Fractures may manifest as pain on handling. Long bone fractures may present with swelling and decreased movement of affected site. Rib fractures are often discovered incidentally on a chest x-ray taken for another reason. Diagnosis remains largely subjective because most babies do not manifest overt signs or symptoms. Diagnosis has been based on criteria that include clinical signs, biochemical markers, and radiologic findings (a late sign). X-ray will generally show poor mineralisation. There is no single diagnostic biochemical test.

Markers of Bone Biochemistry

1. Low serum phosphate concentrations (<1.1 mmol/L) have low sensitivity but high specificity. Low concentrations of inorganic phosphate (<1.8 mmol/L with elevated alkaline phosphatase (>900 IU/L) may be more sensitive (100%) and specific (70%) for diagnosing inadequate intake and low bone mineral density.

2. Elevated alkaline phosphatase (ALP) values (>400u/l) are seen with osteopenia of prematurity, as well as in normal growth, healing rickets, fractures, or copper deficiency; ALP elevated more than is usual (>600u/l quoted in literature) is in keeping with a diagnosis of osteopenia of prematurity. Very high values (>1200u/l) have been associated with short stature in childhood.

3. Serum calcium values may remain normal or be low or high. Serum calcium is maintained by increasing PTH, so a high PTH can indicate calcium deficiency, even if serum calcium is normal. Low calcium is associated with vitamin D deficiency, so should prompt measurement of serum vitamin D (25 hydroxy vitamin D) and parathyroid hormone (PTH.)

4. There have been recently reported cases of metabolic bone disease of prematurity associated with skeletal mineralisation due to secondary hyperparathyroidism in infants treated with phosphate alone7. Therefore, routine vitamin D and PTH measurements are required for correct management of supplements.

5. Urinary calcium, phosphate and creatinine should be measured if infants require higher dose phosphate or calcium supplementation. This is due to a small association with nephrocalcinosis, which is largely multifactorial in origin (and occurs most often with normal urinary calcium.)

Management

Management of infants born ≤32 weeks gestation and ≤1500g until term corrected gestational age is summarised on flowcharts on page 2&3.

Key messages:

- Consider early fortification of breast milk as a preventative measure (see *West of Scotland preterm enteral feeding* guideline.)
- Ensure recommended intake of calcium and phosphate are met from feeds.
- **Check parathyroid hormone (PTH) and vitamin D as well as bone profile**, to target supplementation.
- **Previously used 'routine' phosphate supplementation should no longer be used**.
- Calcium deficiency can occur with normal serum calcium levels.
- Prescribing phosphate supplements without calcium supplementation in the correct ratio may worsen metabolic bone disease status due to secondary hyperparathyroidism. In addition to normal vitamin supplements, additional vitamin D supplementation will be required if deficient (<25 nmol/L) or insufficient levels (25-50nmol/L) (see WoS drug monographs).
- MBDP can lead to bone fragility; peak timing for fractures is term corrected age.

Summary of Management

1. Ensure an adequate intake of calcium and phosphate from feeds: consider fortified breast milk, fortified donor human milk or preterm formula. Preterm infants absorbing fortified maternal expressed breast milk at 150-165mls/kg/day should be getting adequate calcium and phosphate, however need to be monitored and may still need supplements.
2. Bone biochemistry (bone profile) should be monitored from 2 weeks old, every 1-2 weeks.
    a. **Infants born ≤28 weeks gestation and/or ≤1000g birthweight:** PTH and 25-hydroxyvitamin D should also be measured at 2 weeks old, as they are at highest risk of MBDP. If infants are found to be phosphate depleted or have a rising alkaline phosphatase (ALP) then they should have their nutritional intake assessed and the need for supplements reviewed. Follow the flowchart to guide supplementation. PTH measurement is key to guiding supplementation.
    b. **Infants born between 28-32 weeks gestation and/or 1000-1500g birthweight:** PTH and vitamin D should be checked if bone biochemistry is abnormal (phosphate <1.8mmol/l and/or ALP>600u/l.) If infants are found to be phosphate depleted or have a rising ALP then they should have their nutritional intake assessed and the need for supplements reviewed. Follow the flowchart to guide supplementation. PTH measurement is key to guiding supplementation.
    c. Once on supplements bone biochemistry and PTH should be measured every 1-2 weeks thereafter.
3. Ensure a daily intake of at least 400 IU Vitamin D per day. Multivitamins can be given once enteral feeds reach 100mls/kg/day.
4. Vitamin D deficiency is common in the West of Scotland, and often co-exists with MBDP. Infants of mothers who did not take vitamin D supplements during pregnancy or mothers at higher risk of vitamin D deficiency e.g. religious

coverings are also at greater risk of vitamin D deficiency. Measure serum 25-hydroxyvitamin D and parathyroid hormone (PTH) as per the flowchart and also if serum calcium is low. If serum vitamin D level is <25nmol/l and PTH is high then high dose vitamin D treatment should be prescribed. Cholecalciferol can be given once babies are tolerating 30mls/kg/day enteral feeds. Vitamin D levels should be repeated after 6 weeks of treatment if the infant is still an inpatient if possible although this is not necessary if local labs are unable to do so.

5. Measurement of bone biochemistry and treatment with supplements should be continued until biochemical indices are serially normal. **Once an infant is >34 weeks corrected and has a serially normal PTH then you can consider stopping supplements.** Once stopped, bone profile and PTH should be repeated in 1-2 weeks if still an inpatient. If discharged, then consider checking bloods at first outpatient review.
6. Some infants will need supplements to continue after discharge from the neonatal unit, usually infants who have had a need for increased doses of supplements. Vitamin D 400 IU daily should be continued after discharge as a multivitamin until 1 year old, and throughout childhood as vitamin D alone.
7. Regularly review medications that increase mineral excretion (diuretics, dexamethasone, sodium bicarbonate) and reduce dose or stop as soon as clinical condition allows.
8. Fragile preterm infants should be handled carefully. Passive range of motion should be gentle. Care should be taken even during routine manipulation of extremities including, nappy changes and placing IV lines. Be aware that term corrected age is the peak time for fractures.

Phosphate: Calcium ratios

Note all pre-prepared enteral feeds and parenteral nutrition are formulated with the correct ratio of calcium: phosphate minerals for prevention of metabolic bone disease of prematurity (MBDP.) Only if one of these is changed for treatment purposes will the ratio need to be addressed.

Based on the results of a baby's bone profile and PTH, they may be found to be calcium or phosphate deficient. It is important not to give excess phosphate supplements as this may lead to secondary hyperparathyroidism. To prevent this, recommended ratios should be used. If calcium supplements are required (in calcium deficiency), these can safely be given alone. However, if phosphate supplements are required, care should be taken to maintain the ratio below and calcium supplements should be prescribed alongside. The ratio will differ dependent upon feeding route (PN or EN.) **This is a molar ratio, expressed in mmol.**

Maintenance/prevention
Calcium: Phosphate
PN 1:1
Enteral 1:1 to 1.3:1

Treatment
Calcium: Phosphate
PN 1.3:1 to 1.7:1
Enteral 1.2:1 to 1.3:1

Note that simultaneous enteral administration of calcium and phosphate supplements with feeds will result in precipitation and poor absorption. These minerals should therefore be administered separately and between feeds. Administration of parenteral calcium/phosphate alongside PN will result in precipitation and therefore must be given via a separate line.

NOTE: treatment of MBDP should not be considered to be urgent and can be commenced in usual working hours.

Note that the flowchart includes prescription of calcium and phosphate to give the correct ratios. This need only be looked at in greater detail if biochemistry is not improving despite supplements, and can be looked at jointly with dietetics, pharmacy and the metabolic bone team.

Discharge and follow up

There is some uncertainty around how long supplements should continue, but it is worth considering that preterm babies can still be growing fast beyond term. Some infants will need supplements to continue after discharge from the neonatal unit. Bone profile and PTH should be reviewed as part of discharge planning. Generally, only infants with abnormalities on the bone profile that have not resolved prior to discharge and those who remain on higher doses of additional calcium, phosphate, or vitamin D supplementation at the time of discharge need further specific monitoring regarding their

bone health. In such cases, consideration should be given to at least checking a bone profile 4-6 weeks following discharge from the hospital.

Vitamin D 400 IU daily should be continued after discharge and throughout childhood[7, 8]. This is normally provided via multivitamin preparations until one year, then as children's vitamin D drops.

Management of Fractures

The most common age is 6-8 weeks postnatally for rib fractures to occur and 11-12 weeks for long bone fractures. For the vast majority, there is no associated incident or particular type of handling that has been described and resulted in these fractures 1, 2. They have often occurred/ been identified incidentally and can occur even with normal handling. Rib fractures are the most common [1-3]. Long bone fractures are metaphyseal or diaphysis, can be transverse or greenstick with either angulations or complete displacement. Callus is seen in less than a week and complete remodelling within 6-12. Lone bone fractures can be aligned and immobilised in a simple splint. Immobilisation can stop once baby is no longer tender and it feels stable with x-ray healing, usually within 2 weeks.

In general, staff and families can be reassured that fractures are often incidental and occur with normal handling. If multiple rib fractures or a long bone fracture is diagnosed then medical and family history, examination and further investigations should be considered by a senior neonatal physician. Family history of bone fragility should be sought, and full clinical examination of the infant including sclera, should be carried out. X-rays should be reviewed by a consultant radiologist, and if significant under mineralisation is present, a skull x-ray (to look for wormian bones) should be considered. This is to exclude any other underlying bone abnormality. A baby with any positive findings should be discussed with the paediatric bone and endocrinology team at the Royal Hospital for Children (contact via hospital switchboard). [6]

Areas outside remit of this guideline

- **Infants <2 weeks old**
  Abnormal bone biochemistry at this age is unlikely to be due to metabolic bone disease of prematurity. Correct acute disturbances as per unit policy.

- **Acutely unwell infants**
  Acute electrolyte disturbances should not be managed as metabolic bone disease of prematurity.

Referral to metabolic bone team

Although metabolic bone disease is a common pathology and is usually easily managed, there will be occasions when specialist input is required. This should be considered in the following circumstances:

- Overt bone disease on x-ray
- Bone disease or blood results not responding to treatment pathways above
- Any other concerns about bone health/bone deformity/bone related bloods.

Referral is via the paediatric bone and endocrinology team at the Royal Hospital for Children (contact via hospital switchboard).

Document Properties

Document Title

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Document Author

Dr Helen McDevitt – Consultant Neonatologist – RHC, Glasgow
Anisa Patel – Senior Neonatal Pharmacist – RHC, Glasgow
Peter Mulholland – Senior Neonatal Pharmacist (retired) – RHC, Glasgow
Lorraine Cairns – Senior Neonatal Dietician – RHC, Glasgow.

Other Professionals consulted

Dr Jennifer Mitchell – Consultant Neonatologist – RHC, Glasgow
Dr Andrew Brunton – Consultant Neonatologist – RHC, Glasgow

Implementation and review dates

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