Practical approach to managing metabolic bone disease of prematurity in the neonatal unit

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INTRODUCTION

Metabolic bone disease of prematurity (MBDP) is a significant cause of morbidity within the neonatal population. However, there is uncertainty about which babies need screening and at what thresholds treatment is warranted, and the consensus approach to management has shifted in recent years. This has led to confusion surrounding timing of investigations, result interpretation and the optimum way to administer prescribed supplementations. Due to the lack of clear cut-offs and thresholds for investigation and management within current literature, a consensus approach at best can be recommended, with an aim to be practical and deliverable across the full range of neonatal services.

Key points

- Infants born <32 weeks or <1500 g are at risk of developing metabolic bone disease of prematurity (MBDP). Additional risk factors increase the need for regular screening.
- Most babies with MBDP are calcium deficient. Parathyroid hormone (PTH) should be used to guide initial treatment and treatment response.
- Calcium deficiency may occur even with normal serum calcium levels.
- Phosphate deficiency may also occur and be co-existent with calcium deficiency. This is caused by the action of an elevated PTH and vitamin D deficiency.
- Vitamin D deficiency can co-exist with calcium deficiency and concentration should be maintained >50 nmol/L.

BACKGROUND

MBDP affects 55% of infants <1000 g and 23% of those <1500 g, with increasing prevalence in those with additional risk factors such as diuretic or steroid use.[1] During the final trimester of pregnancy, the placenta delivers significant concentrations of phosphate and calcium, and infants born prior to this are most at risk of developing deficiencies. Delivering comparative concentrations of electrolytes either enterally or within parenteral nutrition (PN) is challenging.[2] MBDP is often diagnosed with radiographic changes between weeks 8 and 12 postnatally, though a reduction in bone density of 20–40% is required before this is apparent. Biochemical markers can be useful to guide preventative treatment.[1]

CLINICAL CASE

An infant is born at 25 weeks' gestation weighing 650 g. He requires intubation at delivery and has umbilical lines sited to facilitate delivery of PN. Enteral feeding is commenced once mother's own milk (MOM) is available.

On day 7 while still establishing feeds, his alkaline phosphatase (ALP) is noted to be increasing to 750 IU/L (normal range 82–249, target <700), and his phosphate falls to 1.2 mmol/L (normal range 1.36–2.49, target >1.8). His feeds continue to be graded up and breast milk fortifier and multivitamins are added. He remains ventilated with high oxygen requirements.

On day 20, he has been fully fed with MOM plus fortifier for a week, but his ALP continues to rise and his phosphate remains low at 1.6 mmol/L. His parathyroid hormone (PTH) is checked along with his vitamin D levels. The PTH is found to be raised at 36 pmol/L (normal range 1.5–8.0) and his vitamin D is 35 nmol/L (normal range 50–100). Vitamin D and calcium deficiency are diagnosed, and he is commenced on calcium supplements at 0.5 mmol/kg/day and cholecalciferol

600 units/day for a planned 4 weeks in addition to his regular multivitamins. Over the next 2 weeks, his ALP reduces to 450 IU/L with an increase in phosphate to 2.0 mmol/L. His PTH is still raised but has fallen to 12 pmol/L. Treatment is continued with a plan to monitor his bloods every 2 weeks.

He required a course of steroids to facilitate extubation and has evolving chronic lung disease, requiring ventilator support again at 7 weeks of age. A second course of steroids is commenced and he is also receiving diuretics. His chest X-ray shows evidence of osteopenia.

After a period of stable ALP levels, it begins to rise and his PTH increases to 40 pmol/L. Vitamin D levels are now 90 nmol/L. Calcium deficiency is again diagnosed, with the combined action of steroids and diuretics contributing. Calcium supplements are increased, but his ALP and PTH remain abnormal. His total enteral delivery of calcium and phosphate are reviewed based on his current intake of fortified MOM, and his mmol:mmol ratio of calcium to phosphate is found to be 1.6:1. This is felt to be too high, with a ratio of 1.3:1 mmol:mmol enabling more efficient absorption of calcium and phosphate. Phosphate supplements are commenced to adjust the ratio back to 1.3:1 and his bloods are re-checked in 2 weeks. His ALP has fallen to 420 IU/L, and his PTH has reduced to 14 pmol/L. His blood tests normalise over the coming weeks and at discharge his medications are ceased, with a further set of blood tests planned for 2 weeks following discharge.

INVESTIGATIONS

There are two main groups to consider, those under 3 weeks of age receiving predominantly PN and those who are older receiving mainly enteral feeds. In the first group, management is electrolyte delivery within PN.[2] In older infants predominantly on enteral feeds, it is important to check PTH/vitamin D levels to guide treatment.[3]

Timing of blood tests and identifying the infants who need such investigations are important. Babies at risk of MBDP require weekly monitoring of ALP and phosphate.[4] Serum calcium is an unreliable marker as it is maintained by PTH and can be raised or within the normal range even in states of deficiency. Infants with additional risk factors should have 2 weekly monitoring of their PTH regardless of other biochemistry, these are outlined in Box 1 below.[3]

MANAGEMENT

Historically, a raised ALP or a low phosphate would trigger commencement of phosphate supplementation due to a presumed deficiency.[5 6] We now realise that most babies with MBDP actually have a primary calcium deficiency, with phosphate falling through the action of PTH. PTH and vitamin D should therefore be checked when deciding on whether this is a primary calcium (raised PTH) or phosphate (low/normal PTH) deficiency.[3]

Box 1 Identifying at-risk infants and subsequent monitoring

- Infants born <32 weeks or <1500 g
  - Weekly bone profile including total serum calcium, phosphate and ALP
  - Check PTH and vitamin D if ALP >700 IU/L or phosphate <1.8 mmol/L
  - PTH and vitamin D should only be checked once the infant is fully fed for >1 week with either full fortified expressed breast milk or formula feeds
- Infants with additional risk factors require 2 weekly monitoring of PTH irrespective of other biochemistry
  - Birth weight <1000 g
  - Gestation <28 weeks
  - PN greater than 4 weeks
  - More than one course of steroids or prolonged course (ie, decision to extend course beyond normal period)
- Monitoring should cease once the infant is >32 weeks with a normal PTH

There may be other indications for checking electrolyte levels prior to this timeframe. These recommendations are for management of metabolic bone disease of prematurity.
ALP, alkaline phosphatase; PN, parenteral nutrition; PTH, parathyroid hormone.

Initial management with electrolyte supplementation can be initiated with standard quantities regardless of milk choice, as calcium:phosphate ratios are largely preserved at this point. Phosphate supplementation on its own can however reduce levels of ionised calcium, further increasing PTH and driving the process of MBD, so any phosphate supplementation should be given alongside additional calcium.[3] See figure 1 treatment flow chart.

Individualised supplementation should be considered if biochemistry is worsening despite treatment, with attention given to the calcium:phosphate ratio delivered by the current milk and supplement intake. To optimise absorption, a ratio of 1.3:1 (mmol:mmol) or 1.7:1 (mg:mg) should be targeted.[3] This can be a challenge due to varying amounts in different types of milk and may require discussion with a dietitian.

Calcium and phosphate should not be given together as they can precipitate within the stomach, which impacts absorption. Unavailability of licensed liquid calcium and phosphate preparations means that often effervescent calcium oral tablets of various formulations have to be used, all containing different quantities. The various different products and methods required to accurately dissolve them are a risk for potential error, and care must be taken to be aware of the formulation being used locally (Medicines for Children; How to give phosphate or calcium from effervescent tablets).

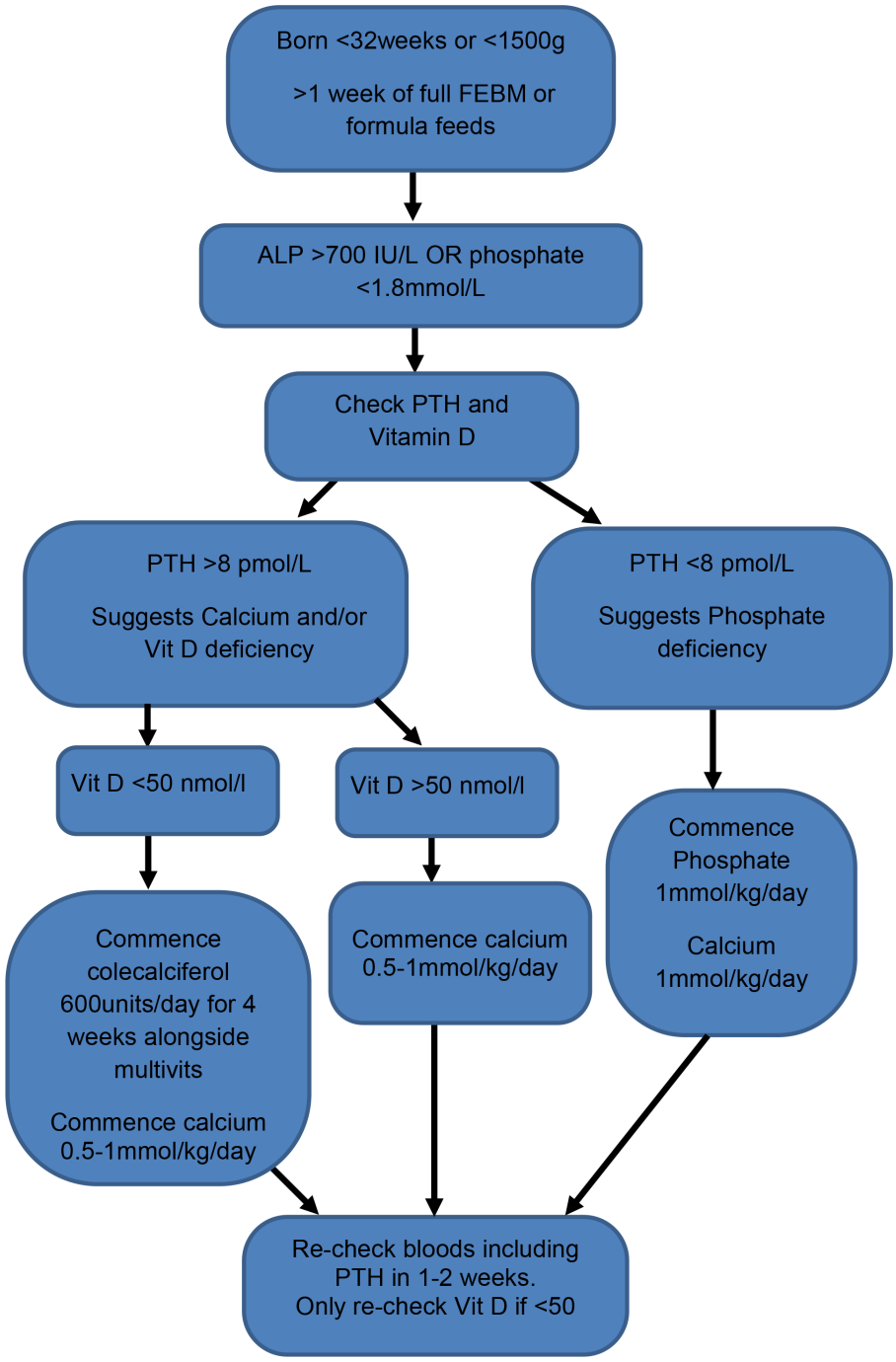

Figure 1 Treatment flow chart. ALP, alkaline phosphatase; FEBM, fortified expressed breast milk; PTH, parathyroid hormone.

VITAMIN D

Vitamin D is important in facilitating calcium and phosphate absorption from the gut, and supplementation at a dose of 400 IU/day in addition to that in milk is recommended for preterm infants. This can be provided via 0.6 mL of Abidec or Dalivit.

Vitamin D deficiency (<50 nmol/L) can co-exist with calcium or phosphate deficiency and will require additional supplementation. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition[7] suggest that daily doses of 400–700 IU/day may be required for routine supplementation but up to 1000 IU/day may be required, and in some instances replacement doses may be in excess even of this amount.[7 8] Toxicity can occur so treatment at elevated doses should not be continued indefinitely and vitamin D levels should be monitored.

For infants who are nil by mouth, vitamin D and electrolyte delivery can be challenging. In infants with MBDP requiring longer term PN, a similar ratio of calcium:phosphate should be targeted. This can be difficult to deliver, with variation in local ability to formulate non-standard PN regimes along with compatibility issues, especially

with regard to calcium which can precipitate at amounts greater than 2 mmol/kg/day.

Vitamin D can be administered intramuscularly (IM) if needed. A dose of 30 000 IU as ergocalciferol injection can be given once a month if levels are below 50 nmol/L. Standard supplementation at 400 IU/day can subsequently be commenced if the enteral route becomes available, but vitamin D levels should be checked before repeated IM doses to safeguard against toxicity.

DISCONTINUING MEDICATIONS

Medications can be stopped once the infant is more 32 weeks corrected gestation and has a serially normal PTH. Repeat ALP, phosphate and PTH should be checked again 1–2 weeks following discontinuation of medications to ensure values remain within accepted ranges.

WHEN DO I NEED SOMEONE ELSE?

Infants with persistent biochemical derangement or with a high PTH despite treatment should be discussed either with a dietician or a paediatric endocrinologist. Special attention should be given to preserving calcium:phosphate ratios and consideration of an alternative endocrine or skeletal diagnosis.

- Persistent abnormal biochemistry despite administration of calcium and vitamin D in babies with suspected MBDP
- Suspected neonatal hyperparathyroidism (inappropriately raised PTH with hypercalcaemia)
- Pseudohypoparathyroidism (raised PTH, low calcium, raised phosphate, normal vitamin D)
- Suspected bone mineralisation defects (asymmetrical skeletal changes including limb bowing, skeletal hypomineralisation and low ALP)
- Osteopetrosis (hypocalcaemia and high PTH, osteosclerotic bones on X-ray)
- Suspected structural bone defect (osteogenesis imperfecta with multiple fractures, normal bone profile)

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