Screening & Treatment for Metabolic Bone Disease

NICU Clinical Pathway

Nationwide Children's — When your child needs a hospital, everything matters.

Center for Clinical Excellence

Inclusion Criteria:
- Infant born ≤28 weeks GA or born ≤1500 g AND
- Infant receiving full enteral feeds

Exclusion Criteria:
- Infants receiving parenteral nutrition

Abbreviations:
- Metabolic bone disease (MBD)
- Alkaline phosphatase (Alk Phos)
- Parathyroid hormone (PTH)
- Tubular reabsorption of phosphate (TRP)
- Calcium (Ca)
- Phosphorus (Phos)
- 25-Hydroxy Vitamin D (25-OH-D)
- Human milk fortifier (HMF)

[β]Consulting services might vary but could include:
- GI/Hepatology
- Nephrology
- Endocrinology

Is the patient receiving preterm infant formula or human milk + HMF?
- Yes → Once receiving goal calories as defined by the clinical team, add Vitamin D, Ca and/or Phos supplements to meet total recommended intake:
  - Vitamin D: 400 International Units/day
  - Ca: 120-220 mg/kg/day
  - Phos: 70-120 mg/kg/day
- No → Is the patient receiving non-preterm formula?
  - No → Exit pathway
  - Yes → Once receiving goal calories as defined by the clinical team, add Vitamin D, Ca and/or Phos supplements to meet total recommended intake:
    - Vitamin D: 400 International Units/day
    - Ca: 120-220 mg/kg/day
    - Phos: 70-120 mg/kg/day

At 2 weeks after achieving goal recommended calories, Ca, Phos, and Vitamin D intake:
- Order serum Ca, Phos, and Alk Phos
- Request Radiologist comment on bone status within next routine x-ray order. If fractures are seen on XRays, primary teams to follow clinically appropriate management

Are Ca, Phos, and Alk Phos within lab reference range?
- Yes → Exit pathway
- No →

If Ca is <8 mg/dL or >10.5 mg/dL on 2 consecutive lab results
OR
If Alk Phos >800 U/L
OR
If Alk Phos >500 U/L and trending up + Phos <5.5 mg/dL
- Order serum PTH and 25-hydroxy Vitamin D (25-OH-D)

Is 25-OH-D <30 ng/mL?
- Yes → Supplement Vitamin D intake to goal range of **800 - 1200** International Units/day, or as recommended by consulting service[β]
- No → Continue with current Vitamin D supplementation

Is PTH >65 pg/mL?
- Yes → Suggests calcium deficiency, start or increase Ca supplementation
- No →

Is Phos level ≥5.5 mg/dL?
- Yes → Check TRP
  - If TRP <95%, no Phos supplementation needed
  - If TRP ≥95%, start Phos supplementation
- No → Start Phos supplementation

If patient is started on any supplements, suggest:
- Continue to recheck Ca, Phos, Alk Phos, PTH, TRP, and/or 25-OH-D every **2-4 weeks**
- Adjust Ca, Phos, and Vitamin D supplements based on lab values
- Continue to have Radiologist comment on bone status on routine x-rays at least **monthly**

Duration of treatment:
- Can stop therapeutic treatment doses of Ca, Phos, and Vitamin D once values are in normal range x 1-2 lab checks.
- Pathway ends at discharge.
- If patient remains on therapeutic treatment at discharge, clinical teams should consider appropriate consulting service[β] follow-up.

Calcium & Phosphorus Supplementation Recommendations

	Starting Dose	Increase By	Max Dose
Calcium Carbonate 1250 mg/5 mL **1250 mg calcium carbonate = 500 mg elemental calcium**	**50-75 mg/kg/DAY div BID** (20-30 mg/kg/DAY elemental Ca)	**50-100 mg/kg/DAY** (20-40 mg/kg/DAY elemental Ca)	**200 mg/kg/DAY div 3-4 times/day** (80 mg/kg/DAY elemental Ca) Doses ≥100 mg/kg/DAY should be div into 3-4 doses
Sodium Phosphate 3 mmol/mL¶ **1 mmol sodium phosphate = 1.33 mEq Na + 31 mg phos**	**0.3-0.6 mmol/kg/DAY div BID** (Na 0.4-0.8 mEq/kg/DAY) (Phos 9-19 mg/kg/DAY)	**0.3-0.6 mmol/kg/DAY** (Na 0.4-0.8 mEq/kg/DAY) (Phos 9-19 mg/kg/DAY)	**1.6 mmol/kg/DAY div 3-4 times/day** (Na 2 mEq/kg/DAY) (Phos 50 mg/kg/DAY) Doses ≥1 mmol/kg/DAY should be div into 3-4 doses
Potassium Phosphate 3 mmol/mL^ **1 mmol potassium phosphate = 1.47 mEq K + 31 mg phos**	**0.3-0.6 mmol/kg/DAY div BID** (K 0.4-0.9 mEq/kg/DAY) (Phos 9-19 mg/kg/DAY)	**0.3-0.6 mmol/kg/DAY** (K 0.4-0.9 mEq/kg/DAY) (Phos 9-19 mg/kg/DAY)	**1.6 mmol/kg/DAY div 3-4 times/day** (K 2.4 mEq/kg/DAY) (Phos 50 mg/kg/DAY) Doses ≥1 mmol/kg/DAY should be div into 3-4 doses

¶ Consider if patient is not on a diuretic or has a need for Na supplementation
^ Consider if patient is on a diuretic or has a need for K supplementation

Administration considerations:

- Separate calcium and phosphorus supplements so that the doses are given at different times to prevent binding and subsequent decreased absorption (suggest a minimum of 3 hours between doses)
- Sodium and potassium phosphate oral solutions are compounded from the intravenous products. If patients need to be discharged home with phosphorus supplementation, suggest to transition to potassium phosphate tablets or sodium phosphate-potassium phosphate packets for easier outpatient access.

Algorithm

Diagnosis & Definition

Formerly known as rickets or osteopenia of prematurity, metabolic bone disease (MBD) is a condition primarily affecting preterm infants characterized by a significant reduction in bone mineralization in combination with biochemical and radiographic changes. MBD is a consequence of chronic illness and multiple morbidities. There are no formal diagnostic criteria, but the earliest clinical features are biochemical in nature, including an elevated serum alkaline phosphatase (Alk Phos) level, hypophosphatemia, elevated parathyroid hormone (PTH), and increased tubular reabsorption of phosphate (TRP)[2,5,11,12]. A serum Alk Phos level >900 units/L in preterm infants with serum phosphorous (Phos) levels <4.6 mg/dL has 100% sensitivity and 70% specificity for low bone mineral density[11]. Serum PTH levels >100 pg/mL indicate an increased risk for developing MBD. TRP >95% is a significant marker of insufficient Phos supplementation[11,12]. Significant bone demineralization may be detected on radiographs once 20-40% reduction has occurred[5,11].

Algorithm

Testing

- Check serum Ca, serum Phos, serum Alk Phos
- Recommend Radiologist comment on bone status on next routine x-ray
- Check serum PTH and serum 25-Hydroxy Vitamin D (25-OH-D)
- TRP: order serum Phos, serum Creatinine, urine Phos, & urine Creatinine
- Continue to recheck serum Ca, serum Phos, serum Alk Phos, serum PTH, TRP, and/or serum 25-OH-D every 2-4 weeks
- Continue to have Radiologist comment on bone status on routine x-rays at least monthly.

Algorithm

Severity Assessment

MBD may progress to osteomalacia, osteopenia, and rickets. PTH and Vitamin D are hormones involved in the regulation of bone mineralization and abnormalities in either may indicate the primary etiology for demineralization. Elevations in serum PTH may indicate either insufficient Vitamin D and/or insufficient Ca status. An elevated TRP may indicate insufficient Phos status that may not be apparent biochemically. The degree of derangement should guide the supplementation used and the frequency for rechecking follow-up labs. Once fractures are evident radiographically, a significant amount of demineralization has occurred (estimated to be anywhere between a 20-40% reduction).

Algorithm

Tubular Reabsorption of Phosphate (TRP)

Tubular reabsorption of phosphate (TRP): quantifies the degree of phosphate wasting	
Labs Needed:	• serum Phosphorus • serum Creatinine • urine Phosphorus • urine Creatinine
Calculation:	TRP = [1-(urine Phosphorus/urine Creatinine X serum Creatinine/serum Phosphorus)] x 100

Algorithm

Assessment & Monitoring

- If enteral feeds do not provide 120-220 mg/kg/day of Ca and 70-120 mg/kg/day Phos, additional supplementation is needed to achieve values in the target range.
- If serum Alk Phos >800 U/L or >500 U/L and uptrending with serum Phos <5.5 mg/dL, serum 25-OH-D and serum PTH levels are needed to determine if the potential etiology of the elevated serum Alk Phos is related to MBD
- If serum 25-OH-D is <30 ng/mL and serum PTH >65 pg/mL: low Vitamin D status and insufficient Ca delivery may cause the elevated PTH
- If serum 25-OH-D level ≥30 ng/mL and serum PTH >65 pg/mL: suboptimal Ca delivery may cause the elevated PTH
- If serum PTH <65 pg/mL but serum Phos <5.5 mg/dL: suboptimal Phos delivery may cause the elevated Alk Phos
- If serum PTH <65 pg/mL and serum Phos ≥5.5 mg/dL: suboptimal Phos delivery may cause the elevated Alk Phos, but may not be apparent biochemically. A TRP will be helpful in determining whether additional Phos supplementation is needed

Algorithm

Recommended Treatment

- If enteral feeds do not provide 120-220 mg/kg/day of Ca and/or 70-120 mg/kg/day Phos, add or increase supplementation in order to achieve values in the target range: Neonatal Dietitian to review and provide assistance
- If serum 25-OH-D <30 ng/mL: Supplement Vitamin D intake (including enteral feeds) to a minimum goal range of 800-1200 International Units daily
- Treatment for an elevated Alk Phos depends on serum PTH and other labs:
  - Serum 25-OH-D is <30 ng/mL and serum PTH >65 pg/mL: Add additional Vitamin D supplementation to at least goal range of 800-1200 International Units daily. May need to exceed goal range to achieve an adequate serum 25-OH-D level
  - Serum 25-OH-D level ≥30 ng/mL and serum PTH >65 pg/mL: Add Ca Carbonate supplementation
  - Serum PTH <65 pg/mL but serum Phos <5.5 mg/dL: Start Phos supplementation
  - Serum PTH <65 pg/mL and serum Phos ≥5.5 mg/dL: Obtain serum Phos, urine Phos, serum creatinine, and urine creatinine to calculate TRP. Supplement Phos if TRP ≥95%
- Available supplements below with formulation chosen based on the clinical team's assessment and/or patient comorbidities:
  - Vitamin D (either cholecalciferol or ergocalciferol, multivitamin, multivitamin with iron, fat soluble multivitamin [Complete MVW])
  - Ca Carbonate oral suspension
  - Sodium Phos oral solution
  - Potassium Phos oral solution
  - Potassium Phos oral tablet (home-going)
  - Potassium Phos and sodium Phos (Phos-Nak) powder packets (home-going)
- Separate administration times of Ca and Phos supplementation if they are currently co-administered (suggest a minimum of 3 hours between doses)

Algorithm

Discharge Criteria & Planning

Follow Up:

- PCP if Vitamin D 400-800 International Units daily
- Specialty outpatient clinical referral for patients going home on >800 International Units Vitamin D and/or Ca/Phos supplementation

Algorithm

Patient & Caregiver Education

Education on MBD

Algorithm

Risk Awareness & Zero Hero

- Provider may erroneously order serum 1,25-Hydroxy Vitamin D level instead of the intended serum 25-OH-D
- Attention should be paid to adjusting all medications for growth and changes to fortification/formula
- The Phos supplementation is available as a salt form, and will provide additional sodium and potassium ions. This amount of additional sodium or potassium should be considered for each patient
- If Phos-Nak powder packets are used for home-going, an unusual regimen (i.e. 3 times weekly administration or partial packets) may be needed to provide appropriate weight-based doses given the fixed amount of Phos, sodium, and potassium in each packet
- If potassium Phos tablets are used for home-going, an unusual regimen (i.e. crushing whole tablet, mixing with liquid, and administering partial volumes of the resulting suspension) may be needed to provide appropriate weight-based doses

Algorithm

References

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Algorithm

Quality Metrics

Measures

- For eligible pathway patients at 14-21 days (babies on full enteral feeds and no order of TPN for 72 hours) – percent of patients with Ca, Phos, Alk Phos and 25-OH-D obtained

Algorithm

Pathway Team & Process

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Advisory Committee Date: *May, 2023*

Origination Date: *June, 2023*

Next Revision Date: *June, 2025*

Clinical Pathway Development

This clinical pathway was developed using the process described in the NCH Clinical Pathway Development Manual Version 6, 2022. Clinical Pathways at Nationwide Children's Hospital (NCH) are standards which provide general guidance to clinicians. Patient choice, clinician judgment, and other relevant factors in diagnosing and treating patients remain central to the selection of diagnostic tests and therapy. The ordering provider assumes all risks associates with care decisions. NCH assumes no responsibility for any adverse consequences, errors, or omissions that may arise from the use or reliance on these guidelines. NCH's clinical pathways are reviewed periodically for consistency with new evidence; however, new developments may not be represented, and NCH makes no guarantees, representations, or warranties with respect to the information provided in this clinical pathway.

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Algorithm