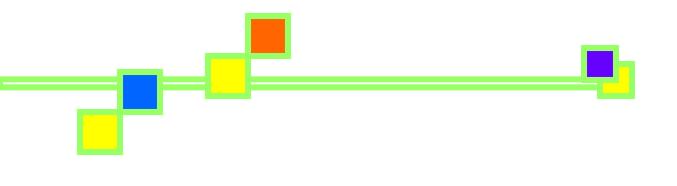




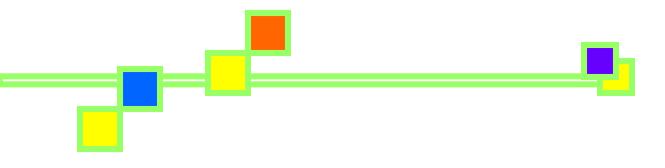
Osteopenia of prematurity





- The peak of fetal accretion of minerals occurs during the
- third trimester, placing the infant born prematurely at
- risk for osteopenia of prematurity.
- In addition to having low stores at birth, it is difficult to
- provide an adequate amount of minerals in parenteral
- solutions or to rapidly achieve sufficient supply by the
- enteral route.

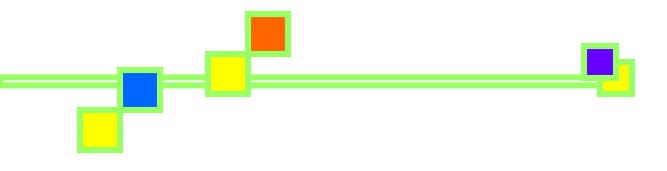






 and corticosteroids can further negatively impact bone mineralization.





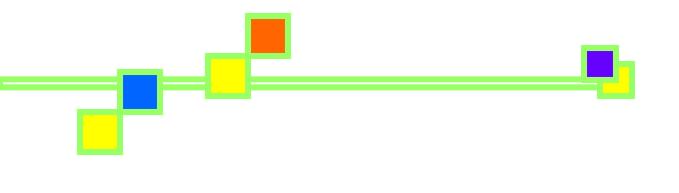


- enough calcium and phosphorus to support optimal bone mineralization in premature infants using currently
- available solutions.

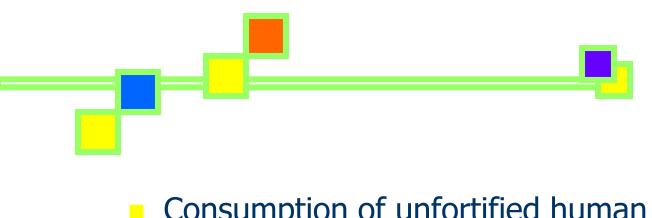


The solubility of calcium and phosphorus in parenteral nutrition solutions depends on

- temperature,
- amino acid concentration
- glucose concentration,
- pH
- type of calcium salt
- sequence of addition of calcium and phosphorus to the solution
- the calcium and phosphorus ratio
- and the presence of lipid.
- Adding cysteine to parenteral nutrition lowers the pH, which improves calcium and phosphorus solubility



- Mineral concentrations have been increased in preterm
- formulas and human milk supplements designed for
- feeding premature infants in an attempt to meet requirements.
- Significant increases in calcium and phosphorus
- content may affect magnesium retention.
- Several studies have shown improvement of mineral retention or bone mineralization in preterm infants who receive higher calcium and phosphorus intakes compared with their un supplemented peers



- Consumption of unfortified human milk by infants
- with very low birth weights after hospital discharge
- resulted in bone mineral deficits that persisted through 52 weeks postnatally, indicating the need for additional minerals after discharge.
- Fortification of human milk with minerals has been shown to increase linear growth during hospitalization.

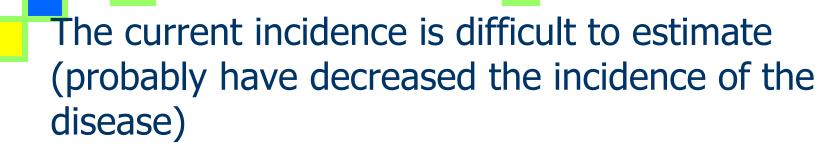
daily requirement

- Based on rates of fetal accretion and an estimate of 50% to 70% absorption, the recommended daily requirement calcium is 150 to 220 mg/kg and for phosphorus is 75 to 140 mg/kg.
- The Ca: P ratio should be approximately -1.5
 1.7, which is similar to the ratio in human milk.
- Daily requirements for magnesium are 8 to 12 mg/ kg, assuming 40% absorption.



Osteopenia of Prematurity

- Premature babies are at increased risk for developing
- bone disease by reduced bone mineral content.
- Increased survival of infants with VLBW has been associated with an increased incidence of osteopenia of prematurity, which is also called *metabolic bone disease* or *rickets of prematurity*.
- The incidence is inversely proportional to gestational age and birth weight, and two decades ago, it was estimated to be 50% in infants weighing less than
- 1000 g and 23% to 32% in infants weighting less than 1500 g.



- because the nutritional strategy has changed.
- Maximizing calcium and phosphorus intake from parenteral and enteral nutrition
- early initiation of feeding decreased use of paralysis during mechanical ventilation



- In utero mechanical stimulation is likely to be higher although there is inadequate information about the effects of this on bone
- mineral development after birth in VLBW infants.
- Finally, the hormonal situation is different postnatally because the placental supply of estrogen and many other hormones has been cut off.



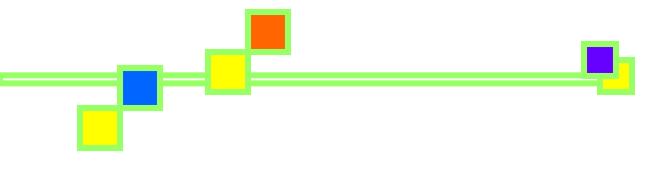
Role of vitamin D

- Although vitamin D deficiency can cause rickets, it is
- not the primary cause in most cases in preterm infants,
- and provision of vitamin D supplementation alone does
- not reduce the incidence of rickets in preterm infants.
- The role of maternal vitamin D status in the development of osteopenia of prematurity is not clear, although low
- maternal vitamin D status is associated with reduced
- bone mineralization in term infants

risk factors for bone disease in preterm infants include:

- Prematurity and VLBW
- prolonged parenteral nutrition feeding with unsupplemented human milk fluid restriction,
 - chronic illness
- use of hypercalciuric drugs such as furosemide for the treatment of bronchopulmonary dysplasia and
- methylxanthines for the treatment of apnea and bradycardia, both of which increase calcium loss.
- The use of postnatal steroids can decrease bone formation.
- immobility, especially for prolonged periods of sedation during mechanical ventilation, could enhance calcium loss and demineralization.
- NEC



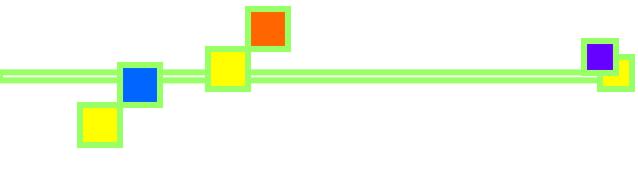




- placental insufficiency has a role in increasing the risk of low bone mass as well.
- •

- There may be an increased incidence
- of rickets in growth-restricted infants.

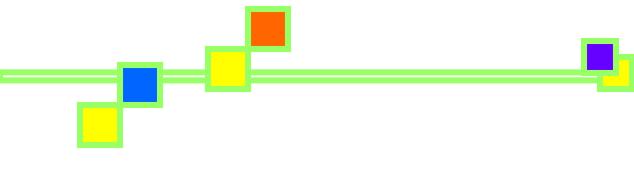
Prenatal risk factors Postnatal risk factors Inadequate supply of Ca and P Prematurity—decreased in Limited Ca and P delivery by TPN utero Ca, P accretion Delayed or inadequate enteral feeding • Feeding with unfortified human milk Fluid restriction Maternal vitamin D Vitamin D deficiency deficiency? • Inadequate intake Malabsorption of vitamin D Osteopenia prematurity **Immobility** Placental insufficiency Sedation or paralysis • IUGR Sepsis Preeclampsia Neurologic disease Drugs Genetics Diuretics Steroids Male gender Caffeine Homozygous allelic variants of high number of (TA)n repeats in the ER gene



Fortification of feeds

- For all infants with birth weights <1500 g, we recommend fortifying feeds with calcium and phosphorus.
- We also routinely use multinutrient-fortified feeds for infants up to 2000 g birth weight.
- For infants with birth weight between 1500 and 2000 g, the primary benefits of fortified feeds are for growth since rickets is uncommon in this population.

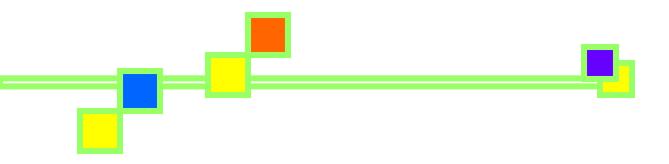




Fortification

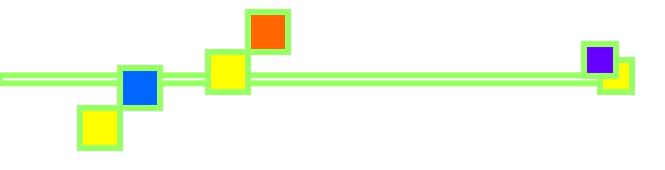
- Fortification can be accomplished by:
- adding a human milk fortifier (HMF) to expressed human milk
- using a formula designed for preterm infants
- either strategy supplies the necessary high mineral content in addition to supplemental energy (calories) and protein





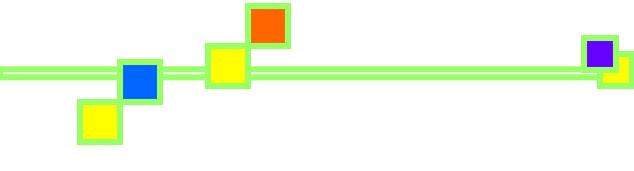
The recommendations for these products are based on weight rather than gestational age because infants with intrauterine growth restriction (also referred to as small for gestational age) also have impaired bone mineralization





- Full enteral feedings of 150 to 160 mL/kg/day of fortified human milk or preterm formula provide estimated intakes of :
- calcium of 150 to 220 mg/kg/day
- phosphorus of 90 to 140 mg/kg/day
- and vitamin D of 7.5 to 10 micrograms (300 to 400 international units) daily
- which meet the recommended intake for these neonates





Laboratory monitoring

- Infants with VLBW or other risk factors :
- Measure serum phosphorus and alkaline phosphatase activity beginning four weeks after birth
- and repeated every two weeks thereafter until discharge.
 Other risk factors include :
- prolonged parenteral nutrition
- prolonged postnatal corticosteroids, regardless of birth weight





Infants with short bowel syndrome or other malabsorptive syndromes

- In addition to the above for alkaline phosphatase and phosphorus, measure serum vitamin D concentrations
- inorganic phosphorus
- and magnesium as parenteral nutrition is weaned and periodically thereafter

DIAGNOSIS

- Clinical Symptoms
- Clinical symptoms of osteopenia are rare in infants with
- VLBW because of the widespread use of well-balanced
- parenteral solutions, human milk fortifiers, and preterm
- formulas.
- Fractures and rickets, which represent the major
- symptoms, have diminished, although they remain a
- concern in the smallest infants, especially those less than
- 1000 g





Clinically MBD presents as

- enlargement of anterior fontanelle
- widening of skull sutures
- frontal bossing
- craniotabes
- thickening of costo-chondral junctions, wrist joints
- and fractures of ribs and long bones.



Radiological examination shows:

 osteopenia, enlargement of the epiphysis, irregular border between growth cartilage and metaphysis.
 Fractures and softening of ribs may also be evident in more advanced cases.



The arrow demonstrates frayed metaphysis and also a dense white line at the end of the long bones. This white line can be associated with early healing of the rickets. When rickets is identified on radiographs, it generally requires approximately 6 weeks for healing to occur after therapeutic intervention.



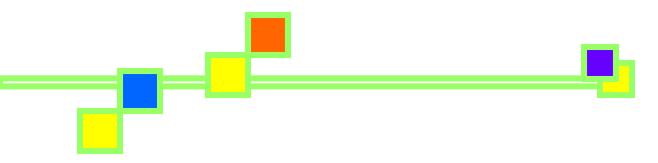
Biochemical Features

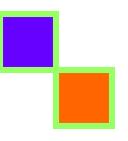
- Biochemical features are relatively nonspecific.
- Usually serum calcium concentrations are within the normal range
 - and serum phosphorus concentrations are normal or low at the time of diagnosis.
 - Alkaline phosphatase is frequently used to screen for osteopenia of prematurity despite conflicting evidence about its sensitivity and specificity



low renal phosphate reabsorption

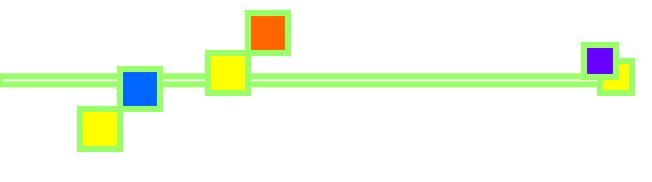
- The occurrence of a prolonged reduction of serum phosphorus during the early weeks of life could be predictive of the occurrence of rickets and osteopenia because:
- infants with ELBW are at risk for low renal phosphate reabsorption (tryptophan and GFR values), leading to urinary phosphate excretion even in the presence of low serum phosphate levels.





 Therefore, the absence of, or very low urinary phosphate excretion also needs to be considered as an indicator of phosphate depletion.



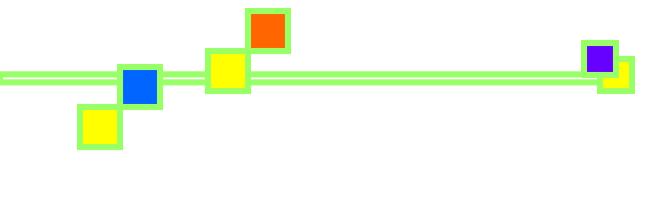


The peak alkaline phosphatase level is inversely related to the serum phosphorus concentration.

Therefore, the combination of alkaline phosphatase and serum phosphorus concentration could be more useful to screen for osteopenia of prematurity than alkaline phosphatase alone.

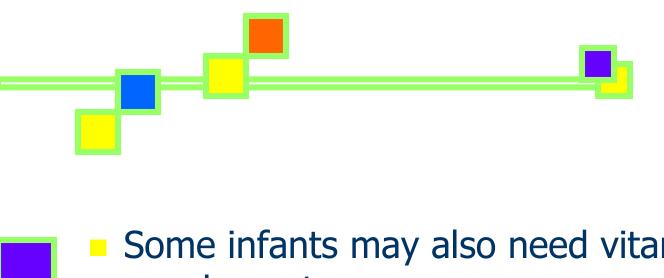


- - An alkaline phosphatase level higher than 900 IU/L has predicted radiographic osteopenia by DEXA scan with 88% sensitivity and 71% specificity, but the sensitivity is much higher with concomitant lower serum phosphorus concentrations (<1.8 mmol/L).
 - Measuring sequential levels of alkaline phosphatase, rather than a single level, could be more useful to screen for and to monitor treatment of osteopenia of prematurity



- Serum calcium level is usually well maintained within normal levels due to the effect of PTH on the bones.
- Serum phosphate correlates well with MBD and it is highly specific.
- However the test is not sensitive enough to identify the preterm infants with MBD.
- Serum alkaline phosphatase (ALP) is a marker for the bone turnover.
- MBD is characterised by low serum phosphate and elevated ALP levels. Serum ALP levels higher than 900 IU/l associated with a serum phosphate level lower than 1.8 mmol/l have a diagnostic sensitivity of 100% and specificity of 70% for MBD.





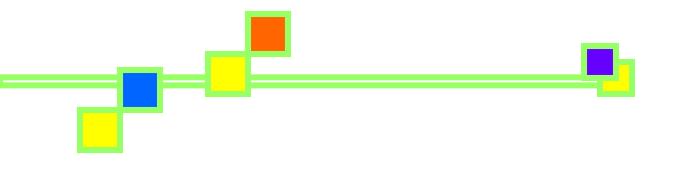
Some infants may also need vitamin D supplements.

Babies born to mothers with lower vitamin D levels are at particular risk.



If ALP persistently remains high (more than 500 IU/L) despite providing adequate prophylaxis

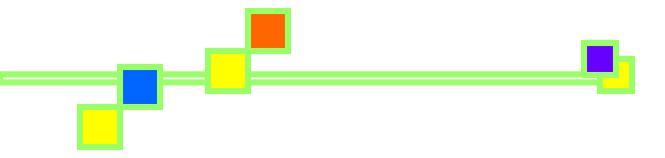
- further investigations may be necessary e.g. the urinary tubular reabsorption of phosphate(TRP).
- If the TRP is more than 95%, it may be suggestive
- of inadequate phosphate supplementation.
- Increasing or additional phosphate supplementation may be necessary as appropriate.





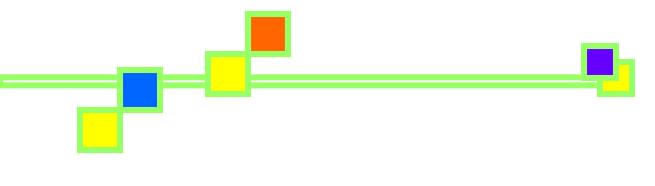
- rising ALP then it may be necessary to check Vitamin D levels and
- consider addition of Vitamin D supplementation if necessary





- An ideal approach to assess the adequacy of mineral intake in VLBW or other very high-risk infants may involve the following recommendations:
- Preterm infants, especially those less than 27 weeks' gestation or with birth weight less than 1000 g with a Maximize nutrient intake.
- Consider increasing human milk fortifier and/or feeding volume of preterm formula, as clinically indicated.
- If unable to tolerate human milk fortifier or preterm formula, then will likely need elemental minerals added as described below.

- - 2. If no further increases in these can be made, add elemental calcium and phosphorus as tolerated.
 - Usually beginning at 20 mg/kg per day of elemental calcium and 10-20 mg/kg per day elemental phosphorus and increasing, as tolerated, usually to a maximum of 70-80 mg/kg per day of elemental calcium and
 - 40-50 mg/kg per day elemental phosphorus.

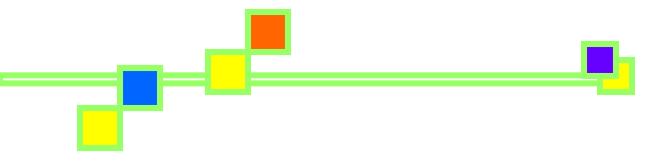


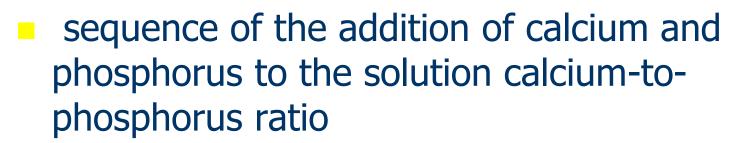
- Solution 2. Evaluate cholestasis and vitamin D status. May consider measuring 25-OH-D concentration, targeting serum 25-OH-D concentration of >20 ng/mL (50 nmol/L).
 - 4. Follow serum phosphorus concentration and serum alkaline phosphatase weekly.
- 5. Recheck radiographs for evidence of rickets at 5- to 6-week intervals until resolved.
- 6. Advise caregiving team to be cautious in handling of infant.
- 7. Limit use of steroids and furosemide, as clinically

- Calcium and phosphorus cannot be provided through parenteral solutions at the concentrations needed to support in utero accretion because of precipitation.
 The solubility of calcium and phosphorus in
- the temperature
- type, and concentration of amino acids

parenteral solutions depends on:

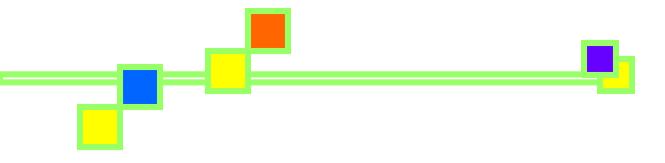
- dextrose concentrations
- pH of the calcium salt







- and presence of lipids.(first p, then ca)
- More acidic pediatric amino acid solutions improve calcium and phosphorus solubility.

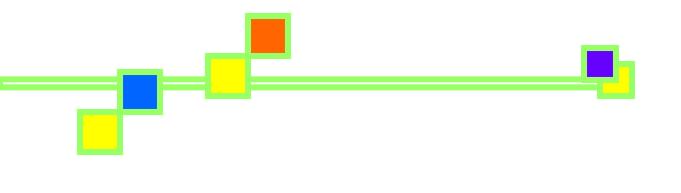


- With a range of fluid intake of 120 to 130 mL/kg per day, it is advisable to supply a calcium content of 1.5 to 2.0 mmol/dL, and a
- calcium-to-phosphorus ratio of 1.3 : 1 by weight and 1 : 1
- by molar ratio in the total hyperalimentation solution.
- This quantity of calcium provided by the parenteral route
- is about 60% to 80% of that deposited by the fetus during the last trimester of gestation



Enteral Nutrition

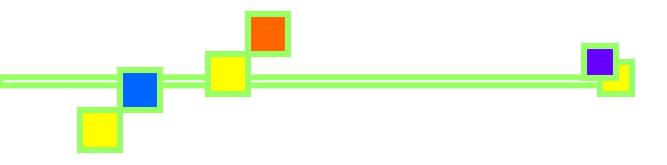
- The exclusive use of human milk without phosphorus
 - and mineral fortification promotes the occurrence of
- osteopenia and rickets in infants with VLBW.
- Both liquid and powdered human milk fortifiers are commercially available.
- Their use has dramatically reduced the incidence
- of fractures and radiographically diagnosed osteopenia.
- A similar reduction has also been observed in preterm infants fed preterm formulas.

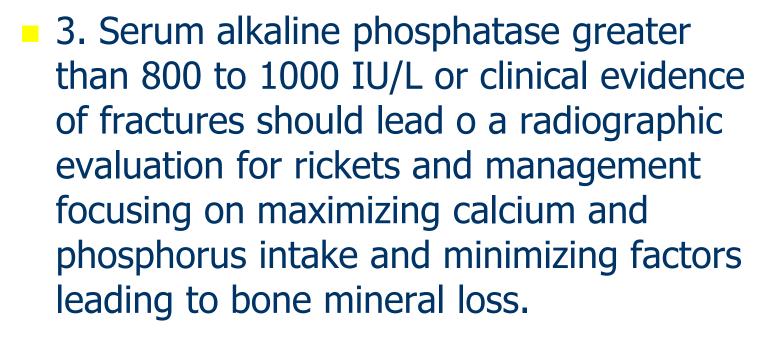


- Although both the absorption and retention rates of
- calcium and phosphorus are higher in infants than adults,
- intestinal absorption of minerals remains a limiting
- factor of mineral accretion.
- In contrast, phosphorus is generally well absorbed, but phosphorus retention is related to calcium and protein accretion.
- Absorption of calcium is currently best evaluated using stable isotope techniques, taking into consideration the endogenous intestinal calcium secretion

1-history of multiple medical problems, are at high-risk of rickets.

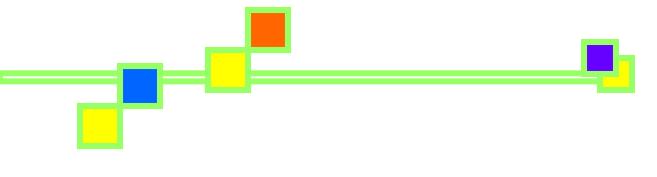
- 2. Routine evaluation of bone mineral status using biochemical testing is indicated for infants with birth weight less than 1500 g but not those with birth weight greater than 1500 g.
- Biochemical testing should usually be started 4 to 5 weeks after birth.



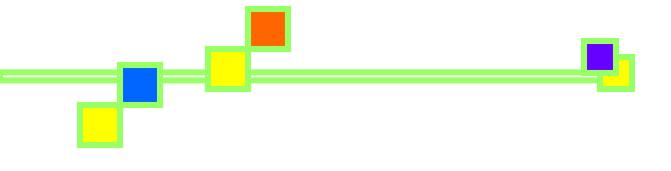




- - 4. A persistent serum phosphorus concentration less than approximately 4.0 mg/dL should be followed and consideration should be given for phosphorus supplementation.
 - 5. Routine management of preterm infants, especially those with birth weight less than 1800 to 2000 g, should include human milk fortified with minerals or formulas designed for preterm infants.



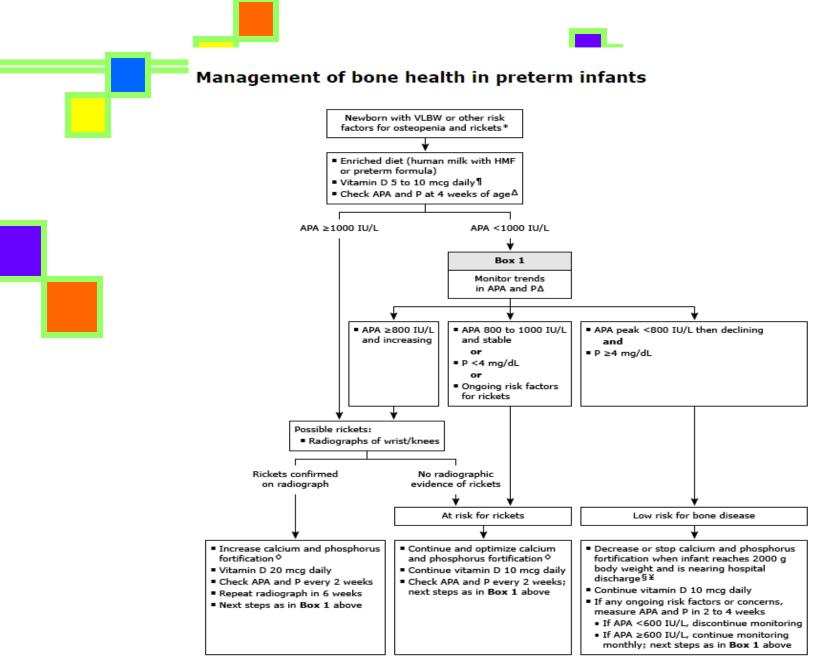
- 6. At the time of discharge from the hospital, VLBW infants will often be provided higher intakes of minerals than are provided by human milk or formulas intended for term infants through the use of transitional formulas.
- If exclusively breastfed, a follow-up serum alkaline phosphatase at 2 to 4 weeks after discharge from the hospital may be considered.
- 7. When infants reach a body weight greater than 1500 g and tolerate full enteral feeds, vitamin D intake should generally be approximately 400 IU/day, up to a maximum of 1000 IU/day

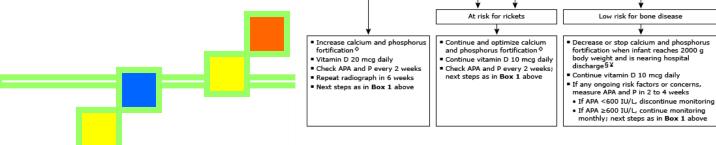


OUTCOME

- Catch-up growth occurs after discharge in VLBW infants.
- At 6 months of corrected age, spine and total bone
- mineral density, corrected for anthropometric values, is
- in the range of normal term newborn infants.
 Nevertheless,
- peak bone mass may be less during adulthood. Fewtrell
- et al. found that at 8 to 12 years of age, formerly
- preterm infants were shorter, lighter, and had lower BMCs
- than controls.







This algorithm summarizes the author's approach to the management of bone health in preterm infants and is consistent with guidance from the American Academy of Pediatrics $^{[1]}$. Practice varies in certain aspects of care, including specific targets for calcium, phosphorus, and vitamin D intake and timing of laboratory testing. Rickets rarely develops in infants \geq 1500 g unless other risk factors are present, provided that they are fed an enriched diet (human milk with HMF or preterm infant formula) until they reach weight \geq 2000 g.

VLBW: very low birth weight (<1500 g); HMF: human milk fortifier; APA: serum alkaline phosphatase activity; P: serum phosphorus; IU: international units.

- * Risk factors for neonatal rickets include VLBW (<1500 g), birth weight 1500 to 1800 g with suboptimal mineral intake (eg, sole nutrition from unfortified human milk), long-term parenteral nutrition (>4 weeks), bronchopulmonary dysplasia treated with loop diuretics and fluid restriction, long-term corticosteroid use, or history of necrotizing enterocolitis.
- ¶ We suggest enteral vitamin D 5 mcg (200 units) daily for infants <1500 g and 10 mcg (400 units) daily for those ≥1500 g. Some authorities prefer to give 10 to 12.5 mcg (800 to 1000 units) daily; this dose is safe for infants >1500 g but is unlikely to affect disease course because neonatal bone disease is primarily caused by calcium and phosphorus deficiency. Infants with cholestasis or renal disease may require higher doses of vitamin D and laboratory monitoring of vitamin D status. Either vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) may be used.

 Δ Measure serum APA and P beginning 4 weeks after birth, then every 2 weeks until the infant is on full enteral feeds and APA values are decreasing.

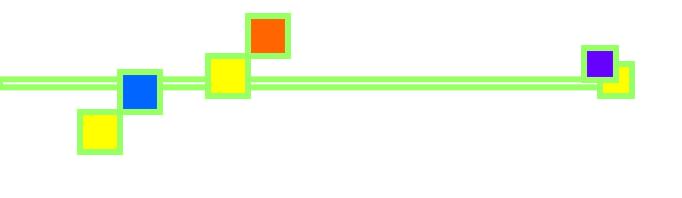
- ♦ Targets for mineral intake are calcium 150 to 220 mg/kg/day and phosphorus 75 to 140 mg/kg/day. The high end of these ranges should be used for infants with radiographic evidence of rickets or for those who develop biochemical signs of bone disease (elevated APA or low P) while on lower levels of mineral supplementation.
- § Switching from high-mineral content sources should be delayed in infants who have additional risk factors for rickets (eg, prolonged parenteral nutrition or fluid restriction of <150 mL/kg/day).

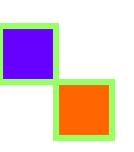
¥ For infants who are ready to taper off of a high-mineral diet, several strategies can be used, including alternating direct breastfeeding with several daily feeds of fortified human milk or the use of a transitional (also called "post-discharge" infant formula), which has moderate levels of minerals. Refer to UpToDate content on bone health in preterm infants.

Reference:



Abrams SA, Committee on Nutrition. Calcium and vitamin D requirements of enterally fed preterm infants. Pediatrics 2013; 131:e1676.



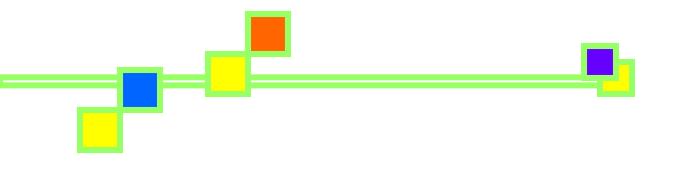


In most cases, prematurity-associated rickets appears to spontaneously resolve, although the potential long term consequences on the attainment of peak bone mass are not clearly known.



benefits of prevention and treatment include

- Even spontaneously in most infants, this discovery does not imply that a period of demineralization is acceptable.
- Although the long-term consequences are unclear, the
- benefits of prevention and treatment include avoidance
- of fractures and possibly improved linear growth and
- peak bone mass.
- Severe rickets may also limit pulmonary status, because historically it was thought that rickets was, in part, a pulmonary disease caused by poor lung expansion in the absence of a normal rib cage.





- rising ALP then it may be necessary to check Vitamin D levels and
- consider addition of Vitamin D supplementation if necessary



Fracture prevention and management

- Premature infants with rickets are at high risk for fractures, which may occur accidentally during routine care by the medical team or family.
- Caregivers should be advised to handle the infant gently.
- If fractures occur, they are managed conservatively with supplemental minerals and vitamin D rather than surgical intervention.
- Because fractures are common in infants with neonatal rickets, further evaluation for genetic causes of bone fractures such as osteogenesis imperfecta is generally unnecessary.



Infants with cholestasis or renal disease

- Infants with severe cholestasis or other chronic illnesses may need prolonged supplementation with high doses of calcium, phosphorus, and vitamin D.
- If cholestasis or renal disease is severe, oral vitamin D may not be adequate to form active 1,25-dihydroxyvitamin D and vitamin D may need to be administered directly as the active form calcitriol (1,25-dihydroxyvitamin D), with appropriate monitoring of serum calcium to avoid hypercalcemia.

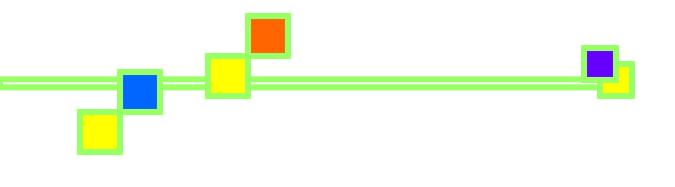
Monitoring and subsequent management

- After initiating calcium and phosphorus supplementation, as outlined above, the next steps are:
- Measure phosphorus and alkaline phosphatase activity every two weeks
- Obtain follow-up radiographs after approximately six weeks
- Most infants treated with increased calcium and phosphorus have improved radiographic findings after several weeks, and serum phosphorus concentration and alkaline phosphatase activity normalize.



When we stop mineral supplementation

- Once biochemical values have improved and radiographs show signs of healing, supplemental calcium and phosphorus may be weaned over two to four weeks and ultimately stopped.
- No specific laboratory criteria have been defined, but we typically stop the mineral supplements when the serum alkaline phosphatase value is <500 to 600 international units/L and trending downward, unless the infant has malabsorptive disease or other reasons for a high mineral requirement





- 1 ml: 1 mmol phosphate
- 2 mmol sodium
- calcium globionate: 115 mg elemental calcium/5 ml



Nutritional support in premature infants

Zohreh Badiee Professor of pediatrics, neonatologist Premature infants have greater nutritional needs to achieve optimal growth in the neonatal period than at any other time of their life. There are several reasons for this:

- Infants born at the beginning of the third trimester of pregnancy often are growth-restricted because they have smaller nutrient stores compared with infants born at term.
- Medical conditions, including hypotension, hypoxia, acidosis, infection, and surgery, increase metabolic energy requirements and, thus, nutrient needs.
- physiologic immaturity of the gastrointestinal tract, including decreased gastrointestinal motility and reduced intestinal enzyme activity
- Therapies such as corticosteroids.

Energy requirements

- The energy (caloric) requirements to achieve optimal growth are calculated from:
- the estimated resting energy expenditure
- plus the energy requirements for activity (including feeding)
- thermoregulation
- fecal loss
- growth
- and chronic medical conditions.
- In term infants between 8 to 63 days of postnatal age, resting energy expenditure varies from 49 to 60 kcal/kg per day.



Estimated daily energy requirements for growing premature infants

Factor	Kcal/kg	Comment
Resting energy expenditure	50	Resting metabolic rate
Activity	15	30 percent above resting
Cold stress	10	Thermoregulation
Synthetic effect of feeding	8	Dietary thermogenesis
Fecal loss	12	10 percent of intake
Growth	25	Calories stored
Total caloric requirement	120	

Adapted from: Sinclair JC. Clin Obstet Gynecol 1971; 14:840.

Intakes of key nutrients from various enteral nutrition feedings for preterm infants in the United States, assuming milk intake of 160 mL/kg per day

	Target intake*	Unfortified human milk¶∆ (≈20 kcal/oz)	Fortified human milk¶\$ (≈24 kcal/oz)	Preterm formula (24 kcal/oz)
Energy (kcal/kg/day)	128	104	128	129
Protein (g/kg/day)	3.5 to 4	1.6	4.1 to 4.3	4.3 to 4.6
Fat (g/kg/day)	5 to 7	5.6	6.3 to 8.3	5.6 to 7.0
Carbohydrate (g/kg/day)	12 to 14	11.2	11.2 to 13.6	12.9 to 13.6
Calcium (mg/kg)	150 to 220	40	192 to 197	210 to 234
Phosphorus (mg/kg)	75 to 140	22	103 to 110	117 to 129
Vitamin D (international units/day)	400	0.3	189 to 253	194 to 384

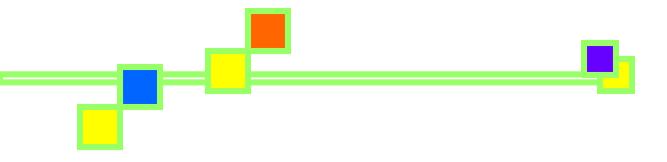
^{*} Recommendations for preterm infants weighing 1000 to 1500 g.

Δ For human milk, the energy content is based on mean content of 65 kcal/dL; protein content is based on mean of 1 g/dL; fat content is based on mean of 3.5 g/dL; and carbohydrate content is based on a mean of 11.5 to 13 g/dL.^[2]
⋄ Human milk fortifier (HMF) nutrition information is based upon common liquid HMF available in the United States.^[2]

References:

- Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. BMC Pediatr 2014; 14:216.
- 2. American Academy of Pediatrics. Pediatric Nutrition Handbook, 7th ed, Kleinman RE, Greer FR (Eds), American Academy of Pediatrics, Elk Grove

[¶] Human milk data are based on mature human milk.



- For premature infants, the clinical condition and activities dictate the daily energy requirements as follows:
- For enterally fed premature infants, the average daily energy requirements are 120 kcal/kg per day.
- For parenterally fed premature infants, the energy requirements are reduced to 80 to 100 kcal/kg per day because of less fecal energy loss, fewer episodes of cold stress, and somewhat less activity.
- For infants with chronic illness, such as bronchopulmonary dysplasia, energy needs may be as high as 150 kcal/kg per day because of increased resting energy expenditure, activity, and possibly fecal losses

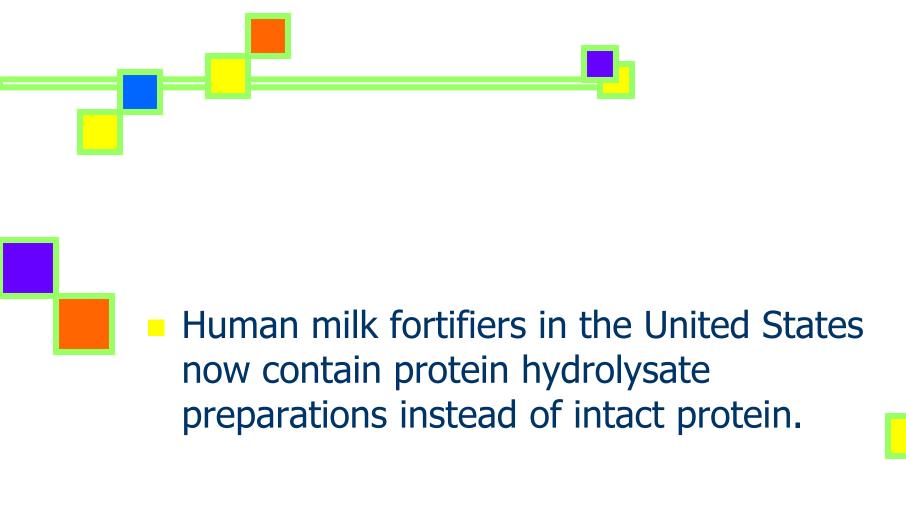


PROTEIN — In milk, there are two fractions of protein defined by their solubility in acid: whey and casein

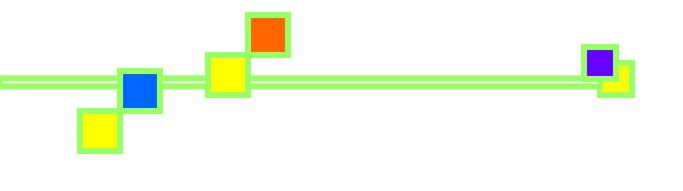
- The predominance of whey and the amino acid composition of human milk and premature formula are beneficial for premature infants as compared with bovine milk, and also when compared with term infant formulas.
- Whey predominance Both human milk and premature formula contain an increased proportion of whey to casein. Human milk is 70 percent whey and 30 percent casein, and premature formula is 60 percent whey and 40 percent casein. in contrast, bovine milk contains predominantly casein (82 percent).

The high proportion of whey in human milk or premature formula is beneficial for premature infants for several reasons:

- Whey-dominant milk promotes more rapid gastric emptying than does caseindominant milk.
- The whey fraction in human milk consists of soluble proteins that are easily digested.
- The major human whey protein is alphalactalbumin, a nutritional protein. The major bovine whey protein is betalactoglobulin, which may contribute to protein allergy and colic.







- Other specific human whey proteins are lactoferrin, lysozyme, and secretory immunoglobulin A (IgA).
- These proteins are resistant to hydrolysis, line the gastrointestinal tract, and may play a role in host defense.
 Bovine milk contains only trace amounts of these proteins



Amino acid composition

- The amino acid composition of human milk or whey-dominant formula may promote brain development in premature infants as compared with the amino acid composition of casein-dominant formula.
- In one study, human milk providing 1.6 g/kg protein per day was compared with whey or casein-dominant formulas providing 2.25 or 4.50 g/kg protein per day.
- Infants fed human milk had the <u>lowest</u> concentrations of methionine, phenylalanine, and tyrosine
- high levels of these amino acids are thought to interfere with brain development.
- In addition, human milk and premature formula contain cysteine and taurine, two amino acids that are "conditionally essential" in premature infants (ie, required because of prematurity).
- Cysteine is needed to synthesize the antioxidant glutathione, and taurine is needed for bile conjugation and brain development.

Recommended daily parenteral and enteral requirements for premature infants

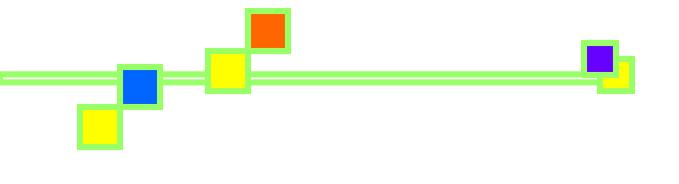
Component (unit)	Parenteral intake, unit/kg	Enteral intake, unit/kg			
Water (mL)	150	150			
Energy (kcal)	80 to 100	120 to 130			
Protein (g)	3 to 3.5	3.5			
Fat (g)	1 to 4	5 to 7			
Carbohydrate (g)	16	12 to 14			
Electrolytes, minerals, and trace	elements				
Sodium (meq)	2 to 4	2 to 8			
Potassium (meq)	2 to 3	2 to 3			
Chloride (meq)	2 to 3	2 to 3			
Calcium (mg)	80 to 120	200 to 220			
Phosphorus (mg)	60 to 90	100 to 110			
Magnesium (mg)	9 to 10	7 to 10			
Zinc (mcg)	350 to 450	1000 to 2000			
Copper (mcg)	65	65 to 300			
Chromium (mcg)	0.4	0.1 to 0.4			
Manganese (mcg)	1	7.5			
Vitamins					
Vitamin A (int. unit)	500	700 to 1500			
Vitamin D (int. unit)	160	400*			
Vitamin E (int. unit)	2.8	6 to 12			
Vitamin K [¶] (mcg)	80	8 to 10			
Folic acid (mcg)	56	25 to 50			
Niacin (mg)	16.8	3.6 to 4.8			
Pyridoxine (mcg)	180	150 to 210			
Riboflavin (mcg)	150	250 to 360			
Thiamine (mcg)	350	180 to 240			
Vitamin B12 (mcg)	0.3	0.1 to 0.5			
Vitamin C (mg)	15 to 25	18 to 24			

^{*} Intake is not adjusted for weight.

Adapted from:

- Greene HL, Hambidge KM, Schanler RJ, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of The American Society for Clinical Nutrition. Am J Clin Nutr 1988; 48:1324.
- American Academy of Pediatrics, Committee on Nutrition. Nutritional needs of low-birth-weight infants. Pediatrics 1985: 75:976.

 $[\]P$ Does not include 0.5 to 1 mg vitamin K given at birth.



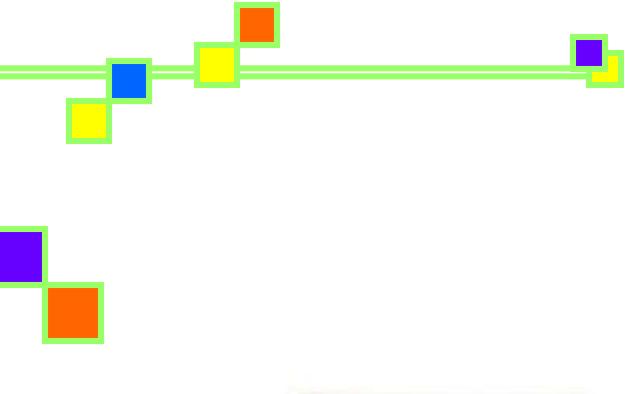
- higher protein intake is tolerated by premature infants and is associated with improved growth compared with lower protein intake.
- Supplementation If human milk is used for feeding preterm infants less than 1500 g at birth, we recommend use of a human milk fortifier to increase the protein content of the feeding.
- This is because human milk does not meet the protein requirements for premature infants.
- Although the protein content of milk from mothers who deliver premature infants (preterm milk) may be as high as 3.2 g/dL initially, protein content declines over four weeks of lactation to a level of 1.8 g/dL.



Fortification of milk with a human milk fortifier to achieve a protein intake of 3 to 4.0 g/kg per day improves

- 1- Rates of weight gain
- 2- indices of protein nutritional status such as blood urea nitrogen (BUN), serum albumin, and transthyretin.
- Most commercially available human milk fortifiers in the United States also provide adequate quantities of calcium, phosphorus, magnesium, sodium, zinc, copper, and multivitamins



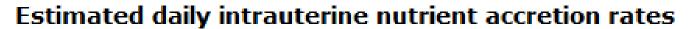




DR, Badiee. Neonatologist

CALCIUM AND PHOSPHORUS

- Human milk Preterm human milk contains approximately 6.25 mmol/L (250 mg/L) of calcium and 4.5 mmol/L (140 mg/L) of phosphorus.
- The content of calcium and phosphorus in human milk is insufficient for premature infants to achieve normal bone mineralization or mineral accretion rates similar to those achieved in utero.
- Therefore, human milk should be supplemented with calcium and phosphorus to improve bone mineralization as well as linear growth.
- For premature infants, we recommend the addition of calcium (2 to 3 mmol/kg per day, or 80 to 120 mg/kg per day) and phosphorus (1.5 to 2 mmol/kg per day, or 45 to 60 mg/kg per day) to human milk after enteral feeding is established. Most human milk fortifiers that are commercially available in the United States provide appropriate supplementation for these minerals



Nutrient*	Unit/kg
Calcium (mg)	105
Copper (mcg)	50
Magnesium (mg)	2.7
Nitrogen (mg)	325
Phosphorus (mg)	70
Potassium (meq)	0.7
Sodium (meq)	1.2
Zinc (mcg)	240

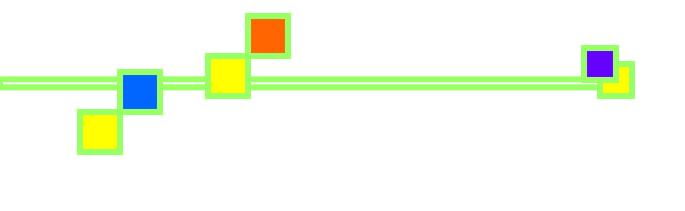
^{*} Values are averaged from last trimester and adjusted for body weight.

Adapted from: Widdowson EM. Importance of nutrition in development, with special reference to feeding low-birth-weight infants. In: Meeting Nutritional Goals for Low-Birth-Weight Infants, Sauls HS, Bachhuber WL, Lewis LA. (Eds), Ross Laboratories, Columbus, 1982, p.4; and

After hospital discharge

- After discharge, sufficient calcium and phosphorus must be provided for premature infants to maintain adequate bone mineralization for growth.
- Infants who are discharged feeding on breast milk exclusively should be monitored for growth and possible mineral deficiency.
- For such infants, we suggest measuring serum phosphorus concentration and alkaline phosphatase activity four to eight weeks after discharge.
- If these values are abnormal, a radiograph of the long bones is obtained to assess mineralization.





- Mineral supplementation is provided if osteopenia is present.
- In general, laboratory monitoring is not needed in formula-fed infants after hospital discharge unless the alkaline phosphatase activity is markedly elevated at the time of discharge, which is uncommon

MAGNESIUM

- Preterm human milk contains approximately 1.3 mmol/L
 (30 mg/L) of magnesium (Mg).
- Magnesium absorption is greater in unfortified human milk than in formula (73 versus 48 percent).
- Balance studies show that net magnesium retention in premature infants fed human milk meets intrauterine estimates, indicating that supplementation is not needed.
- In premature infants fed premature formulas, magnesium accretion is greater than intrauterine estimates, even though absorption is less than with human milk.
- the effect of this greater magnesium intake and retention is unknown

SODIUM

- A sodium (Na) intake of 2 to 3 mmol/kg (2 to 3 mEq/kg) per day allows growth and maintains an appropriate serum sodium concentration in premature infants.
- Because the sodium concentration of human milk is low and declines as lactation progresses, premature infants fed unsupplemented human milk may develop hyponatremia.
- Human milk fortifiers provide adequate sodium supplementation to ensure normal serum sodium levels

POTASSIUM

The recommended intake of potassium (K) is 2 to 3 mmol/kg (2 to 3 mEq/kg) per day, the amount provided by both human milk and premature formula.



IRON

- The concentration of iron (Fe) declines in human milk as lactation continues, from approximately 0.6 mg/L at two weeks to 0.3 mg/L after five months
- Bioavailability of iron in human milk is approximately 50 percent, which is considerably higher than bioavailability in formula (3 to 4 percent).
- Bioavailability is increased by mild anemia and reduced by blood transfusion .
- Premature infants fed human milk develop iron deficiency, which can be prevented by iron supplementation .
- We recommend iron supplementation of 2 to 4 mg/kg per day for all preterm infants after enteral feeding is established, as recommended by the American Academy of Pediatrics (AAP).
- For infants receiving human milk, an iron supplement is started after two weeks of age. Infants who are fed formula should be given iron-fortified formula from the onset. Iron intake at a dose of at least 2 mg/kg per day, via supplements or fortified formula, should be continued through the first year of life



- In premature infants, absorption of zinc (Zn) is greater in human milk (both unsupplemented and supplemented) compared with either term or premature formula.
- However, premature infants fed human milk can develop zinc deficiency at several months of age because the zinc concentration in the milk declines as lactation continues.
- Human milk fortifiers should contain zinc, since the decline in zinc as lactation continues puts the rapidly growing premature infant at risk for zinc deficiency.
- The zinc content in premature formula is approximately 1250 micrograms/dL, which is sufficient to maintain adequate zinc status and net retention equal to intrauterine accretion rates

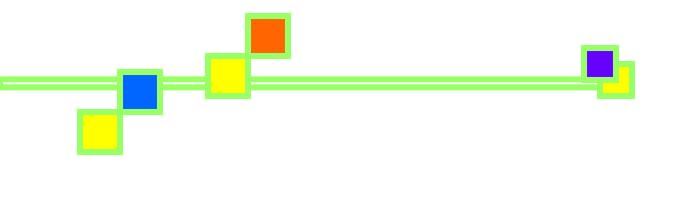
COPPER

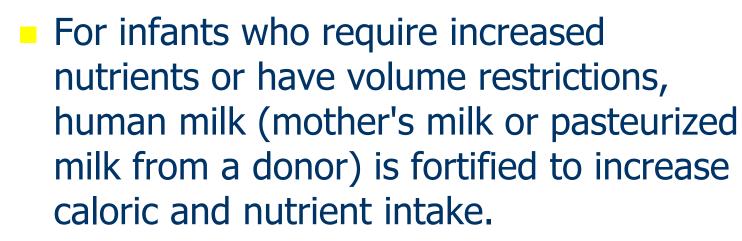
- Fortified human milk provides a copper (Cu) intake of 180 mcg/kg per day and premature formula provides copper intake of 200 to 300 mcg/kg per day.
- Both surpass the intrauterine accretion rates for premature infants



VITAMINS

- Premature infants need higher amounts of some vitamins than term infants do because of increased requirements for growth and/or greater losses.
 - Human milk may not provide sufficient amounts. As an example, plasma concentrations of vitamin C fell rapidly in one study of premature infants fed human milk. Exposure of human milk to light and its passage through feeding tubes reduce concentrations of vitamins such as vitamin A and riboflavin.
- Premature formulas generally provide adequate vitamins.
- Human milk fortifiers do not supply recommended intake for vitamin D intake (400 international units daily for infants weighing >1500 g), and should be used in conjunction with a vitamin supplement.
- Otherwise, a multivitamin supplement should be added when the premature infant begins feeding with unfortified human milk or standard term formula, and continued until the infant is consuming >300 kcal/day or 450 mL/day or weighs more than 2.5 kg







This typically applies to infants weighing <1800 grams who require tube feeding.</p>

When mother's own milk is not available

 or the supply is inadequate, the preferred alternative is pasteurized fortified donor human milk from an established milk bank that follows safety regulations for optimal milk collection, pasteurization, storage, and shipping



Fortification of human milk

- For preterm infants weighing <1500 grams, and for those between 1500 and 1800 grams who require tube feedings, human milk (from the mother or a donor) should be supplemented with multinutrient human milk fortifier (HMF)
- This is because very low birth weight (VLBW) premature infants fed unfortified human milk during hospitalization and after discharge do not grow optimally and have nutritional deficits.
- Our practice is to start tube feeding with unfortified human milk, and add the fortifier when the feeds have reached 80 mL/kg/day (50 percent of target volume).

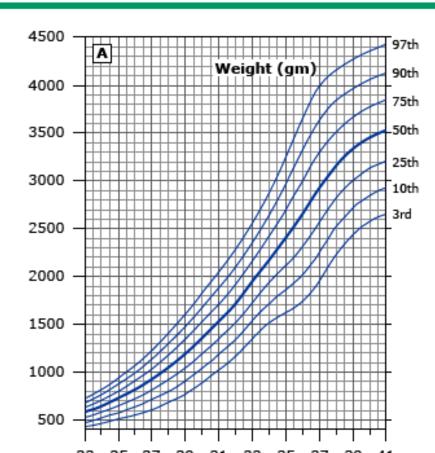
When we can discontinue fortification

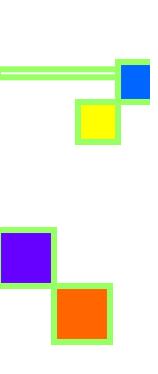
- We continue fortification until the infant is feeding orally and is growing well without any evidence of nutritional issues (eg, abnormal alkaline phosphatase, phosphorus, or blood urea nitrogen [BUN]).
- Most neonatal intensive care units (NICUs)
 use a similar protocol but specifics of timing,
 composition, and advancement of feeds
 vary.

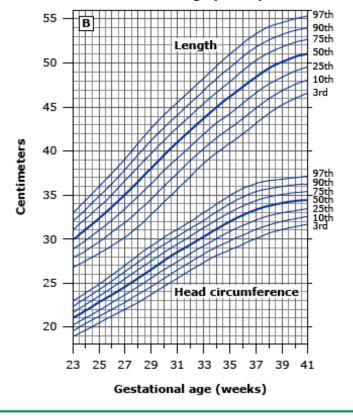
Rate of growth

- Adequate growth is monitored by serial measurements of:
- weight, length, and head circumference.
- For each parameter, adequate growth is defined by a minimum increment of growth between measurements as follows:
- Weight is assessed daily, targeting a minimum increment of 18 g/kg per day
- Once the infant reaches 2 kg body weight, the goal should be a weight gain of 20 to 30 g per day.
- Length is assessed weekly, targeting an average increment of 1 cm per week.
- Head circumference is assessed weekly, targeting an average increment of 1 cm per week

Olsen growth chart for preterm and term infants - Girls







Intrauterine growth curves for girls.

- (A) Weight-for-age in grams (gm).
- (B) Length- and head circumference (HC)-for-age.

Of note, 3rd and 97th percentiles on all curves for 23 weeks should be interpreted cautiously, given the small sample size.

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Enriched diet

- Birth weight ≤1800 g and whose weight remains below the 10th percentile for age.
- Unable to consume at least 180 mL/kg/day due to fluid restriction or poor feeding.
- Abnormalities in routine laboratory tests suggesting suboptimal bone health, such as low serum phosphorus or elevated alkaline phosphatase activity with a persistently abnormal trend, or low blood urea nitrogen (BUN) suggesting inadequate protein intake.
- For breastfed infants, the enriched diet may consist of providing supplemental booster feedings with a premature infant formula at 30 cal/oz; adding human milk fortifier to breastmilk; or mixing the premature infant formula with mother's milk.
- For infants fed only formula, we use a premature infant formula (typically 24 kcal/oz). A "postdischarge" formula (22 kcal/oz) is usually substituted just before or at the time of discharge

Standard diet

For infants who do not meet the above criteria for an enriched diet, we provide feedings of unfortified human milk or term infant formula at 20 kcal/oz, with target volumes of 180 mL/kg/day.



- Ongoing monitoring of growth after discharge is important to verify whether optimal growth will continue on ad libitum breastfeeding or standard term formula.
- When an enriched diet is used, we suggest continuing it for at least six months postdischarge, as long as the infant does not gain too rapidly and cross growth channels upward.
- It is important to communicate the plan for an enriched diet to the clinician who will manage the infant's care after discharge

Special formula for premature infants

- Aptamil premature
- Bebelac premature
- Prenan
- Aptamil PDF
- Similac neosure





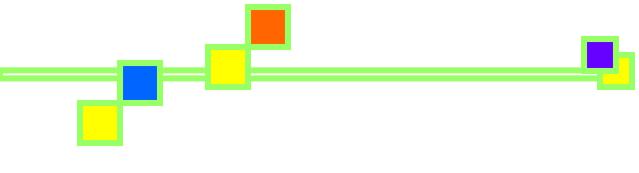
OSTEOPENIA OF PREMATURITY

- also called metabolic bone disease of prematurity
- is defined as postnatal bone mineralization that is less than intrauterine bone density at a comparable gestational age
- Osteopenia occurs commonly in preterm infants
- the incidence and severity increase with decreasing birth weight
- Characteristic radiographic changes are seen in
 55 percent of infants with birth weight <1000 g
- High bone turnover appears to be more important than decreased bone formation in the pathogenesis of this disorder



- 1- immaturity
- 2-deficiency of Ca and P because of inadequate intake.
- Other risk factors include:
- prolonged parenteral nutrition
- medications that affect mineral metabolism, such as <u>caffeine</u>, loop diuretics, and corticosteroids.
- Decreased bone mineralization also occurs in infants who are small-for-gestational age or are born to diabetic mothers

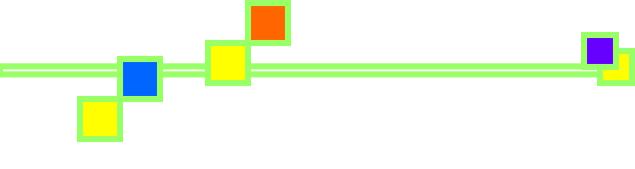




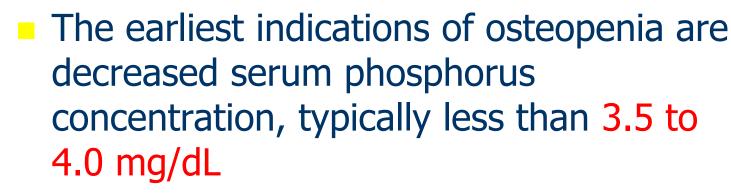
Clinical features

- Osteopenia typically develops in premature infants at 3 to 12 weeks of age.
- The condition is not clinically apparent and is detected by routine laboratory monitoring.





Laboratory features





 and increased alkaline phosphatase activity>1200



- feature characteristic of osteopenia is:
- decreased lucency of the cortical bone
- with or without epiphyseal changes
- Most infants with decreased bone mineralization do not have fractures, even when osteopenia is severe.
- However, in rare cases, a fracture can be the earliest sign.

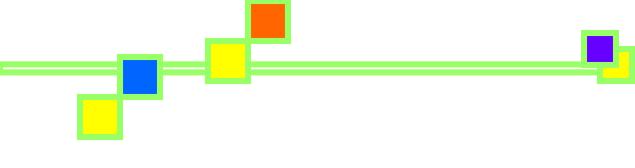


Osteopenia of prematurity Radiograph of the wrist in an infant with severe osteopenia of prematurity. The major findings are the highly "washed out" appearance of the bones of the arm and hand and the cupping and fraying of the distal ends of the long bones (arrow). This appearance is similar to that seen in classical vitamin D deficient rickets in older children. Courtesy of Steven A Abrams, MD.





- Studies are obtained at two week intervals until full feeds are achieved and stable values are demonstrated.
- Infants with additional risk factors for osteopenia, such as prolonged parenteral nutrition or inadequate enteral intake of Ca and P, are tested weekly.
- If these laboratory values are abnormal, we obtain radiographs of the wrist to confirm the diagnosis



Management

- fortified human milk or premature formula
- Infants who do not tolerate human milk fortifiers or premature formula because of lactose intolerance or cow's milk protein allergy should be given supplements of calcium and phosphorus.
- The maximum allowable parenteral mineral concentrations should be provided to infants not receiving enteral feeding.

Nutrient Composition of Human Milk and Premature, Term, and Enriched Formulas[†]

Nutrient per100 mL milk	Mature human milk	Enfamil® Premature 24	Similac® Special Care 24	Similac® 20	Enfamil® 20	NeoSure® 22	Enfamil® 22
Energy (kcal)	70	81	81	67	67	75	75
Protein (g)	1.8	2.4	2.2	1.4	1.4	1.9	2.1
Whey/casein	70/30	60/40	60/40	48/52	60/40	50/50	60/40
Fat (g)	4.0	4.1	4.4	4.8	4.9	4.1	4.0
Percent	2/98	40/60	40/60	20/80	80	25/75	9/91
MCT/LCT (死))						
– Carbohydrate (i	g) 7.0	9	8.6	7.3	7.4	7.7	8.0
Lactose (%)	100	40	50	100	100	50	55
Calcium (mg)	22	133	145	53	53	78	90
Phosphorus (mg	j) 14	67	81	28	36	46	50
Magnesium (mg) 2.5	5.5	9.7	4.1	5.4	6.7	6.0
Sodium (meq)	1.3	1.4	1.5	0.7	0.8	1.1	1.1
– Potassium (med	į) 1.5	2.1	2.7	1.5	1.8	2.7	2.2
Chloride (meq)	1.7	2.0	1.9	1.9	1.2	1.6	1.7
Zinc (μg)	320	1210	1210	507	676	900	940
Copper (µg)	60	100	200	61	51	90	90
- Vitamin A (IU)	400	1008	1008	203	203	345	340
Vitamin D (IU)	4	219	122	41	41	52	60
Vitamin E (IU)	0.3	5.1	3.2	2.0	1.4	2.7	3.0
Osmolality (mosmol/L)	252	270	270	270	270	224	230

*Plus Enfamil® Human Milk Fortifier (4 packets/100 mL); MCT = medium chain triglycerides; LCT = long chain triglycerides.

[†]Data from Butte, NF, Garza, C, Johnson, CA, et al, Early Hum Dev 1984; 9:153; Gross, SJ, David, RJ, Bauman, L, Tomarelli, RM, J Pediatr 1980; 96:641; Schanler, RJ. Water soluble vitamins: C, B1,B2, B6, niacin, biotin, and pantothenic acid. In: Nutrition During Infancy, Tsang, RC, Nichols, BL (Eds), Hanley & Belfus, Philadelphia 1988. p. 236; Newman, V, Food Nutr Bull 1994; 15:161; Slagle, TA, Gross, SJ. Vitamin E. In: Nutrition During Infancy, Tsang, RC, Nichols, BL (Eds), Hanley & Belfus, Philadelphia 1988. p. 277; Specker, BL, Greer, F, Tsang, RC, Vitamin D. In: Nutrition During Infancy, Tsang, RC, Nichols, BL (Eds), Hanley & Belfus, Inc., Philadelphia 1988. p. 264; Moran, JR, Vaughan, R, Stroop, S, et al, J Pediatr Gastroenterol Nutr 1983; 2:629.

