

Alert	<p>Colecalciferol (Vitamin D3) is the inactive form of vitamin D.</p> <p>1 microgram colecalciferol = 40 international units (hereafter referred to as “units”) of vitamin D3. Vitamin D content in preterm and term human milk and formulas may not provide enough vitamin D to meet the recommended daily intake of vitamin D 400 units/day.⁽¹⁾</p> <p>Some preparations may contain sodium benzoate - Avoid exposure to sodium benzoate of >99 mg/kg/day in neonates.</p>
Indication	Prevention and treatment of vitamin D deficiency and nutritional rickets (in combination with adequate mineral intake)
Action	Regulating body levels of calcium and phosphorus, and mineralisation of bone
Drug type	Fat soluble vitamin
Trade name	<p>Oral: Bio-Logical Vitamin D3 solution, Ostelin Vitamin D3 1000 IU liquid, OsteVit-D liquid, OsteVit-D Vitamin D3 Kids Drops Pentavite infant liquid</p> <p>Intramuscular injection: Biological Therapies Vitamin D3 Forte ampoules.</p>
Presentation	<p>Ostelin Vitamin D3 1000 IU Liquid - vitamin D3 1000 units (colecalciferol 25 microgram)/0.5 mL.</p> <p>Pentavite infant Liquid - Per 0.45 mL: vitamin D3 400 units (colecalciferol 10.1 microgram).</p> <p>Biological Therapies Vitamin D3 Forte ampoules – 600,000 units/mL (15 mg/mL of colecalciferol) for intramuscular injection.</p> <p>The following preparations contain sodium benzoate as an excipient:</p> <p>Bio-Logical Vitamin D3 Oral Solution – 1000 units per 0.2 mL vitamin D3.</p> <p>OsteVit-D Vitamin D3 Liquid - vitamin D3 1000 units (colecalciferol 25 microgram)/0.2 mL.</p> <p>OsteVit-D Vitamin D3 Kids drops - vitamin D3 400 units (colecalciferol 10 microgram) per 2 drops (0.08 mL).</p>
Dose	<p>Prevention dose in infants at risk of vitamin D deficiency (see <i>practice points</i>)^(2,3):</p> <p>400 units/day (colecalciferol 10 microgram/day) up to 12 months corrected age.</p> <p>Example: Ostelin Vitamin D3 1000 IU/0.5 mL liquid – 0.2 mL/day. This equates to 400 units/day.</p> <p>Cholestasis: Refer to Vitamins in cholestasis formulary.</p> <p>Treatment of nutritional rickets:</p> <p>2000 units/day (colecalciferol 50 microgram/day) for a minimum of 3 months.⁽³⁾</p> <p>Example: Ostelin vitamin D3 1000 IU/0.5 mL liquid – 1 mL/day for a minimum of 3 months.</p> <p>If oral administration is difficult, consider intramuscular vitamin D3 100,000 units (colecalciferol 2.5 mg) every 3 months (3 doses).</p> <p>Continue maintenance vitamin D3 after resolution of nutritional rickets.</p> <p>Ensure adequate calcium intake – See special comments.</p>
Dose adjustment	<p>Therapeutic hypothermia - No information.</p> <p>ECMO - Adult patients on ECMO were at high risk of vitamin D deficiency.⁽⁵⁾</p> <p>Renal impairment - Hydroxylated vitamin D agents (eg. calcitriol) may be needed in addition to control progressive secondary hyperparathyroidism.^(6,7)</p> <p>Hepatic impairment - Absorption of fat-soluble vitamins is impaired in cholestasis.⁽⁸⁾</p>
Maximum dose	<p>Dosage to cause toxicity varies with individual sensitivity, but in individuals without malabsorption problems, 10,000 units per day for more than several weeks or months is the maximum dose.</p> <p>A dose of vitamin D3 1600 units/day produced vitamin D toxicity (hypercalcaemia and 25OH vitamin D >250 nmol/L) in 94% of healthy, term, breastfed infants.⁽¹⁰⁾</p> <p>Single dose of vitamin D3 600,000 units (15 mg) in infants produced prolonged vitamin D excess and transient hypercalcaemia, whereas doses of 100,000 to 200,000 units every 3 months did not.^(2, 11)</p>
Total cumulative dose	
Route	<p>Oral</p> <p>Intramuscular</p>
Preparation	Administer undiluted

Administration	Oral: May be administered without regard to meals. Intramuscular: Inject slowly into anterolateral thigh.
Monitoring	<p>Healthy infants: No routine 25OHD screening recommended.⁽²⁾</p> <p>Infants with cholestasis: Monitor 25OHD every 1 to 3 months. Maintain vitamin D sufficiency (25-hydroxyvitamin D \geq 50 nmol/L).^(4, 8)</p> <p>For very low birth weight or preterm infants with nutritional rickets: Serum phosphate and alkaline phosphatase weekly to achieve serum levels of 1.8 mmol/L for term infants (range 1.2-2.6) and 1.3-1.7 mmol/L for preterm infants.⁽³⁾ Urine calcium and phosphate may be monitored with the goal of achieving a slight surplus of supply of calcium and phosphate (urinary calcium \geq 1.2 mmol/L and phosphate \geq 0.4 mmol/L).⁽⁹⁾ In daily practice, monitoring can be ceased after the preterm infant is on full feeds of fortified human milk or preterm formula and is $>$ 1500 g body weight. Routine evaluation for nutritional rickets should be considered for infants born $<$1500 g.⁽³⁾ Biochemical testing should usually be started 4 to 5 weeks after birth, and a serum alkaline phosphatase $>$800 to 1000 units/L or clinical evidence of fractures should lead to a radiographic evaluation for rickets and management focusing on maximising calcium and phosphorus intake and minimising factors leading to bone mineral loss.⁽³⁾</p>
Contraindications	Hypersensitivity to colecalciferol, hypervitaminosis D
Precautions	<p>Hypercalcaemia and hyperparathyroidism – avoid a high calcium intake and limit vitamin D supplementation with colecalciferol.</p> <p>The formulations of colecalciferol available in Australia are unlikely to cause vitamin D toxicity. However, if toxicity from colecalciferol occurs, stopping treatment might not lead to rapid resolution because colecalciferol is stored extensively in fat. In addition to rehydration, oral glucocorticoids can be effective in severe or protracted vitamin D toxicity.</p>
Drug interactions	<p>Magnesium-containing antacids (concurrent use with vitamin D may result in hypermagnesaemia, especially in patients with chronic renal failure).</p> <p>Barbiturates may reduce effect of vitamin D by accelerating metabolism by hepatic microsomal enzyme induction; patients on long-term anticonvulsant therapy may require vitamin D supplementation to prevent osteomalacia.</p> <p>Calcitonin – reduces serum calcium levels.</p> <p>Bisphosphonates (etidronate, pamidronate) prevent bone resorption and act synergistically with vitamin D to increase bone mineral density but antagonise the effect of vitamin D on serum calcium level.</p> <p>Calcium-containing preparations in high doses.</p> <p>Diuretics, thiazide (concurrent use with vitamin D may increase the risk of hypercalcaemia).</p> <p>Cholestyramine, colestipol and mineral oils may interfere with fat soluble vitamin absorption.</p> <p>Corticosteroids – vitamin D supplementation may be recommended for prolonged corticosteroids use, because corticosteroids may interfere with vitamin D action.</p> <p>Digitalis glycosides – hypercalcaemia caused by vitamin D may potentiate the effects of digitalis glycosides resulting in cardiac arrhythmias.</p> <p>Phosphorus containing preparations in high doses may cause hyperphosphataemia as vitamin D enhances of phosphate absorption.</p> <p>Vitamin D and analogues – concurrent use with another analog, especially calcifediol, is not recommended because of additive effects and increased potential for toxicity.</p>
Adverse reactions	<p>A dose of vitamin D3 1600 units/day produced vitamin D toxicity (hypercalcaemia and 25-hydroxy vitamin D $>$250 nmol/L) in 94% of healthy, term, breastfed infants.⁽¹⁰⁾</p> <p>Single doses of vitamin D3 600,000 units (colecalciferol 15 mg) in infants produced prolonged vitamin D excess and transient hypercalcaemia, whereas doses of 100 000 to 200 000 units every 3 months did not.^(2, 11)</p> <p>Ingestion of excessive doses of vitamin D over prolonged periods 2000 to 4000 units a day for several months in children can result in severe toxicity.</p> <p>Acute excessive doses of vitamin D can also result in severe toxicity.</p> <p>Chronic vitamin D induced hypercalcaemia may result in generalised vascular calcification, nephrocalcinosis, and other soft tissue calcification that may lead to hypertension and renal failure.</p>

	<p>These effects are more likely to occur when the hypercalcaemia is accompanied by hypophosphatemia.</p> <p>Growth may be arrested in children, especially after prolonged administration of 1800 units of ergocalciferol per day.</p> <p>Death may occur as a result of renal or cardiovascular failure caused by vitamin D toxicity.</p> <p>Symptoms (all age groups) may include bone pain, constipation, diarrhoea, drowsiness, dry mouth, headache (continuing), increased thirst, increase in frequency of urination (especially at night) or in the amount of urine, loss of appetite, metallic taste, muscle pain, nausea or vomiting, unusual tiredness or weakness, cloudy urine, conjunctivitis (calcific), decreased libido, ectopic calcification, high fever, high blood pressure, increased sensitivity of eyes to light or irritation of eyes, irregular heartbeat, itching of skin, lethargy, loss of appetite, pancreatitis, psychosis (overt), rhinorrhoea, and weight loss.</p>
Compatibility	No information – do not mix.
Incompatibility	No information
Stability	No information
Storage	Vitamin D3 Forte Injection: Store below 25°C. For other brands – refer to product information.
Excipients	<p>Sodium benzoate: Some vitamin D preparations contain sodium benzoate. Avoid exposure of >99 mg/kg/day in neonates.</p> <p>Ostelin Vitamin D Oral Liquid – contains orange flavour</p> <p>Bio-Logical Vitamin D3 Solution – contains sodium benzoate</p> <p>OsteVit-D Oral Liquid – contains sodium benzoate; caramel flavour</p> <p>OsteVit-D Vitamin D3 Oral Drops for Children – contains sodium benzoate 2 mg/mL; butterscotch flavour.</p> <p>Pentavite Infant Liquid – contains sodium saccharin; pineapple flavour.</p> <p>Biological Therapies Vitamin D3 Forte Injection – contains ethyl oleate.</p>
Special comments	<p>Vitamin D content in preterm and term human milk averages 8 and 6 units/100 mL, respectively with median intake averaging 77 units/day (interquartile range 55 to 110).⁽¹²⁾</p> <p>For human milk fed preterm or low birthweight infants, the addition of a human milk fortifier may not reach the recommended daily intake of vitamin D 400 units/day.⁽¹⁾</p> <p>Pentavite Infant 0.45 mL contains 400 units vitamin D3.</p> <p>The adequate calcium intake for term infants based on breast milk calcium content is 200 mg/day and 260 mg/day for babies from 0–6 and 6–12 months of age, respectively.⁽²⁾</p> <p>The recommended intake for very low birth weight infants are: Calcium 150–220 mg/kg/day; and Phosphorous 75–140 mg/kg/day.⁽³⁾</p> <p>For treatment of nutritional rickets, oral calcium 500 mg/day, either as dietary intake or supplements, should be routinely used in conjunction with vitamin D in the treatment regardless of age or weight.⁽²⁾</p> <p>Recommendations in cholestasis: In daily practice, if the infant has severe cholestasis from parenteral nutrition, it is often not possible to achieve vitamin D sufficiency with 1200-8000 units/day cholecalciferol and alternative is to commence calcitriol at a dose of 0.1 microgram/kg daily and follow parathyroid hormone (PTH) and 25-OHD. This is safe, effective and requires less monitoring. Hypercalcemia doesn't occur at this dose. (Expert opinion)</p>
Evidence	<p>Vitamin D intake: Vitamin D has two physiological forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is formed from ultraviolet radiation in plants and yeast, while vitamin D3 is synthesised in the skin from 7-dehydrocholesterol. Vitamin D2 and D3 undergo hydroxylation in the liver to 25-hydroxy vitamin D (calcidiol) and further in the renal tubules to 1,25-(OH)₂ vitamin D (calcitriol), which is the active form of vitamin D.</p> <p>The major forms of vitamin D present in breastmilk are cholecalciferol (vitamin D3), ergocalciferol (vitamin D2), and their respective 25-hydroxylates (25-OH).⁽¹³⁾ Median (IQR) infant daily intake through breast milk of vitamin D and 25-hydroxy vitamin D was 0.1 mg (0.02–0.4 mg) and 0.34 mg (0.24–0.47 mg) respectively, equal to a median (IQR) antirachitic activity of 77 units/day (52–110 units/day).⁽¹²⁾ Exclusively breastfed infants receive <20% of the daily dose (400 units/day) recommended by the Institute of Medicine for infants during the first year of life.^(12, 13) Holder pasteurisation further decreases levels of the major forms of vitamin D in breastmilk by 20%.⁽¹⁴⁾</p>

Vitamin D status: Serum 25-hydroxy vitamin D is the best indicator of vitamin D status. It reflects vitamin D produced cutaneously and obtained from food and supplements⁽¹²⁾ and has a long circulating half-life of 15 days. The classification of vitamin D status, based on serum 25-hydroxy vitamin D is:

Sufficiency: 25-hydroxy vitamin D level >50 nmol/L; insufficiency: 25-hydroxy vitamin D level 30–50 nmol/L; and deficiency: 25-hydroxy vitamin D level <30 nmol/L.^(2, 13)

Nutritional rickets: Rickets is a disorder of growth plate mineralisation and ossification. The diagnosis of nutritional rickets is made on the basis of history, physical examination, and biochemical testing and is confirmed by radiographs – see reviews.^(2, 15-17) Most commonly diagnosed between ages 6 months to 3 years, rickets may present with failure to thrive, short stature, soft skull (craniotables) with delayed closure of the fontanels, muscle weakness, protruding abdomen, enlarged growth plates of long bones (swelling of the ankle, knee, or wrist), costochondral junction rib swelling (rachitic rosary), abnormal chest shape from diaphragmatic pulling (Harrison’s sulcus), late teeth eruption, and delayed motor development. Hypocalcaemia may also cause seizures, cardiac abnormalities including prolonged QT syndrome, and potential cardiac failure.⁽¹⁸⁾

Nutritional rickets is caused by vitamin D deficiency and/or low calcium intake in children.⁽²⁾ Surveys in the UK, Canada and Australia have reported the incidence of symptomatic vitamin D deficiency (radiographic rickets or hypocalcaemic seizures due to vitamin D deficiency) to be between 2.9 and 7.5 per 100,000 children, but vitamin D deficiency rickets is rare in white Caucasian children and the majority of cases are reported in children of African and Asian ethnicity.⁽¹⁹⁾ The estimated incidence of vitamin D deficiency in children ≤ 15 years of age in Australia was 4.9/100000/year, most (98%) had dark or intermediate skin colour and 18% of girls were partially or completely veiled.⁽²⁰⁾

Vitamin D toxicity: Is defined as hypercalcaemia and serum 25-hydroxy Vitamin D > 250 nmol/L, with hypercalciuria and suppressed PTH.⁽²⁾

Vitamin D supplementation for prevention of nutritional rickets:
 A Cochrane systematic review of Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health found 19 studies with a total of 2837 mother-infant pairs assessing vitamin D given to infants (7 studies), vitamin D given to breastfeeding mothers (7 studies) and vitamin D given to infants versus vitamin D given to lactating mothers (6 studies). No studies compared vitamin D given to infants versus periods of infant sun exposure.⁽²¹⁾

Vitamin D supplementation given to infants: Vitamin D at 400 units/day increased 25-hydroxyvitamin D levels and reduced the incidence of vitamin D insufficiency (25-hydroxy vitamin D < 50 nmol/L) (RR 0.57, 95% CI 0.41 to 0.80; participants = 274; studies = 4). The effect was found in subgroup analysis of studies in infants at higher and at lower risk of vitamin D deficiency. However, there was insufficient evidence to determine if vitamin D given to the infant reduces the risk of vitamin D deficiency (25-hydroxy vitamin D < 30 nmol/L) up to 6 months age (RR 0.41, 95% CI 0.16 to 1.05; participants = 122; studies = 2), affects bone mineral content, incidence of biochemical or radiological rickets, or growth. There were no studies of higher doses of infant vitamin D (> 400 units/day) compared to placebo.

Vitamin D supplementation given to lactating mothers: Vitamin D supplementation of lactating mothers increased infant 25-hydroxy vitamin D levels, reduced the incidence of vitamin D insufficiency (RR 0.47, 95% CI 0.39 to 0.57; participants = 512; studies = 5) and vitamin D deficiency (RR 0.15, 95% CI 0.09 to 0.24; participants = 512; studies = 5). Vitamin D supplementation of lactating mothers reduced the incidence of biochemical rickets (RR 0.06, 95% CI 0.01 to 0.44; participants = 229; studies = 2). The two studies that reported biochemical rickets used maternal dosages of oral D3 60,000 units/day for 10 days and oral D3 60,000 units postpartum and at 6, 10, and 14 weeks. However, infant bone mineral content was not reported and there was insufficient evidence to determine if maternal vitamin D supplementation has an effect on radiological rickets (RR 0.76, 95% CI 0.18 to 3.31; participants = 536). All studies of maternal supplementation enrolled populations at high risk of vitamin D deficiency.

Vitamin D supplementation to infants compared with supplementation to lactating mothers:
 Infant vitamin D supplementation compared to lactating mother supplementation increased infant

25-hydroxy vitamin D levels, reduced the incidence of vitamin D insufficiency (RR 0.61, 95% CI 0.40 to 0.94; participants = 334; studies = 4) and vitamin D deficiency (OR 0.32, 95% CI 0.14 to 0.72; participants = 334; studies = 4). Infant bone mineral content and radiological rickets were not reported and there was insufficient evidence to determine if maternal vitamin D supplementation had an effect on infant biochemical rickets. All studies enrolled patient populations at high risk of vitamin D deficiency. Studies compared an infant dose of vitamin D 400 units/day with varying maternal vitamin D doses from 400 units/day to >4000 units/day.

In subgroup analysis there was a significant association between maternal dose of vitamin D and infant 25-hydroxy vitamin D levels with trials supplementing mothers with less than 4000 units/day reporting lower infant 25-hydroxy vitamin D levels.

Higher versus lower dose vitamin D supplementation in term infants: Seventeen trials⁽²²⁻³⁸⁾ reporting 2508 mother-infant pairs compared higher versus lower dose vitamin D supplementation in term infants. Dosages ranged from no supplementation to a maximum 1600 units/day. (10) An intermittent high dose 50,000 units every two months to 6 months was compared to oral D3 200 units/day and 400 units daily to 6 months by a single study.⁽³⁵⁾

Meta-analysis of three trials^(22, 35, 38) including 223 mother-infant pairs found no difference in incidence of vitamin D deficiency (25-hydroxy vitamin D <30 nmol/L) for infant doses 600 units/day to 1200 units/day compared to 400 units/day (RR 0.25, 95% CI 0.01 to 4.92; RD -0.01, 95% CI -0.05 to 0.03). The studies largely enrolled infants at lower risk of vitamin D deficiency.

Meta-analysis of 5 trials^(10, 33, 35, 38, 39) including mother-infant pairs found a reduction in incidence of vitamin D insufficiency (25-hydroxy vitamin D <50 nmol/L) for infant doses 600 units/day to 1600 units/day compared to 400 units/day (RR 0.17, 95% CI 0.05 to 0.54; RD -0.02, 95% CI -0.03 to -0.01). Higher doses of vitamin D have been associated with vitamin D excess (25-hydroxy vitamin D >250 nmol/L) (RR 7.32, 95% CI 1.68 to 31.94; participants = 269; studies = 6). Although vitamin D excess has been reported with doses ranging from as low as 200 units/day⁽³²⁾, the incidence was <5% at doses of 800 and 1200 units/day but occurred in 15 of 16 infants in a trial with a group receiving 1600 units/day which resulted in premature stopping of that study group.⁽¹⁰⁾ Vitamin D toxicity (hypercalcaemia and serum 25OHD > 250 nmol/L) has also been reported with doses of 800 units/day (2 of 32 infants), 1200 units/day (2 of 27 infants) and 1600 units/day (2 of 16 infants) in a single study.⁽¹⁰⁾

There are limited data finding no effect of vitamin D supplementation for term infants on measures of bone health including bone mineral content (MD 1.54 mg/cm, 95% CI -9.61 to 12.70; participants = 760; studies = 3) at doses from no supplementation to 1200 units/day^(25, 26, 39); bone mineral density (MD 0.50 mg/cm², 95% CI -0.70 to 1.70; participants = 704; studies = 1) comparing supplementation with 1200 units/day versus 400 units/day⁽³⁹⁾; or ultrasound speed in bone (MD 6.00, 95% CI -19.72 to 31.72; participants = 212; studies = 1) comparing supplementation with 400 units/day versus no supplementation.⁽²⁸⁾ The incidence of biochemical or radiological rickets has not been reported in studies using >400 units/day supplementation.

Higher versus lower dose vitamin D supplementation in preterm infants: A Cochrane systematic review is currently underway.⁽⁴⁰⁾ Eleven trials⁽⁴¹⁻⁵¹⁾ reporting infants compared higher versus lower dose vitamin D supplementation in term infants. Dosages ranged from no supplementation to a maximum 1600 units/day.⁽¹⁰⁾ An intermittent high dose 50,000 units every two months to 6 months age was compared to oral D3 200 units/day and 400 units daily to 6 months of age in a single study.⁽³⁵⁾

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doses of 800 and 1200 units/day but occurred in 15 of 16 infants in a trial with a group receiving 1600 units/day which resulted in premature stopping of that study group.⁽¹⁰⁾ Vitamin D toxicity (hypercalcaemia and serum 25-hydroxy vitamin D > 250 nmol/L) has also been reported with doses of 800 units/day (2 of 32 infants), 1200 units/day (2 of 27 infants) and 1600 units/day (2 of 16 infants) in a single study.⁽¹⁰⁾

There are limited data in the effect of vitamin D supplementation for preterm infants on measures of bone health. Overall, there was no effect on bone mineral content (MD -5.10 mg/cm, 95% CI -14.13 to 3.93; participants = 68; studies = 1) in a single study comparing 800 units/day versus 400 units/day (49); or bone mineral density (MD -2.50 mg/cm², 95% CI -10.28 to 5.28; participants = 107; studies = 2).^(45, 49) Meta-analysis of 2 trials comparing 1000 units/day versus 400 units/day in preterm infants without human milk fortification or additional mineral supplementation found a reduction in biochemical rickets (RR 0.25, 95% CI 0.12 to 0.50; participants = 149; studies = 2).^(48, 51) No studies reported biochemical rickets in preterm infants receiving additional mineral supplements. There was no difference radiological rickets in trials comparing 400 units/day versus 200 units/day in preterm infants without human milk fortification or additional mineral supplementation (RR 3.00, 95% CI 0.66 to 13.69; participants = 101; studies = 2)^(43, 47), and no infant had radiological rickets in a single trial comparing 800 units/day versus 400 units/day (n=42).⁽⁴⁷⁾ A single trial comparing 1000 units/day versus 400 units/day reported a reduction in radiological rickets in preterm infants without human milk fortification or additional mineral supplementation (RR 0.40, 95% CI 0.19 to 0.86; participants = 50).⁽⁴⁸⁾

Vitamin D supplementation for management of nutritional rickets: Nutritional rickets (NR) is caused by vitamin D deficiency and/or low calcium intake. The diagnosis of NR is made on the basis of history, physical examination and biochemical testing [decreased 25-hydroxyvitamin D, serum phosphorus and calcium, urinary calcium, and elevated PTH, ALP, and urinary phosphorus levels] and is confirmed by radiographs.^(2, 16, 17)

A systematic review of vitamin D, calcium or a combination of vitamin D and calcium for the treatment of nutritional rickets included 4 RCTs enrolling 286 children found low-certainty evidence that vitamin D plus calcium or calcium alone improved healing in children with nutritional rickets compared to vitamin D alone.⁽⁵²⁾ Three of the studies used a single oral or IM dose of vitamin D 600,000 units and the other vitamin D2 50,000 units orally once every 4 weeks for 24 weeks. [LOE I GOR B – children]

Recommendations for dose of vitamin D treatment of nutritional rickets are largely based on review of observational studies.⁽²⁾ The minimal recommended dose of vitamin D is 2000 units/day (50 µg/day) for a minimum of 3 months. Oral treatment more rapidly restores 25-hydroxy vitamin D levels than IM treatment. For daily treatment, both D2 and D3 are equally effective. Oral calcium, 500 mg/day, either as dietary intake or supplements, should be routinely used in conjunction with vitamin D in the treatment regardless of age or weight.

Infants with cholestasis/malabsorption: Limited data support the dosing of vitamin D in infants with cholestasis or intestinal malabsorption – see reviews.^(8, 53, 54) Cholestasis (conjugated bilirubin ≥34 micrograms/L) predisposes to the development of fat-soluble vitamin deficiency.⁽⁸⁾ In an observational study of 92 infants with cholestasis, colecalciferol or ergocalciferol 1200 units increased by increments of 1200 units to 8000 units orally daily, or alternatively calcitriol at 0.05 to 0.2 microgram/kg per day, did not achieve target 25-hydroxy vitamin D >50 nmol/L in all infants.⁽⁴⁾ [LOE III-3]. Please refer to Vitamins in cholestasis formulary for further guidance.

Safety

Vitamin D toxicity is defined as hypercalcaemia and serum 25-hydroxy vitamin D vitamin D ≥ 250 nmol/L, with hypercalciuria and suppressed PTH.⁽²⁾ High 25-hydroxy vitamin D concentrations can cause hypercalcaemia, hypercalciuria and if prolonged, nephrocalcinosis and renal failure. Vitamin D excess (serum 25-hydroxy vitamin D ≥ 250 nmol/L) is not usually seen in unsupplemented individuals.⁽⁵⁵⁾

Although vitamin D excess has been reported with doses ranging from as low as 200 units/day⁽³²⁾, the incidence was <5% at doses of 800 and 1200 units/day but occurred in 15 of 16 infants in a trial with a group receiving 1600 units/day which resulted in premature stopping of that study group.⁽¹⁰⁾ Vitamin D toxicity (hypercalcaemia and serum 25OH vitamin D > 250 nmol/L) has also been

	<p>reported with doses of 800 units/day (2 of 32 infants), 1200 units/day (2 of 27 infants) and 1600 units/day (2 of 16 infants) in a single study.⁽¹⁰⁾</p> <p>In areas where 25-hydroxy vitamin D assays are not readily available, suppression of PTH in the presence of hypercalcaemia and pharmacological doses of vitamin D may support the diagnosis of vitamin. When PTH assay is also unavailable, the possibility of toxicity should be considered in the presence of symptomatic hypercalcaemia in association with pharmacological doses of vitamin D.⁽²⁾</p> <p>Maternal daily doses of 400 to 6,400 units have not been associated with any short-term biochemical abnormalities in breastfed infants^(13, 18) or adults^(56, 57).</p>
<p>Practice points</p>	<p>Global Consensus Recommendations on Prevention and Management of Nutritional Rickets:</p> <ul style="list-style-type: none"> • Vitamin D supplementation for the prevention of rickets and osteomalacia: 400 units/day (10 micrograms) is adequate to prevent rickets and has been recommended for all infants from birth to 12 months of age, independent of their mode of feeding.^(3,38) [LOE consensus]. • This recommendation has been made as nutritional rickets remains prevalent despite attempts to target at risk populations. However, evidence to date is insufficient to determine if infants at low risk of vitamin D deficiency benefit from supplementation. • The adequate calcium intake for term infants based on breast milk calcium content is 200 mg/day and 260 mg/day for babies from 0–6 and 6–12 months of age, respectively.^(3,38) <p>Infants at risk of vitamin D deficiency:</p> <ul style="list-style-type: none"> • Infants at increased risk of vitamin D deficiency and nutritional rickets due to pigmentation, covering or avoidance of sun exposure, and/or latitude (insufficient UV intensity most of the year at latitudes above 52°N or below 52°S), or preterm or low birthweight delivery, or maternal vitamin D deficiency. • Infants at risk of vitamin D deficiency should receive 400 units/day vitamin D from birth to 12 months age.⁽²¹⁾ [LOE I, GOR B]. • Infants born very preterm or very low birthweight should receive adequate mineral intake through use of human milk fortifiers or preterm infant formula where appropriate. The recommended intake for very low birth weight infants are: Calcium 150–220 mg/kg/day; and Phosphorous 75–140 mg/kg/day.⁽³⁾ • The evidence is insufficient to determine if higher doses of vitamin D (>400 units/day) prevent vitamin D deficiency or nutritional rickets in preterm infants with adequate mineral supplementation. <p>Infants with cholestasis^(4, 8):</p> <ul style="list-style-type: none"> • Commence on vitamin D3 1200 units/day. • Monitor every 1 to 3 months. • Increase vitamin D3 by 1200 units/day to maximum 8000 units/day to maintain vitamin D sufficiency (25OH vitamin D ≥ 50 nmol/L). • Alternatively, calcitriol at 0.05–0.20 µg/kg daily. [LOE III-3, GOR B] • ANMF consensus: Refer to vitamins in cholestasis formulary for the consensus recommendations. <p>Treatment of nutritional rickets</p> <ul style="list-style-type: none"> • For treatment of nutritional rickets, the minimal recommended infant dose of vitamin D is 2000 units/day (50 micrograms) for a minimum of 3 months.^(3,38) [LOE II, GOR B]. • Oral calcium, 500 mg/day, either as dietary intake or supplements, should be routinely used in conjunction with vitamin D in the treatment regardless of age or weight.^(3,38) [LOE I, GOR B].
<p>References</p>	<ol style="list-style-type: none"> 1. South Australian Neonatal Medication Guidelines. Nutrient delivery comparison tables: Preterm Infants. 2019. https://www.sahealth.sa.gov.au/wps/wcm/connect/14e027d5-a21b-40d1-84e8-3b03d9b1bc8a/Nutrient+delivery+comparison+tables_Preterm+Infants_Neo_v1.0.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-14e027d5-a21b-40d1-84e8-3b03d9b1bc8a-n5hZXZA. Accessed 01/09/2020. 2. Munns C F, Shaw N, Kiely M. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. <i>Journal of Clinical Endocrinology and Metabolism</i>. 2016;101(2):394-415. 3. Abrams SA, Bhatia JJS, Corkins MR, De Ferranti SD, Golden NH, Silverstein J, et al. Calcium and vitamin D requirements of enterally fed preterm infants. <i>Pediatrics</i>. 2013;131(5):e1676-e83.

4. Shneider BL, Magee JC, Bezerra JA, Haber B, Karpen SJ, Raghunathan T, et al. Efficacy of fat-soluble vitamin supplementation in infants with biliary atresia. *Pediatrics*. 2012;130(3):e607-14.
5. Nair P, Venkatesh B, Hoechter DJ, Buscher H, Kerr S, Center JR, et al. Vitamin D Status and Supplementation in Adult Patients Receiving Extracorporeal Membrane Oxygenation. *Anaesthesia and Intensive Care*. 2018;46(6):589-95.
6. Hahn D, Hodson EM, Craig JC. Interventions for metabolic bone disease in children with chronic kidney disease. *Cochrane Database of Systematic Reviews*. 2015(11).
7. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. *New England Journal of Medicine*. 2017;377(18):1765-76.
8. Lane E, Murray KF. Neonatal Cholestasis. *Pediatr Clin North Am*. 2017;64(3):621-39.
9. Pohlandt F. Prevention of postnatal bone demineralization in very low-birth-weight infants by individually monitored supplementation with calcium and phosphorus. *Pediatric Research*. 1994;35(1):125-9.
10. Gallo S, Comeau K, Vanstone C, Agellon S, Sharma A, Jones G, et al. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: a randomized trial. *JAMA - journal of the american medical association DBP - EDAT: 2013/05/02 06:00*. 2013;309(17):1785-92 MISC4.
11. Zeghoud F, Ben-Mekhbi H, Djeghri N, Garabedian M. Vitamin D prophylaxis during infancy: comparison of the long-term effects of three intermittent doses (15, 5, or 2.5 mg) on 25-hydroxyvitamin D concentrations. *Am J Clin Nutr*. 1994;60(3):393-6.
12. vi Strey S, Hojskov CS, Moller UK, Heickendorff L, Vestergaard P, Mosekilde L, et al. Vitamin D content in human breast milk: a 9-mo follow-up study. *American Journal of Clinical Nutrition*. 2016;103(1):107-14.
13. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. Vitamin D. [Updated 2020 Apr 20]. Bookshelf URL: <https://www.ncbi.nlm.nih.gov/books/>. 2020.
14. Gomes FP, Shaw PN, Whitfield K, Koorts P, McConachy H, Hewavitharana AK. Effect of pasteurisation on the concentrations of vitamin D compounds in donor breastmilk. *Int J Food Sci Nutr*. 2016;67(1):16-9.
15. Haggerty Linda L. Maternal Supplementation for Prevention and Treatment of Vitamin D Deficiency in Exclusively Breastfed Infants. *Breastfeeding Medicine*. 2010;6:137-44.
16. Shore Richard M, Chesney Russell W. Rickets: Part I. *Pediatric Radiology*. 2013;43:140-51.
17. Shore RM, Chesney RW. Rickets: Part II. *Pediatric radiology*. 2013;43(2):152-72.
18. Haggerty LL. Maternal supplementation for prevention and treatment of vitamin d deficiency in exclusively breastfed infants. *Breastfeeding Medicine*. 2011;6(3):137-44.
19. Moon R J, Harvey N C, Davies J H, Cooper C. Vitamin D and skeletal health in infancy and childhood. *Osteoporosis International*. 2014;25:2673-84.
20. Munns CF, Simm PJ, Rodda CP, Garnett SP, Zacharin MR, Ward LM, et al. Incidence of vitamin D deficiency rickets among Australian children: an Australian Paediatric Surveillance Unit study. *The Medical journal of Australia*. 2012;196(7):466-8.
21. Tan ML, Abrams SA, Osborn DA. Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health. *Cochrane Database of Systematic Reviews*. 2020(6).
22. Ala-Houhala M. 25-Hydroxyvitamin D levels during breast-feeding with or without maternal or infantile supplementation of vitamin D. *Journal of pediatric gastroenterology and nutrition*. 1985;4(2):220-6.
23. Alonso A, Rodriguez J, Carvajal I, Prieto MA, Rodriguez RM, Perez AM, et al. Prophylactic vitamin D in healthy infants: assessing the need. *Metabolism: clinical and experimental*. 2011;60(12):1719-25.
24. Chandy DD, Kare J, Singh SN, Agarwal A, Das V, Singh U, et al. Effect of vitamin D supplementation, directly or via breast milk for term infants, on serum 25 hydroxyvitamin D and related biochemistry, and propensity to infection: a randomised placebo-controlled trial. *The British journal of nutrition*. 2016;116(1):52-8.

25. Greer FR, Marshall S. Bone mineral content, serum vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without vitamin D2 supplements. *The Journal of pediatrics*. 1989;114(2):204-12.
26. Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC. Bone mineral content and serum 25-hydroxyvitamin D concentration in breast-fed infants with and without supplemental vitamin D. *The Journal of pediatrics*. 1981;98(5):696-701.
27. Greer FR, Searcy JE, Levin RS, Steichen JJ, Steichen-Asche PS, Tsang RC. Bone mineral content and serum 25-hydroxyvitamin D concentrations in breast-fed infants with and without supplemental vitamin D: one-year follow-up. *The Journal of pediatrics*. 1982;100(6):919-22.
28. Hibbs AM, Ross K, Kerns LA, Wagner C, Fuloria M, Groh-Wargo S, et al. Effect of Vitamin D supplementation on recurrent wheezing in black infants who were born preterm the D-Wheeze randomized clinical trial. *JAMA - Journal of the American Medical Association*. 2018;319(20):2086-94.
29. Madar AA, Klepp KI, Meyer HE. Effect of free vitamin D(2) drops on serum 25-hydroxyvitamin D in infants with immigrant origin: a cluster randomized controlled trial. *European journal of clinical nutrition*. 2009;63(4):478-84.
30. Moodley A, Spector SA. Single high-dose vitamin D at birth corrects vitamin D deficiency in infants in Mexico. *International journal of food sciences and nutrition*. 2015;66(3):336-41.
31. Ponnappakkam T, Bradford E, Gensure R. Vitamin D supplementation in breastfed infants: Results of a prospective trial in the southern United States. *Journal of Bone and Mineral Research*. 2010;25(SUPPL. 1):S232.
32. Ponnappakkam T, Bradford E, Gensure R. A treatment trial of vitamin D supplementation in breast-fed infants: universal supplementation is not necessary for rickets prevention in Southern Louisiana. *Clinical pediatrics*. 2010;49(11):1053-60.
33. Rothberg AD, Pettifor JM, Cohen DF. Maternal-infant vitamin D relationships during breast-feeding. *Journal of Pediatrics*. 1982;101(4):500-3.
34. Rueter K, Jones AP, Siafarikas A, Lim EM, Bear N, Noakes PS, et al. Direct infant UV light exposure is associated with eczema and immune development. *Journal of Allergy and Clinical Immunology*. 2019;143(3):1012-20.e2.
35. Shakiba M, Sadr S, Nefei Z, Mozaffari-Khosravi H, Lotfi MH, Bemanian MH. Combination of bolus dose vitamin D with routine vaccination in infants: a randomised trial. *Singapore medical journal*. 2010;51(5):440-5.
36. Siafarikas A, Piazena H, Feister U, Bulsara MK, Meffert H, Hesse V. Randomised controlled trial analysing supplementation with 250 versus 500 units of vitamin D3, sun exposure and surrounding factors in breastfed infants. *Archives of disease in childhood*. 2011;96(1):91-5.
37. Tomimoto K. A study of vitamin D supplementation in breast fed infant with vitamin D deficiency. *The Journal of the Japan Pediatric Society*. 2018;122(11):1683-91.
38. Ziegler EE, Nelson SE, Jeter JM. Vitamin D supplementation of breastfed infants: a randomized dose-response trial. *Pediatric research*. 2014;76(2):177-83.
39. Rosendahl J, Valkama S, Holmlund-Suila E, Enlund-Cerullo M, Hauta-Alus H, Helve O, et al. Effect of Higher vs Standard Dosage of Vitamin D3 Supplementation on Bone Strength and Infection in Healthy Infants: A Randomized Clinical Trial. *Jama, Pediatr*. 2018;172(7):646-54.
40. Pharande P, Pammi M, Collins CT, Zhou SJ, Abrams SA. Vitamin D supplementation for prevention of vitamin D deficiency in preterm and low birth weight infants. *Cochrane Database of Systematic Reviews*. 2015(2).
41. Abdel-Hady H, Yahia S, Megahed A, Mosbah A, Seif B, Nageh E, et al. Mediators in Preterm Infants With Late-onset Sepsis: A Randomized Controlled Trial. *Journal of pediatric gastroenterology and nutrition*. 2019;68(4):578-84.
42. Al-Beltagi M, Rowiesha M, Elmashad A, Elrifay SM, Elhorany H, Koura HG. Vitamin D status in preterm neonates and the effects of its supplementation on respiratory distress syndrome. *Pediatric Pulmonology*. 2020;55(1):108-15.
43. Alizadeh Taheri P, Sajjadian N, Beyrami B, Shariat M. Prophylactic effect of low dose vitamin D in osteopenia of prematurity: a clinical trial study. *Acta Med Iran*. 2014;52(9):671-4.

44. Anderson-Berry A, Thoene M, Wagner J, Lyden E, Jones G, Kaufmann M, et al. Randomized trial of two doses of vitamin D3 in preterm infants <32 weeks: Dose impact on achieving desired serum 25(OH)D3 in a NICU population. *PLoS One*. 2017;12(10):e0185950.

45. Backstrom MC, Maki R, Kuusela AL, Sievanen H, Koivisto AM, Koskinen M, et al. The long-term effect of early mineral, vitamin D, and breast milk intake on bone mineral status in 9- to 11-year-old children born prematurely. *Journal of pediatric gastroenterology and nutrition*. 1999;29(5):575-82.

46. Kishore SS, Gadiraju M. Study of daily vitamin D supplementation in preterm infants: A randomized trial. *Journal of Pediatric Gastroenterology and Nutrition*. 2019;68 (Supplement 1):1167.

47. Koo W, Walyat N. Vitamin D and Skeletal Growth and Development. *Current Osteoporosis Reports*. 2013;11:188-93.

48. Mathur NB, Saini A, Mishra TK. Assessment of adequacy of supplementation of vitamin D in very low birth weight preterm neonates: A randomized controlled trial. *Journal of Tropical Pediatrics*. 2016;62(6):429-35.

49. Natarajan CK, Sankar MJ, Agarwal R, Pratap OT, Jain V, Gupta N, et al. Trial of daily vitamin D supplementation in preterm infants. *Pediatrics*. 2014;133(3):e628-e34.

50. Pittard IWB, Geddes KM, Hulsey TC, Hollis BW. How much vitamin D for neonates? *American Journal of Diseases of Children*. 1991;145(10):1147-9.

51. Tergestina M, Rebekah G, Job V, Simon A, Thomas N. A randomized double-blind controlled trial comparing two regimens of Vitamin D supplementation in preterm neonates. *Journal of Perinatology*. 2016;36(9):763-7.

52. Chibuzor MT, Graham-Kalio D, Osaji JO, Meremikwu MM. Vitamin D, calcium or a combination of vitamin D and calcium for the treatment of nutritional rickets in children. *Cochrane Database of Systematic Reviews*. 2020;2020 (4) (no pagination)(CD012581).

53. Dani C, Pratesi S, Raimondi F, Romagnoli C, Task Force for Hyperbilirubinemia of the Italian Society of N. Italian guidelines for the management and treatment of neonatal cholestasis. *Ital J Pediatr*. 2015;41:69.

54. Bhatia V, Bavdekar A, Matthai J, Waikar Y, Sibal A. Management of neonatal cholestasis: consensus statement of the Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics. *Indian Pediatr*. 2014;51(3):203-10.

55. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. *Nature Reviews Endocrinology*. 2017;13(8):466-79.

56. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC. Benefit-risk assessment of vitamin D supplementation. *Osteoporosis International*. 2010;21(7):1121-32.

57. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *American Journal of Clinical Nutrition*. 2007;85(1):6-18.

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