

<b>Alert</b>	Colecalciferol (Vitamin D3) is the inactive form of vitamin D. 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) Some preparations may contain sodium benzoate - Avoid exposure of >99mg/kg/day in neonates.
<b>Indication</b>	Prevention and treatment of vitamin D deficiency and nutritional rickets (in combination with adequate mineral intake).
<b>Action</b>	Regulating body levels of calcium and phosphorus, and mineralization of bone
<b>Drug type</b>	Fat soluble vitamin
<b>Trade name</b>	Bio-Logical Vitamin D3 Solution Ostelin Vitamin D OsteVit-D Liquid OsteVit-D Vitamin D3 Oral Drops for Children Penta-vite Infant Liquid Multivitamin Oral liquid
<b>Presentation</b>	Ostelin Vitamin D Oral Liquid - vitamin D3 1000 units (colecalciferol 25 microgram)/0.5 mL liquid  Penta-vite Infant Liquid Multivitamin Oral Liquid - Per 0.45 mL: <b>vitamin D3 404 units (colecalciferol 10.1 microgram)</b>  Biological Therapies Vitamin D3 Forte ampoules - 600 000 units/mL (15mg/mL of colecalciferol) for intramuscular injection.  <b>The following preparations contain sodium benzoate as an excipient:</b> Bio-Logical Vitamin D3 Oral Solution – 1000 units per 0.2 mL vitamin D3 OsteVit-D Oral Liquid - vitamin D3 1000 units (colecalciferol 25 microgram)/0.2 mL liquid OsteVit-D Vitamin D3 Oral Drops for Children - vitamin D3 200 units (colecalciferol 5 microgram) per drop (0.04 mL)
<b>Dose</b>	<b>Prevention of rickets and osteomalacia in infants at risk of vitamin D insufficiency/deficiency (see practice points):</b> <b>Term infants:</b> vitamin D3 400 units/day (colecalciferol 10 microgram) until 12 months age (2) <b>Preterm infants:</b> (3) <1500 g: vitamin D3 200-400 units/day (colecalciferol 5-10 microgram). >>1500 g: vitamin D3 400 units/day (colecalciferol 10 microgram).  <b>Infants with cholestasis:</b> (Refer to special comments section) (4) Commence on vitamin D3 1200 units/day (colecalciferol 30 microgram). Monitor every 1 to 3 months. Increase vitamin D3 by 1200 units/day (colecalciferol 30 microgram) to maximum 8000 units/day (colecalciferol 200 microgram) to maintain vitamin D sufficiency (25-hydroxy vitamin D ≥ 50 nmol/L). Alternatively, calcitriol at 0.05–0.20 microgram/kg daily.  <b>Treatment of nutritional rickets:</b> Vitamin D3 2000 units/day (colecalciferol 50 microgram) for a minimum of 3 months. (3) Alternatively if oral administration is difficult, consider intramuscular vitamin D3 100 000 units (colecalciferol 2.5 mg) every 3 months (3 doses). Continue maintenance vitamin D3 after resolution of nutritional rickets. Ensure adequate calcium intake – see special comments.
<b>Dose adjustment</b>	Therapeutic hypothermia: no information. ECMO: Adult patients on ECMO were at high risk of vitamin D deficiency and repeated doses of colecalciferol were required to correct the deficiency (5). Renal impairment: Vitamin D supplementation may be offered to patients with chronic kidney disease in whom circulating vitamin D levels have been documented as low. Hydroxylated vitamin D

	agents (eg. calcitriol) may be needed in addition to control progressive secondary hyperparathyroidism (6,7). Hepatic impairment: absorption of fat-soluble vitamins is impaired in cholestasis (see infants with cholestasis). (8)
<b>Maximum dose</b>	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. A dose of vitamin D3 1600 units/day produced vitamin D toxicity (hypercalcaemia and 25OH vitamin D >250 nmol/L) in 94% of infants. (10) Single doses 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)
<b>Total cumulative dose</b>	
<b>Route</b>	Oral Intramuscular
<b>Preparation</b>	Administer undiluted.
<b>Administration</b>	Oral: May be administered without regard to meals. Intramuscular: inject slowly into anterolateral thigh.
<b>Monitoring</b>	<b>Healthy infants:</b> no routine 25OHD screening recommended (2). <b>Infants with cholestasis:</b> monitor 25OHD every 1 to 3 months. Maintain vitamin D sufficiency (25-hydroxyvitamin D $\geq$ 50 nmol/L).(4, 8) <b>For very low birth weight or preterm infants with nutritional rickets:</b> 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 $\geq$ 1.2mmol/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 maximizing calcium and phosphorus intake and minimizing factors leading to bone mineral loss.(3)
<b>Contraindications</b>	Hypersensitivity to colecalciferol, Hypervitaminosis D
<b>Precautions</b>	Hypercalcaemia and hyperparathyroidism - avoid a high calcium intake and limit vitamin D supplementation with colecalciferol. 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.
<b>Drug interactions</b>	Magnesium-containing antacids (concurrent use with vitamin D may result in hypermagnesaemia, especially in patients with chronic renal failure). 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. Calcitonin – reduces serum calcium levels. 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. Calcium-containing preparations in high doses. Diuretics, thiazide (concurrent use with vitamin D may increase the risk of hypercalcaemia). Cholestyramine, colestipol and mineral oils may interfere with fat soluble vitamin absorption. Corticosteroids - vitamin D supplementation may be recommended for prolonged corticosteroids use, because corticosteroids may interfere with vitamin D action.

	<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 analogs - concurrent use with another analog, especially calcifediol, is not recommended because of additive effects and increased potential for toxicity.</p>
<b>Adverse reactions</b>	<p>A dose of vitamin D3 1600 units/day produced vitamin D toxicity (hypercalcaemia and 25-hydroxy vitamin D &gt;250 nmol/L) in 94% of 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 generalized vascular calcification, nephrocalcinosis, and other soft tissue calcification that may lead to hypertension and renal failure. 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>
<b>Compatibility</b>	No information – do not mix.
<b>Incompatibility</b>	No information
<b>Stability</b>	No information
<b>Storage</b>	VITAMIN D3 FORTE – store below 25°C. For other brands – refer to product information.
<b>Excipients</b>	<p>Sodium benzoate: Some vitamin D preparations contain sodium benzoate. Avoid exposure of &gt;99mg/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>Penta-vite Infant Liquid Multivitamin Oral Liquid - contains sodium saccharin; pineapple flavour.</p> <p>Biological Therapies Vitamin D3 Forte Injection - contains ethyl oleate</p>
<b>Special comments</b>	<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>Penta-vite Infant 0.45 mL contains 404 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>
<p><b>Evidence</b></p>	<p><b>Vitamin D intake:</b> 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)<sub>2</sub> 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 0.10 mg (0.02–0.40 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 &lt;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 pasteurization further decreases levels of the major forms of vitamin D in breastmilk by 20%. (14)</p> <p><b>Vitamin D status:</b> 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:</p> <p>Sufficiency: 25-hydroxy vitamin D level &gt;50 nmol/L; insufficiency: 25-hydroxy vitamin D level 30–50 nmol/L; and deficiency: 25-hydroxy vitamin D level &lt;30 nmol/L (2, 13).</p> <p><b>Nutritional rickets:</b> Rickets is a disorder of growth plate mineralization 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 (craniotabes) with delayed closure of the fontanel, 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)</p> <p>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)</p> <p><b>Vitamin D toxicity:</b> Is defined as hypercalcaemia and serum 25-hydroxy Vitamin D &gt; 250 nmol/L, with hypercalciuria and suppressed PTH.(2)</p> <p><b>Vitamin D supplementation for prevention of nutritional rickets:</b> A Cochrane systematic review (21) 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.</p> <p><b>Vitamin D supplementation given to infants:</b> Vitamin D at 400 units/day increased 25-hydroxyvitamin D levels and reduced the incidence of vitamin D insufficiency (25-hydroxy vitamin D</p>

< 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 till 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 given to infants compared with supplementation given to lactating mothers:** Infants 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 has 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/cm<sup>2</sup>, 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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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 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/cm<sup>2</sup>, 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 (47) (n=42). 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 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

	<p>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 600000 units, and the other vitamin D2 50000 units orally once every 4 weeks for 24 weeks. [LOE I GOR B – children]</p> <p>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.</p> <p><b>Infants with cholestasis / malabsorption:</b> 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, coledcalciferol or ergocalciferol 1200 units increased by increments of 1200 units to 8000 units orally daily, or alternatively calcitriol at 0.05 to 0.20 mg/kg per day, did not achieve target 25-hydroxy vitamin D &gt;50 nmol/L in all infants (4). [LOE III-3]</p> <p><b>Safety</b></p> <p>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).</p> <p>Although vitamin D excess has been reported with doses ranging from as low as 200 units/day (32), the incidence was &lt;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 &gt; 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).</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. 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). 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><b>Practice points</b></p>	<p><b>Global Consensus Recommendations on Prevention and Management of Nutritional Rickets:</b></p> <ul style="list-style-type: none"> <li>• 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]</li> <li>• 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.</li> <li>• 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)</li> </ul> <p><b>Infants at risk of vitamin D deficiency:</b></p> <ul style="list-style-type: none"> <li>• 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.</li> </ul>

	<ul style="list-style-type: none"> <li>• Infants at risk of vitamin D deficiency should receive 400 units/day vitamin D from birth to 12 months age. [LOE I, GOR B] (21)</li> <li>• 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)</li> <li>• The evidence is insufficient to determine if higher doses of vitamin D (&gt;400 units/day) prevent vitamin D deficiency or nutritional rickets in preterm infants with adequate mineral supplementation.</li> </ul> <p><b>Infants with cholestasis (4, 8):</b></p> <ul style="list-style-type: none"> <li>• Commence on vitamin D3 1200 units/day.</li> <li>• Monitor every 1 to 3 months.</li> <li>• Increase vitamin D3 by 1200 units/day to maximum 8000 units/day to maintain vitamin D sufficiency (25OH vitamin D ≥ 50 nmol/L).</li> <li>• Alternatively, calcitriol at 0.05–0.20 µg/kg daily. [LOE III-3, GOR B]</li> </ul> <p><b>Treatment of nutritional rickets</b></p> <ul style="list-style-type: none"> <li>• 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]</li> <li>• 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]</li> </ul>
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VERSION/NUMBER	DATE
Original	15/11/2016
Version 2.0	15/10/2020
Current 3.0	20/05/2021
REVIEW	20/05/2026

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