VITAMIN D THERAPY - SCH

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Vitamin D is essential for good bone health and has many other important functions in overall health.
- Deficiency is defined as a 25-hydroxyvitamin D level below 50 nanomol/L.
- Supplementation can be given on a daily basis or in some cases as a once off high dose.
- There is a small but significant risk of hypercalcaemia and nephrocalcinosis following treatment (especially with a once off high dose). Close monitoring and follow-up is therefore important.

CHANGE SUMMARY

- Document due for mandatory review.
- Replaces SCH document C.20.24 ***Vitamin D ("STOSS") Therapy – SCH.***
- Recommendations about Stoss therapy have been changed due to increased awareness of autosomal recessive enzyme mutations that may lead to hypercalcaemia and related significant consequences.

READ ACKNOWLEDGEMENT

- This document should be read by anyone investigating possible Vitamin D deficiency and before initiating treatment.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
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Team Leader:	Staff Specialist	**Area/Dept:** Endocrinology SCH

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Background [2]

In Australia over 90% of vitamin D is derived from sunlight[2]. In the USA, dietary sources form a higher percentage because milk, orange juice & cereals have all been fortified with vitamin D for many decades.

Dietary sources include salmon, mackerel, tuna, sardines and liver with small amounts in eggs. Dietary calcium and iron deficiency occur with increased frequency in the vitamin D deficient population. Rickets may be caused by vitamin D, calcium, or phosphate deficiency.

Daily requirements [1, 2]

Recommended Daily Allowance (RDA) of Vitamin D is 400 international units.
400 international units = 10 micrograms of cholecalciferol (vitamin D3).

Recommendations about increased sun exposure must be balanced against long-term risks of skin cancer. Depending on skin colour and latitude, about 20 minutes per day has been recommended to maintain normal vitamin D levels.[10] See Appendix A for sunlight exposure and protection guidelines in infants, children and adolescents in Australia and New Zealand.

Groups at risk of Vitamin D deficiency [2:]

- Infants born to vitamin D deficient mothers.
- Exclusively breastfed babies in combination with at least one other risk factor.
- Dark skin (Fitzpatrick V and VI).
- Limited sun exposure e.g. chronic disability or hospitalisation, covered clothing.
- Conditions affecting vitamin D absorption, storage and metabolism e.g. inflammatory bowel disease (IBD), coeliac disease, cystic fibrosis, obesity and renal disease.
- Use of medications which increase vitamin D metabolism e.g. rifampicin, corticosteroids and some anticonvulsants.

Vitamin D [2, 3]

"Vitamin D" (calciferol) refers to both cholecalciferol (vitamin D3) derived from animal sources and ergocalciferol (vitamin D2) derived from plant sources. Vitamin D has a half-life of greater than 1- 2 months.

The actions of vitamin D are to:

i. Enhance absorption of calcium and phosphate from the small intestine;

ii. Modify serum calcium concentration, both directly and through parathyroid hormone;

iii. Promote skeletal mineralisation.

To become active these vitamins need to be hydroxylated to 1, 25 dihydroxy-vitamin D (calcitriol). Any excess of cholecalciferol or ergocalciferol is converted to 24, 25 dihydroxy-vitamin D, which is inactive. Mutations in the enzymes involved in the inactivation process such as CYP24A1 have been discovered and may lead to vitamin D sensitivity and potential toxicity with therapy.

Treatment with cholecalciferol is preferred over ergocalciferol due to higher bioavailability. Calcitriol should not be used in the treatment of vitamin D deficiency unless there is severe hypocalcaemia, in which case its use needs to be closely monitored to avoid hypercalcaemia.

Investigations [5]

Baseline blood tests:

- Calcium, Magnesium, Phosphate, ionised Calcium
- Albumin
- Alkaline Phosphatase (ALP)
- 25-hydroxyvitamin D
- Parathyroid hormone (PTH)

Measurement of 1, 25 hydroxyvitamin D is of no value unless an inherited disorder of vitamin D metabolism is suspected.

Vitamin D deficiency is present when[2];

25-hydroxyvitamin D is below 50 nanomol/L, usually with elevated PTH, +/- elevated ALP, +/- hypocalcaemia. Phosphate levels may be variable.

Mild deficiency: 30-49 nanomol/L

Moderate deficiency: 12.5-29 nanomol/L

Severe deficiency: <12.5 nanomol/L

When vitamin D deficiency is diagnosed consider the following:

- X-Ray knee for evidence of radiological rickets if symptomatic or if vitamin D deficiency is severe. If rickets is evident on the initial knee X-Ray, then repeat 6 months after treatment course to check for healing.
- FBC and iron studies (Iron deficiency is associated with vitamin D deficiency)
- In the case of vitamin D deficient breast-fed infant, check 25- hydroxyvitamin D level of the mother

Therapy

If symptomatic hypocalcaemia is present (seizures, tetany) treat initially with IV calcium infusion and oral calcitriol and consult endocrinology.

Ensure dietary calcium intake is adequate and arrange dietician assessment.

Initiate vitamin D and/or calcium supplementation according to age, risk factors, potential for poor compliance and dietary intake.

Options include daily dosing for 3 months or single high dose treatment (Stoss).

Daily dosing: (for 3 months)

	<1yo	>1yo
Mild deficiency	400 international units/ day	1000 international units/ day
Moderate or severe deficiency	1000 international units/ day	2000-4000 international units/ day

Products available for routine Vitamin D supplementation include:

- Vitamin D (Cholecalciferol) capsule:
  - Ostelin® or Vita D®
  - 1000 international units/ capsule
- Vitamin D (Cholecalciferol) solution:
  - Ostevit D® = 1000 international units/ 0.2mL
  - Ostelin Vitamin D Liquid® = 1000 international units/ 0.5mL
  - Ostelin Vitamin D Liquid Kids®= 200 international units/ 0.5mL
- Calcium Carbonate and Vitamin D e.g. Caltrate with Vitamin D®
  - 600mg elemental calcium with 200 international units cholecalciferol per tablet

Blood tests for Vitamin D, calcium, magnesium, phosphate, PTH and ALP should be done after **1 and 3 months.**

Stoss: (Stosstherapie - German; stiessen/stoss-to push)

Indication:

Single high dose therapy has been used since the 1930's to treat rickets. Giving a large dose should last most of a year. Therefore Stoss therapy presents an alternative to daily dosing in patients presenting with symptoms of vitamin D deficiency where adherence to daily medication use may be an issue. In certain groups such as patients with Cystic Fibrosis (CF), Stoss therapy has been shown to maintain normal vitamin D levels for a longer period with equivalent safety to daily dosing.

With new understanding of enzyme mutations leading to potential significant side effects from single high dose treatment, this treatment should only be used where risk of non-compliance is thought to be high or in specific patient groups e.g. CF and IBD. Monitoring is important. Stoss therapy should not be used in patients less than 3 months old [2, 12].

Availability and administration:

Calciferol Strong 50 000 international units (1.25 mg) per chewable tablet is used for Stoss Therapy. It is given in a **single** nurse administered dose. For infants, tablets may be crushed and mixed with water or juice.[10]

Age 3-12 months: 50 000 international units (1 tablet)
Over 12 months: 150 000 international units (3 tablets)

Recheck Vitamin D, calcium, magnesium, phosphate, PTH and ALP after 1 month and 3 months.

If 25- hydroxyvitamin D, PTH and ALP have not normalised, Stoss therapy should be repeated with another set of blood tests 4 weeks later.

If results have normalised, indicating that vitamin D stores have been replenished, Vitamin D bloods should be repeated every 6 months and an ongoing daily supplement considered, unless the factors that caused the initial deficiency have been corrected.

Inflammatory Bowel Disease

Several studies demonstrate that children with Inflammatory Bowel Disease (IBD) have an increased risk of Vitamin D deficiency, both on and off regular oral therapy. This is for a number of reasons, including the inflammatory process itself, decreased sun exposure due to the use of immunomodulator and biological medicines, being less active, use of corticosteroids, anorexia (and thus decreased oral intake) and malabsorption.

A study of 78 IBD patients at Sydney Children's Hospital (SCH) found that 19% had some form of vitamin D deficiency. Patients on corticosteroid therapy were more likely to be deficient.[9]

The Stoss dosing has been used safely and effectively in children with IBD at SCH.

Under 3 years of age: 200 000 international units (4 tablets)
Age 3-12 years: 400 000 international units (8 tablets)
Over 12 years of age: 800 000 international units (16 tablets)

Cystic Fibrosis[11]

Patients with a vitamin D level of less than 75nanomol/L should be considered for vitamin D therapy in line with US Cystic Fibrosis Foundation recommendations.

A study of 142 SCH CF clinic patients found that 56% were vitamin D deficient. From the group studied, those who were treated with Stoss therapy followed by maintenance vitamin D supplementation compared with maintenance vitamin D supplementation over 12 months showed prolonged normal vitamin D levels with equivalent safety. Stoss therapy was safe and effective in achieving vitamin D levels above 75nanomol/L in the majority of treated patients and was sustained over a 12 month period.

Recommended Stoss dose in international units: CF

vitamin D level	Under 3 years	3 to 12 years	Over 12 years
Less than 25nanomol/L	200 000 (4 tablets)	400 000 (8 tablets)	600 000 (12 tablets)
26 to 50nanomol/L	150 000 (3 tablets)	350 000 (7 tablets)	500 000 (10 tablets)
51 to 75nanomol/L	100 000 (2 tablets)	200 000 (4 tablets)	300 000 (6 tablets)

Maintenance supplementation dosing: 400-1000 international units daily.

Refer to CF handbook for further information.

Adverse events

Because of the metabolism of Vitamin D, toxicity is rare. However, symptomatic hypercalcaemia has been reported due to accidental overdose, presumably because the 24-hydroxylation pathway can be overwhelmed. Hypercalcaemia has been reported with high dose (300,000 international units or more) therapy in well-nourished children4 and children with rickets[5]. This is possibly due to mutations in CYP24A1 enzymes[12]. A good history and monitoring post treatment (with blood tests as above) is therefore essential to safe treatment.

Related Information

- CF handbook

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Appendix A

Sunlight protection and exposure guidelines for infants, children and adolescents in Australia and New Zealand, by skin type*

	Light to olive skin, Fitzpatrick types I to IV	Naturally dark (brown and dark brown or black) skin, Fitzpatrick types V and VI
Summer or UV index _3 †	Avoid sunburn; full sun protection with sunscreen, hat, clothing, shade and sunglasses‡ recommended	Avoid sunburn; intermittent sun exposure without sunscreen can be tolerated, but hat and sunglasses ‡ still recommended
	Encourage active play or physical activity outside during and after school or preschool	
Winter	Sun protection recommendations vary with latitude and UV index; if UV index below 3, sun protection not required unless in alpine regions, outside for extended periods or near highly reflective surfaces such as snow or water	Sunscreen not needed in southern states of Australia and in New Zealand unless near highly reflective surfaces such as snow or water; it may not be possible to maintain recommended serum 25(OH)D levels through sun exposure alone in southern states of Australia and in New Zealand
	Encourage active play or physical activity outside during and after school or preschool	

† The peak UV index is _3 throughout the year across most of Australia, including all of Queensland, all of the Northern Territory and most of Western Australia, South Australia and New South Wales.

‡ Sunglasses are generally recommended once children are old enough to wear them safely