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DIVISIONAL DOCUMENT

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DOCUMENT PURPOSE:	Describes how to assess children with Vitamin D deficiency, how to interpret Vitamin D levels and treatment options.

To be read in conjunction with (identify which internal documents)	Royal College of Paediatrics & Child Health UK Guide to Vitamin D in Childhood (October 2013).
SUPPORTING REFERENCES	1. BMJ Group, Pharmaceutical Press (2020) British National Formulary for Children, London. 2. CKS (2016) *Vitamin D deficiency in children*, UK: NICE. 3. Dr Paul Arundel and Prof. Nick Shaw (2018) *Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management in Children and Young People*, UK: National Osteoporosis Society. 4. East Lancashire Hospitals Trust (2010) *Diagnosis & Management of Hypocalcaemia and Vitamin D Deficiency*, UK: Paediatric Department. 5. Royal College of Paediatrics and Child Health (2013) *A Guide for Vitamin D in Childhood*, London. 6. Scientific Advisory Committee on Nutrition (2016) *SACN vitamin D and health report*, UK: Public Health England. Other useful links: 1. http://bpabg.co.uk/position-statements/vitamin-d-and-fractures 2. http://www.elmmb.nhs.uk/guidelines/disease-specific-guidelines/?assetdetesctl516557=39977&p=2 3. www.gov.uk/government/publications/vitamin-d-advice-on-supplements-for-at-risk-groups www.healthystart.nhs.uk 4. www.rcpch.ac.uk/positionstatements

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	extension requested. **November 2021 – Discussed at Paediatric Learning & Development day. Full review. Contents page added. Types of Vitamin D, Assessing the Patient, and Indication for Testing Vitamin D Status added. Prevention and treatment doses updated.**

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1.1 Background

This guideline is based on guidelines issued by the National Osteoporosis Society (NOS), Scientific Advisory Committee on Nutrition (SACN), Royal College of Paediatrics & Child Health (RCPCH) and NICE. The aim of this guideline is to give advice on how to assess children with vitamin D deficiency, how to interpret vitamin D levels and treatment options. This guideline can be used in both primary and secondary care in East Lancashire.

The consensus statement represents the unified views of the British Association of Dermatologists, Cancer Research UK, Diabetes UK, the Multiple Sclerosis Society, the National Heart Forum, the National Osteoporosis Society and the Primary Care Dermatology Society:

'Vitamin D is essential for good bone health and for most people sunlight is the most important source of vitamin D. The time required to make sufficient vitamin D varies according to a number of environmental, physical and personal factors, but is typically short and less than the amount of time needed for skin to redden and burn. Enjoying the sun safely, while taking care not to burn, can help to provide the benefits of vitamin D without unduly raising the risk of skin cancer. Vitamin D supplements and specific foods can help to maintain sufficient levels of vitamin D, particularly in people at risk of deficiency.'

What is vitamin D?

Vitamin D is a fat-soluble pro-hormone. It is an essential nutrient needed for healthy bones, and to control the amount of calcium in our blood. There is recent evidence that it may prevent many other diseases.

What is the natural source of vitamin D?

Most people get little vitamin D in their diet. Only a few natural foods such as oily fish and eggs (20 – 40 units per egg) contain significant amounts of vitamin D.
A few foods are fortified with small amounts of vitamin D (e.g. margarine and some breakfast cereals). All formula milks are fortified, but plain cow's milk is not fortified in the UK. Breast milk generally contains little vitamin D. Sunshine is the main source of vitamin D. However, vitamin D can only be made in our skin by exposure to sunlight when the sun is high in the sky. Therefore, in most of the UK from November to February, and in Scotland from October to March, vitamin D cannot be made from sunshine.

Whether ingested orally or made in the skin under the action of ultraviolet light (UVB), vitamin D is converted to 25hydroxyvitaminD (used as a biomarker of vitamin

D status) in the liver and then on to 1,25-dihydroxyvitaminD in the kidney. It is this which has potent metabolic effects.

There are two types of vitamin D:

1. Ergocalciferol (vitamin D2) a plant product;
2. Colecalciferol (vitamin D3) which is a fish or mammal product.

The BNF and many other authorities regard them as interchangeable. However, the current consensus is that vitamin D3 raises serum vitamin D concentrations more effectively than vitamin D2 (due to higher affinities for liver enzymes, plasma vitamin D binding protein, and vitamin D receptors).

'Activated vitamin D' preparations such as Calcitriol or Alfacalcidol should not be used for the treatment of simple vitamin D deficiency. They should only be used for the treatment of complex cases by specialists (e.g. significant hypocalcaemia, malabsorptive disorders, renal disease and rare disorders affecting calcium and phosphate regulation). They are ineffective in treating simple vitamin D deficiency and can cause severe adverse effects, particularly hypercalcaemia. Simple vitamin D is safe and is the treatment for D deficiency.

1.2 What is Vitamin D Deficiency?

Vitamin D deficiency historically has been defined as a blood level of 25hydroxyvitaminD below 25nmol/L. There is scientific debate about the optimal vitamin D blood level. Current practice in the UK, as recommended by the British Paediatric and Adolescent Bone Group, is to continue to use that as the defined level of deficiency, and to define 'insufficiency' as between 25 and 50 nmol/L. Current practice is based on robust evidence of benefits to bone health when levels are more than 50nmol/L. Vitamin D deficiency can cause seizures and cardiomyopathy in infants, rickets and poor growth in children and muscle weakness at any age.

1.2.1 Interpretation of vitamin D levels (25 Hydroxyvitamin D)

Plasma concentration	Classification	Action
< 25 nmol/L	Deficiency	Need Treatment-see below
25 – 50 nmol/L	Insufficient	Need Prophylaxis in prevention doses- see below
> 50 nmol/L	Adequate	Lifestyle advice

NB. 50nmol/L = 20ng/mL

Most laboratories in UK use nmol/L. Some Laboratories in UK and most in USA use ng/ml.

1.3 Assessing the Patient

Characteristics	Management
No Risk Factors (see below)	No investigations, lifestyle advice and consider prevention
Risk Factors, no symptoms	Lifestyle advice and prevention
Risk Factors and symptoms or signs	Blood Tests and / or X Ray. Treatment and long-term prevention

1.3.1 Blood tests

Perform the following blood tests in those with signs and symptoms or significant risk factors:

- 25 hydroxyvitamin D
- Bone profile – calcium, phosphate, alkaline phosphatase
- PTH (parathyroid hormone)
- X-Ray if clinically indicated.

25 hydroxyvitamin D is the standard blood test and is an excellent marker of body stores. People with risk factors and symptoms of hypocalcaemia or vitamin D deficiency should have a check of their blood level. The blood test requires about 2mL of serum. The cost of this test is approximately £20.

Raised alkaline phosphatase, hypocalcaemia and a high level of PTH may be indicators of vitamin D deficiency but basic bone biochemistry (calcium, phosphate and alkaline phosphatase) can often be normal despite significant vitamin D deficiency.

High alkaline phosphatase is associated with rickets. PTH is produced in the neck glands when the parathyroid calcium-sensing receptors detect a low level of blood calcium. PTH levels are a helpful measure of calcium and vitamin D status. In children a high level of PTH is usually due to vitamin D deficiency or a lack of calcium in the diet. Other causes (e.g. parathyroid tumours or renal failure) are rare.

1.3.2. Treatment of Relatives

If a patient is diagnosed with vitamin D deficiency the family should be screened or treated. At least screening by history taking should take place, and prevention advice given. Investigation of other family members by blood testing may be indicated (refer to adult guidelines for adults). Alternatively, advise/prescribe a vitamin D supplement to those sharing the same sun exposure and diet.

After treatment, children who were deficient or insufficient should continue long-term low-dose supplements until completion of growth, unless lifestyle changes (diet/sun exposure) are assured.

1.3.3 Who is likely to get vitamin D deficiency?

People particularly at risk are those with:

1. Increased need:

- Pregnant and breastfeeding women
- Infants and children under 4
- Twin and multiple pregnancies
- Adolescents
- Obesity

2. Reduced sun exposure:

- Northern latitude, especially above 50 degrees latitude (e.g. UK)
- Season – in winter and spring
- Asian and African people – dark skin needs more sunshine to make vitamin D
- Wearing concealing clothing
- Immobility, e.g. inpatients or those with conditions like cerebral palsy
- Excessive use of sun block – most block UVB more than UVA

3. Limited diet (but remember sunshine is most important source of vitamin D):

- Vegetarians and vegans
- Prolonged breastfeeding – even if mother has sufficient vitamin D
- Exclusion diets – e.g. milk allergy
- Malabsorption
- Liver disease
- Renal disease
- Some drugs which induce liver enzymes– e.g. Anticonvulsants, Anti-TB drugs

Although sunshine is the usual source of vitamin D, diet is of course the source of calcium. It is particularly important to prevent vitamin D deficiency in children with limited calcium intake.

1.3.4 Indications for testing vitamin D status

Indicator	Examples
Signs and symptoms of rickets	• Progressive bowing of legs • Progressive knock knees • Wrist swelling • Rachitic rosary • Craniotabes • Delayed tooth eruption, enamel hypoplasia
Symptomatic vitamin D deficiency	• Chronic unexplained bone pain (>3months) • Muscle weakness e.g. waddling gait, delayed walking, difficulty rising or climbing stairs • Tetany (due to hypocalcaemia) • Seizures (usually in infancy due to hypocalcaemia) • Infantile cardiomyopathy
Abnormal investigations	• Low plasma calcium or phosphate • High alkaline phosphatase • Osteopenia, rickets or pathological fractures revealed by radiographs
Chronic conditions which increase the risk of vitamin D deficiency	• Chronic renal disease • Chronic liver disease • Malabsorption syndromes e.g. Cystic Fibrosis, Crohn's disease, coeliac disease
Drug treatment with bone-targeted drugs	• Use of bisphosphonates requires vitamin D sufficiency • Regular steroid use requires bone protection due to increased osteoporotic risk – calcium and vitamin D levels may need to be monitored

1.3.5 Indications for referral to secondary care

- Repeated low plasma calcium concentrations
    - Symptomatic → immediate referral to hospital if from community
    - Asymptomatic → discuss with paediatrician
- Complex underlying condition
- Signs indicative of rickets in children
- Poor response to treatment i.e. level <50nmol/L after 8-12 weeks of treatment
- Persisting low plasma phosphate or low/high alkaline phosphatase

1.4 Prevention of Deficiency

The Department of Health and the Chief Medical Officers recommend a dose of 8.5-10 micrograms (approx. 340-400 units) for ALL children from birth until 1 year of age. The NHS 'Healthy Start' vitamin drops provide 400 units of vitamin D in the daily dose of 5 drops. The 'Healthy Start' programme aims to provide vitamins free to people on income support. The British Paediatric and Adolescent Bone Group's recommendation is that exclusively/partially breastfed infants receive vitamin D supplements from soon after birth. Formula fed babies do not require supplements if formula intake > 500mL/day. NOS guidelines recommend ensuring adequate intake of dietary calcium (see appendix 1).

Adverse effects of vitamin D overdose are rare but emerging evidence links potential adverse effects to high concentration of vitamin D above 250nmol/L. Care should be taken with multivitamin preparations as vitamin A toxicity is a concern. Multivitamin preparations often contain a surprisingly low dose of vitamin D.

1.4.1 Standard Prevention Doses

Category	Dose and Frequency	Examples of Preparations
Up to 1 year	340-400 units daily recommended as safe intake	Healthy start vitamins
1 year – 4 years	400 units daily recommended as safe intake	Over the counter preparations e.g. Boots high strength vitamin D drops
4 – 18 years	400 units daily recommended as reference nutrient intake. NOS have advised that dose can be increased to 600 units daily for ages 1 month – 18 years to continue unless there is a significant lifestyle change.	Over the counter preparations e.g. SunVit D3 tablets

1.5 Treatment of Vitamin D Deficiency (levels < 25nmol/L)

We recommend using **Colecalciferol** for treatment. After treatment course is finished, all children should be started on oral vitamin D supplements in prevention doses as mentioned above.

Prescribing responsibility for children less than 1 year old is RED traffic (Specialist ONLY). Children under 1 year will be prescribed and supplied with 9 weeks of colecalciferol solution by the paediatrician.

The formulations of choice are Hux D3 20,000 unit capsules (unlicensed) and Invita D3 25,000 units/mL oral solution (licensed). They are suitable for vegetarian, halal and kosher diets and free from gelatine, lactose, peanut oil and soya. **Consult pharmacy if the patient has a citrus allergy.**

1.5.1 ORAL TREATMENT DOSE

Category	Dose and frequency	Duration	Prescribing information
Up to 6 months	25,000 units (1mL) once weekly	9 weeks	Prescribe 3 x 3amp boxes of Invita D3 25,000 units/mL
6 months – 12 years	25,000 units (1mL) twice a week	9 weeks	Prescribe 6 x 3amp boxes of Invita D3 25,000 units/mL
	40,000 units (2 capsules) once weekly **if using capsules**	9 weeks	Prescribe 18 x 20,000 units HUX D3 capsules
12-18 years	80,000 units (4 capsules) once weekly **if using capsules**	9 weeks	Prescribe 36 x 20,000units HUX D3 capsules
	25,000 units (1mL) three times a week	9 weeks	Prescribe 9 x 3amp boxes of Invita D3 25,000 units/mL

If compliance is an issue and the patient refuses to comply with daily or weekly regiments then the dose can be given as a single once only dose orally as below. This is not to be prescribed as first line treatment.

1.5.2 SINGLE ORAL TREATMENT DOSE I.E. STOSS THERAPY

Category	Dose and frequency	Duration	Prescribing information
Up to 6 months	90,000 units (3.6mL)	Single dose	Prescribe 4 amps of Invita D3 25,000 units/mL
6 month – 12 Year	150,000 units (6mL)	Single dose	Prescribe 2 x 3amp boxes of Invita D3 25,000 units/mL
	160,000 units (8 capsules) **if using capsules**	Single dose	Prescribe 8 x 20,000 units HUX D3 capsules
12-18 Years	300,000 units (12mL)	Single dose	Prescribe 4 boxes x 3amps of Invita D3 25,000 units/mL
	300,000 units (15 capsules) **if using capsules**	Single dose	Prescribe 15 x 20,000 units HUX D3 capsules

1.5.3 INJECTION DOSES (TREATMENT DOSE)

Intramuscular vitamin D is no longer recommended and should only be on **specialist advice** where compliance is a serious issue or where other medical circumstances or conditions make it the first choice. It is not usually recommended due to unpredictable bioavailability, slower onset of repletion and burden of administration. Ergocalciferol is available as an injection (300,000 units/mL), please check with pharmacy for further information about availability.

Category	Dose and frequency
Up to 12 months	150,000 units (0.5mL) as a single dose followed by oral supplementation in prophylactic doses as mentioned above.
1 year – 12 Year	300,000 units (1mL) as a single dose followed by oral supplementation in prophylactic doses as mentioned above.
12-18 Years	300,000 units (or 600,000 units; 1-2mL) as a single dose followed by oral supplementation in prophylactic doses as mentioned above.

Calcium supplementation is not routinely recommended and advice on increasing dietary calcium intake should be given in all children. It is essential to check the child

has a sufficient dietary calcium intake (see appendix 1), and that a maintenance vitamin D dose follows the treatment dose and is continued long term (see standard prevention doses above).

1.6 Vitamin D toxicity

Toxicity is defined as hypercalcaemia and a plasma 25(OH)D concentration > 250nmol/L with hypercalciuria and suppressed PTH. (Global Consensus Recommendations on Prevention and Management of Nutritional Rickets).

There is no agreed threshold concentration of vitamin D that results in toxicity. 250nmol/L is a safe cut-off recommended by the National Osteoporosis Society – symptomatic toxicity has been reported at levels > 500nmol/L. Acute vitamin D toxicity is rare, usually resulting from doses much higher than 10,000 units/day. However, caution is required in any child with a granulomatous disease e.g. TB.

1.7 Follow-up

Some recommend a clinical review a month after treatment starts, asking to see all vitamin and drug bottles. Routine monitoring of vitamin D levels is generally unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption and where poor compliance with medication is suspected. A blood test can be repeated then, if it is not clear that sufficient vitamin has been taken. Current advice for children who have had symptomatic vitamin D deficiency is that they continue a maintenance prevention dose at least until they stop growing. Dosing regimens vary and clinical evidence is weak in this area. The RCPCH has called for research to be conducted.

Bone profile and vitamin D tests (and a PTH test if the patient has rickets or hypocalcaemia) are recommended to be repeated at the end of the course of treatment.

If the 25(OH)D level is greater than 50nmol/L and the bone profile is normal:

- Advise multivitamins containing vitamin D 400-600 units per day. Continue unless there is a significant lifestyle change to improve vitamin D status.

If 25(OH)D level is below 50nmol/L:

- Consider poor compliance, drug interactions and underlying conditions e.g. renal disease, liver disease, malabsorption.
- If poor compliance is suspected, a high dose treatment may be considered

If a child's symptoms have not improved despite a satisfactory 25(OH)D concentration they are unlikely to be related to vitamin D deficiency.

Appendix 1. Calcium Intake

"Many children with vitamin D deficiency rickets have a poor dietary calcium intake. As their bones are growing, there is a greater risk of negative calcium balance. Therefore, in children consider the need for calcium supplementation. Many children with vitamin D deficiency will have a depleted calcium status and/or a poor calcium intake and may therefore benefit from advice about dietary calcium intake. In some cases, calcium supplementation may be worthwhile over the period of vitamin D treatment."

Recommended calcium intake to prevent rickets:

Age	Recommended calcium intake to prevent rickets
Birth – 6 months	200mg daily
6 – 12 months	260mg daily
Over 12 months	> 500mg daily

Dietary reference values for calcium:

Age	Calcium reference nutrient intake
0 – 12 months	525mg daily (13.1 mmol daily)
1 – 3 years	350mg daily (8.8 mmol daily)
4 – 6 years	450mg daily (11.3 mmol daily)
7 – 10 years	550mg daily (13.8 mmol daily)
11 – 18 years, female	800mg daily (20 mmol daily)
11 – 18 years, male	1000mg daily (25 mmol daily)

NB. 1mmol calcium = 40mg calcium.