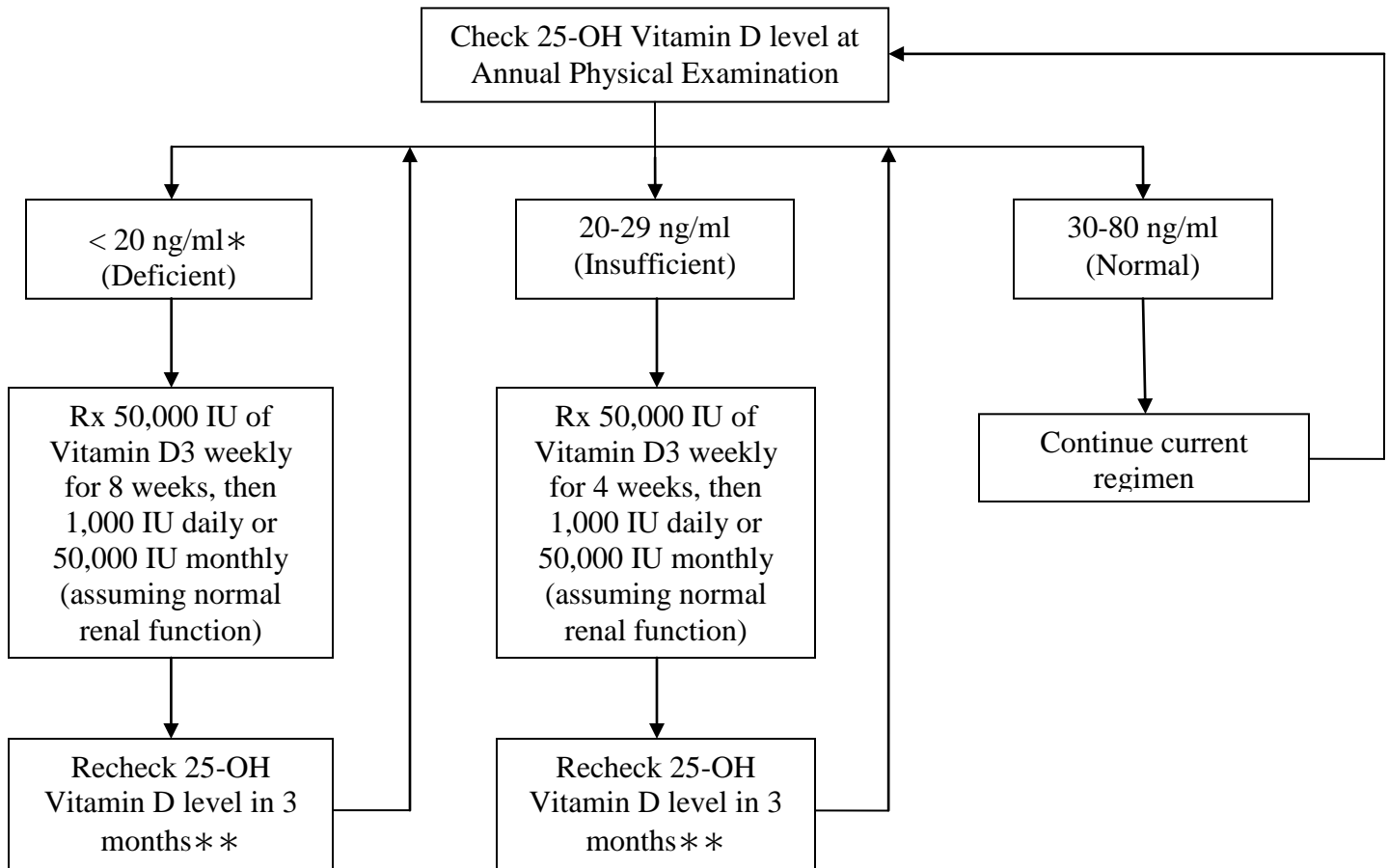


## Clinical Practice Guideline for Vitamin D

### Guideline Decision Flow Diagram



\*Rule out malabsorptive causes of vitamin D deficiency such as celiac sprue, inflammatory bowel disease, and other malabsorptive disorders (Consider GI consult)

\*\*If normal vitamin D levels (30-80 ng/ml) are not achieved despite following the above protocol, ensure that pharmaceutical grade vitamin D is being used. If normal vitamin D levels are not achieved despite the use of pharmaceutical grade vitamin D, obtain endocrinology consult

## Decision Flow Diagram Notes

Vitamin D Levels will be determined initially at the time of the astronaut's annual physical examination. Astronauts who will be flying operational missions prior to their next annual physical examination (or who will be flying a long duration mission in the next few years) should be evaluated and treated appropriately prior to their mission. The timing of this testing for these crewmembers will be left up to the discretion of the Crew Surgeon. The JSC Pharmacy has on formulary the 50,000 I.U. form of vitamin D3, which is authorized for active astronauts only. Other patients, including AOD, flight surgeons, family members, management astronauts and retired astronauts will need to purchase the vitamin D3 on their own, should they choose to take this supplement. Vitamin D2 may be substituted for vitamin D3. However, a recent study demonstrated that vitamin D2 potency is less than one third that of vitamin D3.<sup>1</sup>

### Level of Evidence for Recommendations

Based on the literature reviewed regarding the skeletal consequences of vitamin D inadequacy, optimal vitamin D levels, vitamin D dosing, and vitamin D toxicity, there are sufficient randomized clinical trials supporting the efficacy and safety of the vitamin D recommendations made within this clinical practice guideline to consider the strength of evidence as Level A, Class I.

## Evidence Based Discussion

### Introduction

Vitamin D and its metabolites have clinical significance because they play a critical function in calcium homeostasis and bone metabolism. Although not all of the pathologic mechanisms have been adequately described, vitamin D insufficiency and deficiency, as measured by low levels of 25-OH vitamin D, are associated with a variety of clinical conditions including osteoporosis, falls and fractures in the elderly, decreased immune function, bone pain, and possibly colon cancer and cardiovascular health.<sup>2</sup> Apart from inadequate dietary intake, patients may present with low levels of vitamin D if they receive inadequate sunlight.

The astronaut population is potentially vulnerable to low levels of vitamin D for several reasons. Firstly, they may train for long periods in Star City, Russia, which by virtue of its northern latitude receives less sunlight in winter months. Secondly, astronauts are deprived of sunlight while aboard the International Space Station (ISS). In addition, ISS crew members are exposed to microgravity for prolonged durations and are likely to develop low bone mineral density despite the use of countermeasures. Therefore, closely monitoring and maintaining adequate vitamin D levels is important for the astronaut corps.

## Vitamin D Physiology

Sunlight and ultraviolet light nonenzymatically photoisomerize provitamin D to vitamin D<sub>3</sub> (cholecalciferol) in the skin, at which point cholecalciferol binds to vitamin D binding proteins (DBP) and is transported through the circulatory system to target organs for further metabolism and target organ activity. Intestinal absorption is the other source of vitamin D. Major dietary sources of vitamin D include fortified milk and other dairy products, fatty fish, cod liver oil and eggs. In the United States milk is commonly fortified with vitamin D; in other countries, grain products are more commonly vitamin D fortified.

Dietary Vitamin D is packaged into micelles, absorbed by enterocytes, then further incorporated into chylomicrons. As such, various pathologies associated with intestinal absorption may lead to low levels of vitamin D including, though not limited to: celiac disease, pancreatic insufficiency, cystic fibrosis, cholestatic liver disease, and inflammatory bowel disease (IBD). Chylomicrons are brought to the liver via portal circulation, at which point vitamin D is hydroxylated by 25-vitamin D hydroxylase to form 25-hydroxy vitamin D. Another hydroxylation reaction is accomplished within mitochondria located in proximal convoluted tubules of the kidney, which produces 1, 25 dihydroxy vitamin D.<sup>3</sup> This is the physiologically active form of vitamin D. If a patient is noted to have low levels of vitamin D, the cause will therefore likely be found in inadequate sunlight exposure, inadequate intake or absorption, or inadequate hydroxylation of precursor molecules, either at the liver or at the kidney. Rare cases of end-target insensitivity to 1, 25 dihydroxy vitamin D have been described, but would be virtually impossible to witness within the astronaut corps.

Vitamin D absorption and hydroxylation to the physiologically active form are involved in calcium homeostasis and are linked to parathyroid hormone (PTH), serum calcium concentration, and phosphorous levels.<sup>4</sup> When hypocalcemia occurs, serum PTH rises and acts to increase renal absorption of PTH and increased hydroxylation of Vitamin D to the active metabolite. Increased 1, 25 dihydroxy vitamin D in turn promotes increased intestinal calcium absorption.<sup>5</sup> PTH also induces bone osteoclasts to increase serum calcium from bone calcium stores.<sup>6</sup>

Conversely, lack of vitamin D leads to reduced intestinal absorption of calcium and phosphorous. Persistently low levels of vitamin D lead to a secondary hyperthyroidism that produces phosphaturia, demineralization of bones, and ultimately to osteomalacia in adults and rickets in children.

## Vitamin D Levels

Appropriate levels of vitamin D have been difficult to identify. The main criterion defined has been the physiologic level needed to maximize PTH suppression. Studies of different populations of varying ethnicities and varying geographic areas have yielded varying levels of vitamin D. Estimates of an acceptable lower level therefore vary but are approximately 30-32 ng/ml.<sup>7-11</sup> It should be noted that 30 ng/mL is higher than most previously accepted lower “normal” ranges, which suggests that these lower levels are perhaps set too low for adequate physiologic effect. Higher 25-hydroxy vitamin D levels have been associated with greater calcium absorptive efficiency<sup>12</sup> and

levels of 28 to 40 ng/ml may decrease bone fracture risk.<sup>13,14</sup> In adults, vitamin D deficiency is defined as a serum 25-hydroxy vitamin D level of less than 20 ng/ml, and insufficiency is defined as a serum hydroxyl vitamin D level of 20 to 30 ng/ml.<sup>15</sup>

### Vitamin D Toxicity

Vitamin D toxicity is infrequently witnessed, but hypercalcemia and hypercalciuria are among the first sequelae. Accordingly, symptoms may include bone changes including pathologic fractures, polyuria, kidney stones, abdominal pain, anorexia, constipation, depression, and malaise. Research has shown that these symptoms are only witnessed at levels of vitamin D higher than 88 ng/ml.<sup>16,17</sup> Moreover; 2000 IU/day (50 micrograms/day) has been set as the Safe Upper Limit by the National Academy of Sciences, as well as the “tolerable upper intake level” by the Institute of Medicine. However more recent research has indicated that even higher doses are safe at least over a several-month period.<sup>18</sup>

### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

#### Levels of Evidence

**A:** Data derived from multiple randomized clinical trials or meta-analyses

**B:** Data derived from a single randomized trial, or nonrandomized studies

**C:** Only consensus opinion of experts, case studies, or standard-of-care

### Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT			
		CLASS I	CLASS IIa	CLASS IIb	CLASS III
		<i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment  <b>SHOULD</b> be performed/ administered	<i>Benefit &gt;&gt; Risk</i> <i>Additional studies with            focused objectives needed</i>  <b>IT IS REASONABLE</b> to perform procedure/administer treatment	<i>Benefit ≥ Risk</i> <i>Additional studies with            broad objectives needed;            additional registry data            would be helpful</i>  Procedure/Treatment <b>MAY BE CONSIDERED</b>	<i>Risk ≥ Benefit</i> <i>No additional studies needed</i>  Procedure/Treatment should <b>NOT</b> be performed/administered <b>SINCE IT IS NOT            HELPFUL AND MAY BE            HARMFUL</b>
<b>Estimate of            Certainty            (Precision) of            Treatment Effect</b>	<b>LEVEL A</b>  Multiple (3–5) population risk strata evaluated*  General consistency of direction and	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment of procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>

		SIZE OF TREATMENT EFFECT			
magnitude of effect					
<b>LEVEL B</b>	Limited (2–3) population risk strata evaluated*	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Limited evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment of procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Limited evidence from single randomized trial or nonrandomized studies</li> </ul>
<b>LEVEL C</b>	Very limited (1–2) population risk strata evaluated*	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard-of-care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment of procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard-of-care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard-of-care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard-of-care</li> </ul>

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## **Approvals**

**Approved by the Clinical Practice Guideline Subcommittee on 11/15/10.**

**Approved by the Aerospace Medicine Board on 11/18/10.**

**This Guideline is to be reviewed no less than every 2 years.**