

## Vitamin D in the ICU: More Sun for Critically Ill Adult Patients?

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## Highlights

- While adequate level of vitamin D is associated to improved survival in general population, the causality between mortality and the low levels frequently found in critically ill patients has not been confirmed.
- Vitamin D has a myriad of biological function, including immunomodulation properties essential to the critically ill patients with significant systemic inflammation. The emergence of metabolomics helps understand the pathways relevant to vitamin D effect.
- Pharmacokinetic profile of vitamin D administration remains superficial and various strategies have been studied with various results. The optimal strategy has not been confirmed but high-dose oral/enteral administration is the most studied.
- The largest randomized controlled trial published so far, the VITdAL-ICU trial, showed no benefits on mortality in its primary analysis, but secondary analysis suggest improvement in severely deficient patients ( $<12$  ng/mL). Meta-analysis currently do not support benefits of supplementing all patients.
- Large trials are currently recruiting and could elucidate the potential benefits of vitamin D in critically ill patients. Results of the VITDALIZE trial are expected in 2021.

# Vitamin D in the ICU: More Sun for Critically Ill Adult Patients?

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## Abstract

### Background

Critical illness in patients is characterized by systemic inflammation and oxidative stress. Vitamin D has a myriad of biological functions relevant to this population, including immunomodulation by the alteration of cytokine production and nuclear factor loop amplification. Low serum levels have consistently been found in observational studies conducted on critically ill patients, but the causality with mortality and worse outcomes has not been confirmed. The current focus is on interventional trials while the pharmacokinetic profile of vitamin D administration remains sparse and the optimal strategy has not been confirmed. So far, high-dose oral/enteral supplementation is the most studied strategy.

### Recent trials

The largest randomized controlled trial published so far, the VITdAL-ICU trial, showed no benefits on mortality in its primary analysis. However, secondary analysis suggested improvement in those patients with severe deficiency (i.e.,  $25(\text{OH})\text{D} < 12 \text{ ng/mL}$ ). Smaller trials investigated intramuscular and intravenous administration and found interesting intermediate biochemical findings, including increased cathelicidins, but were not powered to investigate relevant clinical outcomes in the critically ill. The latest meta-analysis, which was recently published, does not support benefits of vitamin D supplementation in the heterogeneous population of critically ill patients.

### Conclusion

The European guidelines, published in the last year, suggest supplementing severely deficient patients with levels  $< 12.5 \text{ ng/mL}$  within the first week after intensive care unit (ICU) admission. However, other societies do not support such supplementation in their older recommendations. Large trials are currently recruiting ICU patients, and could elucidate potential clinical benefits of vitamin D therapy in the critically ill, although the results of new large trials are expected in 2021.

## Introduction

Over the last decade, the body of literature regarding micronutrients supplementation in critically ill patients has grown, due to the frequent association of severe depletion of vitamins and trace elements with systemic inflammation and multi-organ failure (MOF). Vitamin D is a fat-soluble vitamin synthesized in the skin from 7-dehydrocholesterol before being converted in the liver and the kidneys to its most active metabolite, 1,25-dihydroxyvitamin D [ $1,25(\text{OH})_2\text{D}$ ], or calcitriol[1]. In 2011, the Endocrine Society's Clinical Practice Guidelines recommended serum levels  $> 30$  ng/mL as the optimum levels in the general population[2], whereas vitamin D deficiency was defined as 25(OH)D below 20 ng/mL, and vitamin D insufficiency as 25(OH)D levels of 21-29 ng/mL[2]. Similarly, the Institute of Medicine defined vitamin D deficiency as serum levels lower than 20 ng/mL[3]. Regardless of the definition, observational trials have demonstrated that the vast majority of patients hospitalized in the intensive care unit (ICU) are vitamin D depleted[4]. In an observational retrospective study including 655 ICU patients, Amrein et al. found that 60.2% exhibited 25(OH)D levels  $< 20$  ng/mL and up to 86.5% had  $< 30$  ng/mL[4]. In the United States, Dickerson et al. conducted a similar analysis on 158 critically ill adult patients with traumatic injuries admitted to the ICU[5]. The authors reported that 121 patients (77%) were deficient, of which 46 (38%) were severely deficient, and 31 (20%) showed insufficiency, with a 25(OH)D serum level lower than 30 ng/mL. In Brazil, despite the sun exposure, a recent study reported a very high incidence of vitamin D deficiency at ICU admission, reaching 91.6% of patients. Interestingly, African-American patients had lower levels than Caucasians due to skin melanin concentration, whereas no difference were found between the patients admitted in winter and other seasons. Finally, authors examined how healthy blood

donor levels of both calcitriol and 25(OH)D varied in comparison with ICU patients[6] to compensate for the high prevalence of deficiency in the general population. In agreement with previous findings, the prevalence of vitamin D deficiency was significantly higher in the ICU patients, reaching 96.7%, compared to 67% in healthy donors. It must be emphasized that, depending on the geographical latitude of the studied population, serum levels in a healthy non-ICU population can vary greatly and therefore, prevalence of vitamin D deficiency in an ICU population should always be compared to the general population of the same region [1]. Considering the various biological effects of vitamin D, the deficiency found in critically ill patients is of notable interest.

### **Biological effects**

The biological effects of vitamin D are vast and go well-beyond its effect on bones and calcium metabolism (see Figure 1). Apart from cardiovascular and autoimmune diseases, vitamin D contributes to immunomodulation and infection control, which are paramount in critically ill patients[1]. After transformation in the skin to vitamin D<sub>3</sub>, it is metabolized to 25(OH)D by the liver[1]. Kidneys will further metabolize it to 1,25(OH)<sub>2</sub>D, or calcitriol, the most active metabolite of vitamin D, with a shorter half-life. 25(OH)D is the major circulating form and represents the equilibrium between formation and clearance. The frequent presence of vitamin D receptors in various tissues confirms the diverse effects of vitamin D in the human body. In the macrophage, calcitriol will link the nuclear vitamin D receptor (VDR), which will migrate to express mRNA for cathelicidins, an antimicrobial peptide for host defence in barrier tissues of the gastro-intestinal tract, airway and bladder (see Figure 2). hCAP-18 and LL-37 are part of the cathelicidins family and have been studied as biomarkers for functional response of vitamin D supplementation[7].

Calcitriol also links the suppressor of cytokine signaling 1 (SOCS1), to inhibit the activation of P38 mitogen activated protein kinases (P38-MAPK) and the nuclear factor  $\kappa$ B (NF- $\kappa$ B), responsible for loop amplification of cytokine expression and inflammatory response. The net effect is a reduced expression of tumour-necrosis alpha (TNF-alpha), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP1), which can limit the over-reactivity of inflammation pathways in critically ill patients[8]. The development of metabolomics, which analyze the alteration of intrinsic metabolic pathways in the human body, confirmed the differential metabolic profiles during critical illness according to vitamin D status[9] and could elucidate the broad effect of vitamin D on nuclear transcription and cell-cycle reduction. Glutathione and glutamate pathway metabolism were significantly modified when vitamin D deficiency occurred, influencing the redox regulation and the immunomodulation of these pathways. Several animal trials confirmed the influence of vitamin D in the presence of systemic inflammation. Calcitriol exhibited a beneficial effect on lipopolysaccharide-induced acute lung injury in a murine model, notably on lung permeability, as evidenced by using Evans blue dye [10]. Despite the high prevalence of deficiency in critically ill patients, few studies addressed the underlying biological explanation. An observational protocol has recently been published and aims to identify whether acute kidney injury (AKI), often present in critically ill patients, is partly responsible for the high prevalence of vitamin D deficiency in the ICU[11].

## Observational trials

The question remains: How does this deficiency translates to clinical outcomes? A large-scale meta-analysis of nearly 60,000 patients was published in 2012 by Zittermann et al.[12]. This systematic review and meta-analysis included prospective cohort studies with follow-up periods ranging from years to decades and confirmed that optimal levels of 25(OH)D were 28-35 ng/mL for overall survival. Low levels were associated with both increased mortality in the general population (Relative Risk [RR]: 0.71; 95% Confidence Interval (CI) 0.50-0.91), and increased incidence of infectious complications [12] [13] [14].

Similar data were reported specifically for ICU patients. The same 655 previously mentioned patients studied by Amrein et al. showed in a retrospective analysis, that the adequate absolute level of 25(OH)D was associated with an increased cumulative chance of survival ( $P=0.034$ ) [4]. Furthermore, when ICU patients were divided in tertiles according to their serum levels, the highest tertile was associated with increased survival ( $P=0.004$ ). The authors also found that septic patients presented significantly lower levels of calcitriol, with a mean value of  $12.3 \pm 5.0$  ng/mL. These data are in line with previous findings, which reported that after adjustment for Acute Physiological and Chronic Evaluation II (APACHEII) and demographic data, in-hospital mortality, 30-day mortality and 90-day mortality were all significantly increased in 568 septic patients when 25(OH)D levels were  $< 30$  ng/mL with respective adjusted odds ratio (OR) of 1.62, 1.55 and 1.63[15]. The risk of sepsis was also significantly increased in ICU patients with 25(OH)D levels below 15 ng/mL (OR 1.51; 95% CI 1.17-1.94) [15]. Another article worth citing retrospectively analyzed 24,094 adult patients hospitalized in ICU between 1993 and 2011[16].



After adjustment of age, gender, race, medical or surgical patient, season and Deyo-Charlson Index, a U-shaped relationship existed between 25(OH)D levels and 90-day mortality. When compared to patients with levels between 30.0 and 49.9 ng/mL, patients with < 10 ng/mL had a mortality RR of 2.01 (95%CI 1.68-2.40) and, interestingly, those with a 25(OH)D concentration greater than 70 ng/mL had a mortality RR of 1.69 (95%CI 1.09-2.61). Mayr et al. compared cirrhotic and non-cirrhotic patients in an observational study to analyze how hepatic disease could exacerbate the mortality associated with vitamin D deficiency. Once again, a high incidence of 25(OH)D deficiency (group < 10 ng/mL = 55%; group 10-20 ng/mL = 23%) was found. Vitamin D status correlated with APACHE II score, sequential organ failure assessment (SOFA) score and Child-Pugh score. Levels below 10 ng/mL correlated with 180-day mortality (hazard ratio: 2.45) and cirrhotic patients had a higher risk of mortality when the deficiency was severe (i.e., < 10 ng/mL) [17]. Nonetheless, data is not so straightforward and several recent observational trials found no association between 25(OH)D levels and relevant clinical outcomes for ICU patients such as mortality and infections[18, 19] [20] [21], or failed to demonstrate any relationship with mortality was analyzed in multivariate analysis[19].

Apart from mortality, vitamin D deficiency has been linked to adverse outcomes, including hospital-acquired pressure injuries (HAPIs), with an OR value of 2 when 25(OH)D values were below 20 ng/mL [22]. Brook et al. demonstrated that surgical patients' 25(OH)D levels measured within the first 24 hours after ICU admission were correlated with the Functional Status Score for the ICU (FSS-ICU) at ICU discharge [23]. In this retrospective analysis, 25(OH)D levels lower than 20 ng/mL were associated with a > 3-fold risk of low FSS-ICU (score < 17) when compared to patients with 25(OH)D levels greater than 20 ng/mL (OR 3.45; 95%CI 1.96-6.08). Furthermore,

Gomes et al. demonstrated a very strong correlation between 25(OH)D concentration, especially when below 12 ng/mL, and the prognostic indicator Charlson Comorbidity Index when adjusted for age, sex and body mass index (BMI) (OR 1.59 95%CI 1.10-2.34) [24]. Moreover, the authors found an inverse correlation between 25(OH)D levels and cancer (OR 3.42; 95%CI 1.21–9.64) and acute liver failure (OR 9.64; 95%CI 2.28–40.60). No associations were found regarding duration of mechanical ventilation or mortality. Therefore, vitamin D deficiency is both prevalent and relevant in ICU patients, but the literature remains sparse regarding the benefits of supplementing vitamin D in its various forms.

#### **What have clinical trials found to date?**

Through observational trials, it remains impossible to discern causality from a simple epiphenomenon. Despite the varying strategies, the most effective means of evaluating a causality effect of vitamin D deficiency on clinical outcomes is to administer supplementation in RCTs and observe outcomes. Several recent trials tempted strategies of vitamin D supplementation in ICU patients (see Table 1). Notwithstanding, many questions about timing, route of supplementation, dose as pharmaconutrition strategy, and duration of therapy remain unanswered. One of the major difficulties of current research on vitamin D therapy in the critically ill is the limited knowledge regarding pharmacokinetic profile, the biomarkers to assess both vitamin D functional deficiency and functional repletion, as well very heterogeneous supplementation strategies among RCT published. All trials discussed so far used either calcitriol or 25(OH)D as a serum marker to assess functional levels of the vitamins. An interesting RCT by Leaf et al. suggested that cathelicidins (hCAP18), a protein highly expressed after activation of nuclear vitamin D receptor, is a stronger predictor of 90-day mortality than total, bioavailable or

free 25(OH)D[25]. In 121 patients observed prospectively, the tertiles with lowest and intermediate hCAP18 at ICU day 1 had significantly increased sepsis incidence (adjusted OR 2.54 and 3.72 respectively) while 25(OH)D did not. Interestingly, the scope of the effect was lower in the first tertile than in the second, which opposes criteria of causality.

Nair et al. administered to ICU patients with systemic inflammation and APACHE II score of 15-30, a single intramuscular dose of 150,000 IU or 300,000 IU of cholecalciferol[26]. The two groups were initially deficient (21 ng/mL and 17 ng/mL respectively) and exhibited an increase in 25(OH)D levels after supplementation. The biomarker LL-37, a protein from the human cathelicidins family, presented a correlated increase with 25(OH)D at days 1 and 3, while the best correlation was between a 25(OH)D increase and a interleukin-6 (IL-6) decrease[26]. The trial was not powered to evaluate clinical outcomes and mortality was identical in both groups (n = 5/25). Another supplementation strategy was intravenous administration of 2 ug of calcitriol in severe sepsis or septic shock patients[25]. No significant changes were noted in absolute serum levels of hCAP-18, IL-6 or other interleukins, but the messenger RNA (mRNA) for hCAP-18 and IL-18 were both significantly increased, with a correlation between 1,25(OH)<sub>2</sub>D and hCAP-18 mRNA increase (P=0.003). The trial was not powered to evaluate clinical outcomes. Other supplementation strategies included oral/enteral administration of cholecalciferol[27-29].

Over the last decade, six RCTs (see Table 1) addressed this research question and recent meta-analyses were conducted for ICU patients[30] [31]. Most of the trials had small numbers of patients and therefore, the effect is mostly driven by the VITdAL-ICU trial conducted in 2014 [27]. In this trial, Amrein et al. recruited 475 adult patients with an expected ICU stay > 48 hours

and 25(OH)D levels < 20 ng/mL in five ICUs from a single centre. The intervention arm received a loading dose of 540,000 IU of cholecalciferol followed by a maintenance dose of 90,000 IU every month for five months. In the overall statistical analysis, no benefits were found regarding mortality (ICU, 28-day, hospital, 6-month), ICU or hospital length of stay (LOS), infectious complications. Early biochemical outcomes were unchanged (baseline, days 3 and 7) apart from an increase in 25(OH)D serum levels. At day 28, a reduction in C-reactive protein (51 vs 31 mg/L) and procalcitonin (0.2 vs 0.1 ng/mL) as well as an increase in albumin (3.13 vs 3.25 g/dL) were found. At 6 months, no change persisted and biochemical analysis normalized in both arms. Interestingly, when data was restricted to patients with severe vitamin D deficiency defined by 25(OH)D < 12 ng/mL, improvement in mortality was found at day 28 (23% vs 34%), in-hospital (28% vs 47%) and persisted at 6 months (34.7% vs 50%). Finally, no subgroup of patients seemed to benefit more from intervention, including septic, cardiovascular or neurologic patients. A recent RCT evaluated how a single pre-oesophagectomy dose of 300,000 IU of cholecalciferol improved the postoperative pulmonary conditions[32]. The authors concluded that this high dose improved postoperative pulmonary vascular index, but not the extravascular lung water index. No improvement was found regarding 28 and 90-day mortality. In 2017, the protocol for the VITDALIZE study (NCT03188796) was published. In this multicentre, international RCT, the authors aim to recruit 2400 patients with severe vitamin D deficiency (i.e., 25(OH)D < 12 ng/mL) and administer either high dose oral/enteral vitamin D3 or placebo to evaluate 28-day mortality as the primary outcome. The trial is currently recruiting ICU patients and aims for completion in 2021. Similarly, the protocol for VITdAL-PICU was published in 2017, and will reproduce the VITdAL trial in a pediatric population[33]. In this trial, 67 patients should

be recruited to evaluate the feasibility of conducting a larger trial. Additionally, the VIOLET (Vitamin D to Improve Outcomes by Leveraging Early Treatment) study (NCT03096314) is a phase III RCT aimed at evaluating the effects of high-dose vitamin D3 in reducing mortality in patients with vitamin D deficiency (i.e.,  $25(\text{OH})\text{D} < 20 \text{ ng/mL}$ ) at risk for Acute Respiratory Distress Syndrome.

### **Current recommendations and recent meta-analysis**

Based on the two trials by Amrein et al.[27, 28], the latest Canadian Clinical Practice Guidelines published in 2015 concluded that there are insufficient data to make a recommendation regarding vitamin D supplementation in the critically ill[34]. More recently, the guidelines from the American Society of Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) only suggested vitamin D supplementation along with other vitamins and trace elements in obese patients with a previous history of bariatric surgery. This year, the European Society for Clinical Nutrition and Metabolism (ESPEN) has suggested that in critically ill patients with low plasma levels of vitamin D defined as  $25(\text{OH})\text{D} < 12.5 \text{ ng/mL}$ , a high dose of vitamin D3 equal to 500,000 IU as a single dose should be administered within a week after admission (grade of recommendation: B).

The VITdAL-ICU trial has yet been the only RCT powered to evaluate clinical outcomes[27], but several smaller trials also reported some interesting data[25, 26, 28, 29, 35]. Despite the various strategies of administration across the trials, including doses, route of supplementation and the chemical form of vitamin D administered, a recent systematic review and meta-analysis aggregated the 6 RCTs ( $n = 695$  patients) published so far. In this study, the authors were unable to show any effect on mortality (RR 0.84; 95%CI 0.66-1.06;  $P=0.14$ ), including in the subgroup of severely deficient ICU patients. Other clinical

outcomes such as hospital and ICU LOS, as well as infectious complications and duration of mechanical ventilation (MV) were also unchanged[30], although statistical imprecision may be explained by the sparse number of RCTs. In 2017, a meta-analysis by Putzu et al. concluded on a reduced mortality after vitamin D supplementation (OR 0.70; 95%CI 0.50-0.98; P=0.04)[31]. The difference between the two meta-analyses resides in the inclusion criteria, as Putzu et al included a positive RCT conducted in 30 patients with cystic fibrosis, in which the authors had found an improvement in mortality with vitamin D therapy [36].

### **Safety and recommended dietary allowance**

The recommended dietary allowance (RDA) of vitamin D is 600 IU for adults younger than 70 years old and corresponds to the daily dose maximizing bone health and muscle function. However, daily dose of vitamin D associated with nonskeletal health benefits has not been definitively determined. When above 70 years old, RDA is 800 IU. Nonetheless, a daily dose of at least 1500–2000 IU may be needed to raise 25(OH)D levels above 30 ng/mL [2].

In enteral nutrition (EN), 200 IU is present in about 1 L of EN formulas, whereas in ICU patients on parenteral nutrition (PN), commonly-used multivitamin products for adults have a 5 µg per unit dose [37]. In ICU patients, a single dose of 540,000 IU of vitamin D<sub>3</sub> by enteral route has been demonstrated to be able to normalize 25(OH)D levels in critically ill patients[27], although dose as low as 60,000 IU, administered twice over the first week after ICU admission, have been able to significantly improve 25(OH)D concentration[6]. Adverse effects due to vitamin D toxicity include hypercalcemia, which generally occurs when 25(OH)D concentration is greater than 160-200ng/mL. The upper limit of intake is 2000 IU per day, although toxicity occurs only

when daily intakes are in the range of 40.000 IU.

## Conclusion

In conclusion, it is hard not to consider, when treating ICU patients, the increased mortality in the general population when vitamin D levels are below 28 ng/mL. Nonetheless, current strategies of supplementing vitamin D do not seem beneficial unless patients are severely deficient, as proposed by the VITdAL-ICU trial[27]. Many different supplementation strategies have been tried and many functional serum markers have been studied, but the pharmacokinetic profile remain scarcely understood. These issues should be elucidated by currently recruiting large randomized controlled trials, including the VITDALIZE and the VIOLET studies.

## Authors' Contributions

All authors contributed to conception and design of this manuscript. PLL wrote the first draft while WM and FDA critically revised the manuscript. All authors gave final approval for this submission and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Figure caption

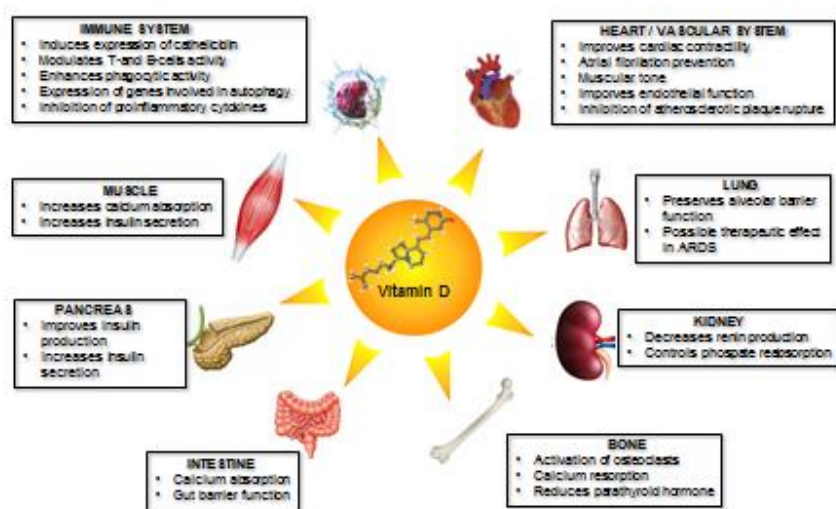


Figure 1.

Figure 1 – Biological effects of vitamin in the critically ill patient.

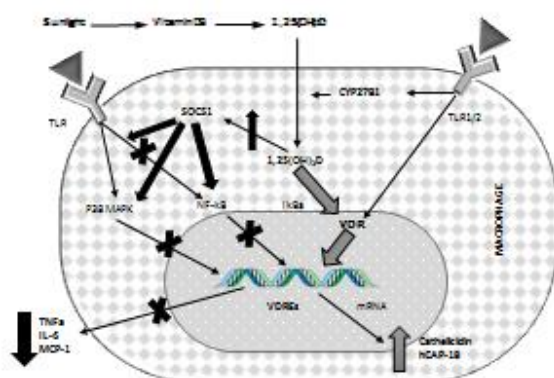


Figure 2.

**Figure 2 – Physiological effects of vitamin D on immunomodulation in the macrophage.**

CYP27B1, Cytochrome p450 27B1; hCAP-18, Human antimicrobial cathelicidin-18; IL-6, interleukin-6; MAPK, Mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; mRNA, messenger ribonucleic acid; NF-κB, Nuclear factor kappaB; SOCS1; TLR, Toll-like receptor; TNFα, Tumor necrosis factor alpha; VDR, Vitamin D receptor; VDREs, Vitamin D receptor elements.

**Table 1. Randomized controlled trials supplementing vitamin D in critically ill patients**

Clinical trial	Sample size, (n)	Intervention	Main findings
Amrein et al. 2011 [28]	25	540,000 IU of vitamin D (cholecalciferol 13, 5 mg) orally or enterally	Confirmation of a single dosis to correct vitamin D deficiency. No changes in clinical outcomes.
Leaf et al. 2014 [25]	67	A single IV dose of calcitriol 2µg	Higher hCAP-18 and IL-10 mRNA expression in interevntion arm. No changes in clinical outcomes.
Amrein et al. 2014 [27]	492	540,000 IU of vitamin D3 (cholecalciferol 13, 5 mg) PO or enterally	No effects on mortality, ICU and hospital LOS in overall analysis. Improvement of hospital, 28-d and 6-mo mortality in patients with severe deficiency (<12ng/mL).
Quraishi et al. 2015 [29]	30	High dose: 400,000 IU cholecalciferol PO or enterally Low dose: 200,000 IU cholecalciferol PO or enterally	Changes in bioavailable 25(OH)D are associated with circulating LL-37, but not overall 25(OH)D. No changes on inflammatory markers or clinical outcomes.
Nair et al. 2015 [26]	50	Two doses of 300.000 IU IM cholecalciferol vs. standard therapy received a single dose of 150.000 IU of IM cholecalciferol.	Increase in 25(OH)D levels were correlated to increase in cathelicidin at day 1 and 3. No changes on inflammatory markers or clinical outcomes.
Han et al. 2016 [35]	31	High dose: 100.000 IU daily for 5 days (500,000 IU total dose) PO Low dose: 50.000 IU daily for 5 days (250,000 IU total dose) PO	Significant reduction in hospital LOS with proportional increment to dose. No changes in other clinical outcomes. No changes in LL-37 levels.
Parekh et al. 2018 [32]	79	A single oral pre-oesophagectomy dose of 300,000 IU	Correction of 25(OH)D concentrations. Reduced postoperative pulmonary vascular permeability index. No change in extravascular water index

**Abbreviations:** hCAP: cathelicidin antimicrobial protein; ICU: intensive care unit; IL: interleukin; IV: intravenous; LOS: length of stay; PO: per os, orally; LL-37: human cathelicidin, LL-37; 25(OH)D: 25-hydroxyvitamin D