Journal of Acute Medicine 14(1): 1-8, 2024
DOI:10.6705/j.jacme.202403_14(1).0001
Review Article

Should I Supplement Vitamin D in a Patient With Sepsis?

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Sepsis is a potentially fatal organ failure produced by the host's immune response to infection. It is critical to identify risk factors associated with a poor prognosis in septic patients in order to develop new therapy options. Vitamin D deficiency (25-hydroxyvitamin cholecalciferol < 20 ng/mL) is common in critical and septic patients. Serum vitamin D concentrations are associated with an increased incidence of mortality in critically ill adult patients. In critically ill patients, vitamin D supplementation (a very high vitamin D_3 or cholecalciferol loading dosage as a single bolus dose ranging from 400,000 to 540,000 IU) is feasible and safe. Some of the trials and their post-hoc analyses evaluating vitamin D supplementation in severely sick individuals, including septic patients, suggested possible benefits in mortality (reduced 28-day mortality in the range of 8.1%–17.5%), and other outcomes (reduction in hospital length in the range from 9 to 18 days, and decrease in duration of mechanical ventilation in the range from 5 to 10 days). Despite the fact that many studies support the provision of vitamin D to septic patients, there are still many studies that contradict this opinion, and there is still debate about the recommendation to use vitamin D in sepsis. A pragmatic clinical approach in severe sepsis could be supplementation of vitamin D if serum levels are diminished (< 30 ng/mL). It appears that a single ultrahigh dose of vitamin D_3 (cholecalciferol) could be administered to the septic patient via an enteral tube, followed by daily or monthly maintenance doses. Parenteral administration might be reserved for a subgroup of septic patients with gastrointestinal, hepatic, or renal dysfunction. Future clinical trials designed exclusively for septic patients are required to assess the potential advantages of vitamin D. Possible impacts of selective activators of vitamin D receptors, such as paricalcitol, should be elucidated in sepsis. This emphasizes the requirement for more study and confirmation of any potential beneficial effects of vitamin D in sepsis.

Keywords: *cholecalciferol, sepsis, critical care*

Vitamin D Deficiency as a Novel Risk Factor for Stratification in Sepsis

Sepsis, a condition characterized by physiologic, pathological, and metabolic abnormalities caused by infection, is a potentially fatal organ malfunction produced by an unbalanced host response to infection and may advance to septic shock with dramatic severe failure of organs and death.[1] Patients suffering from sepsis have an extremely high death rate, and patients suffering from septic shock or multi-organ failure may have a fatality rate of more than 90%.[2] Despite many advances in treatment, sepsis is still a significant public health issue across the world.[3] In 2017, over 11 million sepsis-related fatalities have been documented, accounting for 19.7% of all worldwide mortality.[4] Sepsis pathogenesis is complex, and therefore, the treatment of sepsis is challenging.[5]

Received: April 26, 2023; Revised: June 27, 2023 (2nd); Accepted: July 31, 2023.
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Sepsis is frequent in critically ill patients.[6] Advanced age, increased use of invasive monitoring and treatment, antibiotic resistance, and the use of immunosuppressants are all well-known risk factors for the development of severe sepsis and septic shock in the critical care population.[7]

Sepsis should be considered a treatable condition[8] and the identification of risk variables linked with poor outcomes in sepsis is critical for improved risk stratification and finding out possible therapeutic implications to develop novel treatment targets in sepsis.[9]

Vitamin D is well known for its long-standing role in bone mineralization and calcium homeostasis, despite vitamin D receptors (VDRs) being found in practically all human body tissues and cells.[10]

Consequently, vitamin D, as it mediates many physiological processes, including immune functions,[11] might be an important risk stratification tool and therapeutic target in sepsis.

In vitro, vitamin D has also been shown to modify levels of systemic inflammatory cytokines, such as interleukin 6 or tumor necrosis factor-alpha, and may boost the production of antimicrobial peptides such as cathelicidin and b-defensin, which have been regarded as the body's initial line of defence against viral and bacterial infections.[12]

Indeed, there are plenty of pieces of evidence that vitamin D deficiency has been related to an increase in sepsis incidence and death in a variety of patients. In general, critical patients admitted to the intensive care unit (ICU) have lower serum vitamin D concentrations.[13]

Vitamin D insufficiency should be defined as a serum level of 25-hydroxyvitamin cholecalciferol (or 25[OH]D_3) < 30 ng/mL and the term "deficiency" should be used for 25(OH)D_3 levels < 20 ng/mL.[14]

A recent study found that the prevalence of vitamin D deficiency, defined as a serum level of 25-hydroxyvitamin D_3 (25-OH-cholecalciferol) level < 20 ng/mL, is very high in critically ill patients (59%). Furthermore, despite the fact that vitamin D deficiency was not linked to increased mortality rates, the use of ventilators and length of ICU stays were both increased in patients with vitamin D deficiency.[15] An observational study of 3,386 adult patients reported pre-admission 25-hydroxyvitamin D_3 serum concentration ≤ 15 ng/mL as a major risk factor for sepsis in severely sick patients.[16]

A meta-analysis of seven cohort studies involving 4,204 participants, including a significant number of septic patients, suggests that adult patients who are severely ill and have vitamin D insufficiency have an elevated risk of hospital death.[17] Another meta-analysis including 14 reports and involving 9,715 critically ill patients concluded that serum concentration levels of 25-hydroxyvitamin D_3 less than 50 nmol/L (20 ng/mL) were associated with a rise in the 30-day mortality rate, sepsis rates, in-hospital mortality, and infection rates, which suggests that vitamin D deficiency raises the risk of fatal infections and death from critical illness.[18] Furthermore, a meta-analysis of 10 observational studies reported that vitamin D deficiency was associated with increased susceptibility to sepsis.[19]

In the septic population, decreased levels of vitamin D are common findings. In a recent single-center study in 150 septic patients, the median serum concentration of 25-hydroxyvitamin D_3 was 19.03 ± 13.08 ng/mL, so the frequency of vitamin D insufficiency was 100%.[20]

The causal relationship between lower plasma vitamin D concentrations and sepsis is not entirely clear. There is a possibility that the state of sepsis itself leads to a metabolic disarrangement that is responsible for the reduction of plasmatic vitamin D concentration. Therefore, it is possible that vitamin D deficiency in septic patients is only one of the septic epiphenomena. Still, there is also evidence that decreased vitamin D levels among septic patients show significant associations with adverse outcomes. A surgical-ICU-based study demonstrated that vitamin D deficiency was inversely associated with mortality, cost of care, and length of stay.[21] Another study revealed a deficiency of 25-hydroxyvitamin D_3 before hospital admission as a major risk factor for acute renal injury and death in a critically ill adult patient cohort (the A 25-hydroxyvitamin D_3 deficiency was defined as less than 15 ng/mL).[22] A similar large 11-year multicenter observational study found that pre-admission 25(OH)D_3 deficiency was a predictor of susceptibility to positive blood culture, a significant predictor of ICU and in-hospital mortality, which continued to be a predictor of survival following multivariate comorbidity adjustments.[23]

In a retrospective cohort study among 121 adult patients, mortality was significantly higher in those with low vitamin D, and in a multivariate analysis, age and vitamin D deficiency were independently linked to a higher death rate.[24] A prospective observational study involving adult patients with severe sep-

sis or septic shock discovered a link between higher vitamin D levels and a more significant reduction in the degree of organ malfunction.[25] The same study found that a significant vitamin D deficiency affected 98% of sepsis patients. A study of 81 septic patients found that 79% had 25(OH)D_3 levels of < 75 nmol/L (< 30 ng/mL), and such patients had a higher likelihood of having severe sepsis and higher sequential organ failure assessment scores.[26] In a report of 168 patients with sepsis, the average vitamin D_3 serum level was 19.03 ± 13.08 ng/mL (considering 20–50 ng/mL the normal range, 61.6% had vitamin D deficiency), and the authors discovered a substantial relationship between mortality and serum vitamin D_3 levels.[27] A similar study of 107 adult patients demonstrated vitamin D deficiency during ICU admission (≤ 20 ng/mL) in 93.5% of the subjects, and 53.3% showed levels < 7 ng/mL. Patients had a greater death rate from sepsis if vitamin D levels were < 7 ng/mL. The multivariate regression analysis demonstrated that vitamin D level < 7 ng/mL on ICU admission was an independent predictor of sepsis-related mortality.[28] Recently, a single-center prospective study on 164 patients with severe sepsis demonstrated that at admission time, severe vitamin D deficiency (25[OH]D_3 < 12 ng/mL) was associated with higher mortality.[29]

On the contrary, some reports of a correlation between vitamin D serum levels and outcomes in septic patients could not find a clear relationship.[30] An interesting prospective multicenter observational study (FINNAKI study) conducted on 610 patients with severe sepsis (of these, 29% had septic shock) measured vitamin D levels on admission to the ICU and showed vitamin D deficiency (< 50 nmol/L or 20 ng/mL) in 55% patients. According to their research, there was no difference in 90-day mortality between participants with and without vitamin D insufficiency. The multivariable regression model showed that 90-day mortality could not be predicted by low vitamin D levels, despite the fact that subjects who are vitamin D deficient more commonly showed diabetes, had higher levels of C-reactive protein, had more hospital infections, and more frequently experienced acute renal injury.[31]

Nevertheless, a recent meta-analysis of 8 studies with 1,736 patients showed that lower 25 (OH)D_3 was independently linked to a higher risk of death in septic patients upon admission.[32]

Finally, it should be taken into account that 25(OH)D_3 is an inactive circulating type of vitamin D measured in the studies mentioned above, and 25(OH)D_3 has to be transformed into the active hormone named 1,25-dihydroxyvitamin-D3 or 1,25$(OH)_2D_3$, mostly by a renal 1α-hydroxylase enzyme.[33] Only active 1,25$(OH)_2D_3$ can bind the nuclear VDR, resulting in the production of antimicrobial peptides, cathelicidin, and defensin by neutrophils.[34]

One study aimed to determine the connection between vitamin D and outcomes in sepsis measured serum 1,25$(OH)_2D_3$ and demonstrated a decrease in serum 1,25$(OH)_2D_3$ in sepsis non-survivors versus survivors. Additionally, the serum 1,25$(OH)_2D_3$ level, and not 25(OH)D_3, during the course of 72 hours, was an excellent indicator of outcome among septic patients and was considered related to increased mortality in sepsis patients.[35]

In summary, the findings of the aforementioned studies strongly suggest that in septic patients, vitamin D deficiency may be a new independent predictor of death risk, as well as a novel risk stratification factor in sepsis. It is unclear whether low vitamin D levels in critical patients reflect disease severity or a general poor health status in obese, diabetic, elderly, and other patients, or whether they are an independent factor in sepsis morbidity and mortality.

Possible Therapeutic Approach for Vitamin D Deficiency in Sepsis

In an animal sepsis model, vitamin D deficiency was associated with defective macrophage phagocytosis and decreased local expression of the cathelicidin-related antimicrobial peptide. In the intratracheal lipopolysaccharide model, 1,500 IU of intraperitoneal cholecalciferol (D_3) treatment 6 hours post-injury decreased cellular damage, hypoxia, and alveolar inflammation.[36] A similar study in an experimental model of rat sepsis demonstrated that pre-treatment with 1,25$(OH)_2D_3$ reduced sepsis-induced thrombocytopenia, indicating a protective role for 1,25-dihydroxyvitamin D_3 supplementation against the progression of sepsis-induced disseminated intravascular coagulation.[37]

The results of the above-presented studies supported the theory that vitamin D administration might lower mortality in individuals with sepsis and severe vitamin D deficiency.[38]

In critically ill patients, vitamin D supplementation is feasible and safe, and it has been shown to improve vitamin D deficiency in a matter of days.

Despite the majority of studies indicating potential benefits in terms of mortality or ICU stay, conflicting results have been found in randomized controlled trials examining the impact of vitamin D in critically ill individuals.

A randomized double-blind clinical trial found that a single bolus dose of 300,000 IU vitamin D_3 helped reduce serum procalcitonin concentrations after seven days in patients with ventilator-associated pneumonia.[39] A meta-analysis of seven similar smaller studies published between 2011 and 2016 on a total of 716 patients was conducted to assess if giving vitamin D to very sick individuals lowers mortality and found that intervention, compared to placebo, had a considerably reduced death rate.[40] A meta-analysis of six studies including 695 patients was conducted to assess the therapeutic effects of vitamin D therapy in individuals with severe illnesses. The analysis found no reduction in mortality or other outcomes (ICU and hospital stays, infection rate, and ventilation days), and the authors concluded that daily doses of vitamin D greater than 300,000 IU did not improve mortality or ICU stay.[41]

The large-scale PETAL-VIOLET trial was carried out at 44 hospitals across the United States and included 1,358 severe patients (more than 80% were admitted to the medical ICU) with vitamin D deficiency. The study protocol included very early vitamin D_3 supplementation (a single enteral dose of 540,000 IU) in severely ill patients. The results showed that high-dose vitamin D_3 supplementation in the early stages did not have an advantage over a placebo in preventing 90-day mortality or hospital stay, and there were no differences between the groups of participants.[42]

The second large study, the VITdAL-ICU randomized clinical trial, was conducted among 492 seriously ill adult subjects with low vitamin D levels (20 ng/mL) chosen to receive either vitamin D_3 administered orally or through nasogastric tube once at a dosage of 540,000 IU, followed by monthly maintenance doses of 90,000 IU for 5 months; or a placebo.[43] There was no difference between groups in hospital stay duration, hospital mortality, or 6-month mortality. In the analysis of the severe vitamin D deficiency ($\leq$ 12 ng/mL) subgroup analysis, only hospital mortality decreased significantly for vitamin D_3 recipients (28.6% died in the vitamin D_3 treated group compared with 46.1% died in the placebo group). The authors came to the conclusion that high-dose vitamin D_3 treatment vs. a placebo did not shorten hospital stays or decrease death among critically ill patients with vitamin D insufficiency. These findings would suggest that individuals with sepsis and severe vitamin D insufficiency might have a better chance of surviving with vitamin D therapy. Vitamin D_3 therapy had no survival advantage for those with less severe vitamin D insufficiency. However, after 6 months, the authors report a significant improvement in hand grip strength and a physical performance scale, indicating a possible advantage of vitamin D in the healing and rehabilitation phase of post-intensive care syndrome.[44]

A post-hoc analysis of the VITDAL-ICU study, excluding patients who died or were discharged within 7 days after study drug administration, among the remaining 410 patients, found that a high vitamin D intake was linked to a reduction in mortality (14.7% mortality in the treatment arm, and 22.8% in the placebo arm).[45]

A recent meta-analysis of 10 randomized control trials with 2,058 patients was conducted to confirm the impact of vitamin D_3 on critically ill individuals. Although a high vitamin D_3 dose did not improve mortality in critically ill patients, it did dramatically shorten their time on the ventilator; for example, in one of the included studies, duration of mechanical ventilation was 27.72 ± 22.48 in control vs. 17.63 ± 14.00 days in intervention arm.[46]

A very recent meta-analysis of 11 randomized control trials involving 2,187 critically ill patients concluded that vitamin D administration shortens mechanical ventilation and ICU stays.[47] There was no statistically significant difference in mortality or length of hospital stay. Interestingly, in subgroup analysis, the risk of death, the length of mechanical breathing, and ICU stays were all lower when vitamin D was administered via the parenteral route. Overall, the authors found a nonsignificant tendency toward a lower death rate in the vitamin D group.

The very last meta-analysis was conducted to ascertain the impact of vitamin D on significant clinical outcomes and included 16 randomized clinical trials with 2,449 critically ill patients.[48] It was discovered that supplementing with vitamin D was associated with lower overall mortality (in one report septic patients' 90-day mortality was 34% in the vitamin D supplemented group vs. 66% in the placebo group), shorter lengths of stay in ICUs (according to one of the included trials 18.3 ± 8.4 vs. 25.4 ± 6.6 days in the intervention and placebo arms), and shorter durations of mechanical ventilation (15.7 ± 9.3 vs. 22.6 ± 9.1

days in vitamin D and placebo arms). Compared to enteral administration, parenteral administration had a larger impact on total mortality. The authors concluded that in severely ill individuals, vitamin D treatment may lower mortality, with additional benefits when administered parenterally.

However, the aforementioned systematic reviews and meta-analyses had some limitations, such as the large heterogeneity of the included population and intervention protocols. The only two large-scale studies were the VITdAL-ICU trial and the PETAL-VIOLET trial.

Finally, many of these studies on the ICU population included a mixed ICU population, including septic patients. Only a small number of the studies included in the meta-analyses were conducted specifically for the septic population. Consecutively, interventional studies on vitamin D replenishment in critical ICU populations should not be automatically extrapolated to septic patients and have to be evaluated cautiously for sepsis. Additionally, the VITdAL-ICU and PETAL-VIOLET trials included critically ill patients with a low sepsis prevalence at the time of enrolment (7.7% and 33.3%, respectively), so sepsis subgroup analyses did not allow a clear assessment of vitamin D supplementation's effectiveness in septic patients.

However, some studies were conducted exclusively in a cohort of patients with sepsis. A randomized prospective double-blind placebo research was carried out in 57 septic patients in the ICU, with 29 patients supplemented with 300,000 IU of vitamin D_3 for deficiency (25[OH]D_3 20–30 μg/L) or insufficiency (25[OH]D_3 < 20 μg/L). There was no significant difference in the duration of mechanical ventilation, length of ICU stay, 28-day mortality, or 28-day accumulated survival between the D_3 treatment group and the placebo group. The authors concluded that the outcomes of sepsis patients in ICUs cannot be improved by vitamin D_3 treatment.[49] In an additional study on new-onset severe sepsis or septic shock patients receiving 200,000 IU and 400,000 IU of cholecalciferol versus placebo, within 24 hours, a rapid and safe improvement of bioavailable 25-hydroxyvitamin D_3 levels was reported with concomitant increases in circulating cathelicidin.[50]

Vitamin D can be delivered orally, intravenously, or intramuscularly. In previous studies, an enteral vitamin D_3 excessive loading dosage (a single bolus dose from 400,000 to 540,000 IU) may quickly raise vitamin D levels, and there were very few negative effects observed. However, vitamin D_3 therapy produced serum levels of 25-hydroxyvitamin D higher than 30 ng/mL only in 50% of the patients.[51] Furthermore, as some studies have shown, the route of administration of vitamin D may play an important role in the efficacy of vitamin D. Gao and co-workers[46] observed in their meta-analysis a substantial drop in mortality in the subset of subjects who received intramuscular injections of vitamin D_3. Similar conclusions in the meta-analysis by Singh and co-workers[47] on the reduction of mortality risk and ventilation were found in a subgroup analysis of participants with a parenteral route of vitamin D administration. The same conclusion arises from the last meta-analysis by Menger and co-workers[48] with a greater effect of parenteral vitamin D on overall mortality. Intramuscular supplementation may be a more efficient option than enteral vitamin D replacement due to the frequency of gastrointestinal dysfunction and unreliable enteral absorption in severely ill patients. Additionally, a recent prospective randomized trial included 36 ventilated ICU patients who received either a single intramuscular vitamin D injection of 300,000 IU or a placebo and found that the intervention arm lowered the length of stay (18.3 ± 8.4 vs. 25.4 ± 6.6 days) and mechanical ventilation duration (15.7 ± 9.3 vs. 22.6 ± 9.1 days).[52] As a result, patients with severe vitamin D deficiency who do not respond to oral vitamin D supplementation may benefit from a high parenteral dose of native vitamin D. It should be noted that in critical illness and sepsis, the gastrointestinal function is compromised, which impedes enteral absorption of vitamin D; in addition to renal failure or drug-related cytochrome P450 impairments in the liver, factors interfere with vitamin D_3 hydroxylation. Specifically, supplementations are provided in a form that is inert and requires continuous metabolic processes to become active. However, many very sick patients are unable to properly activate natural vitamin D.

The timing of administration should also be considered an important issue, as the conversion of inactive vitamin D_3 into the active form requires 2–3 days, and consecutively delayed administration might result in ineffective outcomes in critical patients with sepsis.

In conclusion, sufficient serum levels of vitamin D are important for immune system regulation and have the ability to prevent both a severe infection and an excessively active inflammatory response in sepsis.

As the VDR is distributed in many organs and affects different signaling pathways, vitamin D could maintain the function of many organs affected by sepsis.[53]

The results of some studies imply that vitamin D administration may be related to a probability of improving outcomes in critically ill individuals, including septic patients. For example, administration of vitamin D reduced serum procalcitonin, improved physical performance, lowered the length of stay, and decreased mechanical ventilation duration. Those studies that showed the benefit of vitamin D supplementation in critically ill patients demonstrated a significant reduction in hospital length in the range from 9 to 18 days, decrease in ICU length of stay to 7 days, and decrease in duration of mechanical ventilation in the range from 5 to 10 days. More importantly, some of these studies and their post-hoc analyses proved that vitamin D supplementation reduced 28-day mortality in the range of 8.1%–17.5%, and 90-day mortality by 32.3%. These favourable effects are particularly demonstrated if vitamin D is administered parenterally. However, it should be emphasized that not all studies have shown the beneficial effect of vitamin D supplementation in septic patients. The effect of vitamin D supplementation on reducing mortality in patients with sepsis is less clear. Most studies have not demonstrated the effect of vitamin D supplementation in septic patients on mortality reduction, although some studies have shown that in a subpopulation of patients with extremely low initial plasmatic vitamin D levels, administration of vitamin D has an impact on mortality reduction.

Therefore, it is impossible to provide an unequivocal recommendation for vitamin D administration in septic patients due to the conflicting findings of the studies. A reasonable clinical approach in severe sepsis could be supplementation of vitamin D in cases of diminished serum levels (< 30 ng/mL), ideally during the first admission day. It appears that a single ultrahigh dose of up to 540,000 IU of vitamin D_3 (cholecalciferol), which has been shown to be both safe and effective, could be administered to the septic patient via an enteral tube or peroral, followed by a daily maintenance dose of no more than 4,000 IU (or monthly maintenance doses of 90,000 IU). Parenteral administration might be reserved for the subgroup of septic patients with gastrointestinal, hepatic, or renal dysfunction, bearing in mind that the clinical effects of vitamin D parenteral supplementation in septic patients appear to be related to accentuated beneficial effects.

To assess the potential advantages of vitamin D in sepsis, future clinical trials with significant sample sizes and subjects with severe vitamin D insufficiency are required. The ongoing VITDALIZE study, in which ICU patients with severe vitamin D deficiency (25-hydroxyvitamin $D_3 \leq 12$ ng/mL) were given a loading dose of 540,000 IU of cholecalciferol within 72 hours of ICU admission, followed by 4,000 IU daily for 90 days or a placebo, will provide answers to some of the arising questions in this field.[54]

Also, in the future, it will be necessary to investigate the possible impact of selective activators of VDR (for example, paricalcitol) among the population of patients with sepsis, as it is well known that paricalcitol has beneficial anti-inflammatory and antioxidant properties on the renal and cardiovascular systems.[55]

References

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801-810. doi:10.1001/jama.2016.0287
2. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. *BMJ* 2016;353:i1585. doi:10.1136/bmj.i1585
3. Fleischmann C, Scherag A, Adhikari NKJ, et al; International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 2016;193:259-272. doi:10.1164/rccm.201504-0781OC
4. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020;395:200-211. doi:10.1016/S0140-6736(19)32989-7
5. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:840-851. doi:10.1056/NEJMra1208623
6. Stoller J, Halpin L, Weis M, et al. Epidemiology of severe sepsis: 2008-2012. *J Crit Care* 2016;31:58-62. doi:10.1016/j.jcrc.2015.09.034
7. Rudd KE, Kissoon N, Limmathurotsakul D, et al. The global burden of sepsis: barriers and potential solutions. *Crit Care* 2018;22:232. doi:10.1186/s13054-018-2157-z
8. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 2017;376:2235-2244. doi:10.1056/NEJMoa1703058
9. Deutschman CS, Tracey KJ. Sepsis: current dogma and new perspectives. *Immunity* 2014;40:463-475.

doi:10.1016/j.immuni.2014.04.001

10. Giustina A, Adler RA, Binkley N, et al. Consensus statement from 2nd International Conference on Controversies in Vitamin D. *Rev Endocr Metab Disord* 2020;21:89-116. doi:10.1007/s11154-019-09532-w
11. Vanherwegen AS, Gysemans C, Mathieu C. Regulation of immune function by vitamin D and its use in diseases of immunity. *Endocrinol Metab Clin North Am* 2017;46:1061-1094. doi:10.1016/j.ecl.2017.07.010
12. Yılmaz H, Sahiner E, Darcin T, Celik HT, Bilgic MA, Akcay A. Is vitamin D supplementation a new hope for the therapy of the septic shock? *Endocr Regul* 2013;47:133-136. doi:10.4149/endo_2013_03_133
13. Lucidarme O, Messai E, Mazzoni T, Arcade M, du Cheyron D. Incidence and risk factors of vitamin D deficiency in critically ill patients: results from a prospective observational study. *Intensive Care Med* 2010;36:1609-1611. doi:10.1007/s00134-010-1875-8
14. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266-281. doi:10.1056/NEJMra070553
15. Chen KW, Chen CW, Yuan KC, et al. Prevalence of vitamin D deficiency and associated factors in critically ill patients: a multicenter observational study. *Front Nutr* 2021;13;8:768804. doi:10.3389/fnut.2021.768804
16. Moromizato T, Litonjua AA, Braun AB, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill. *Crit Care Med* 2014;42:97-107. doi:10.1097/CCM.0b013e31829eb7af
17. Zhang YP, Wan YD, Sun TW, Kan QC, Wang LX. Association between vitamin D deficiency and mortality in critically ill adult patients: a meta-analysis of cohort studies. *Crit Care* 2014;18:684. doi:10.1186/s13054-014-0684-9
18. de Haan K, Groeneveld ABJ, de Geus HRH, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. *Crit Care* 2014;18:660. doi:10.1186/s13054-014-0660-4
19. Upala S, Sanguankeo A, Permpalung N. Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis. *BMC Anesthesiol* 2015;15:84. doi:10.1186/s12871-015-0063-3
20. Bayat M , Gachkar L , Zahirnia M , Hadavand F. Association between low serum vitamin D levels and sepsis: a single-center study in Tehran, Iran. *Arch Clin Infect Dis* 2021;16:e102926. doi:10.5812/archcid.102926
21. Matthews LR, Ahmed Y, Wilson KL, Griggs DD, Danner OK. Worsening severity of vitamin D deficiency is associated with increased length of stay, surgical intensive care unit cost, and mortality rate in surgical intensive care unit patients. *Am J Surg* 2012;204:37-43. doi:10.1016/j.amjsurg.2011.07.021
22. Braun AB, Litonjua AA, Moromizato T, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and acute kidney injury in the critically ill. *Crit Care Med* 2012;40:3170-3179. doi:10.1097/CCM.0b013e318260c928
23. Braun A, Chang D, Mahadevappa K, et al. Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. *Crit Care Med* 2011;39:671-677. doi:10.1097/CCM.0b013e318206ccdf
24. Rech MA, Hunsaker T, Rodriguez J. Deficiency in 25-hydroxyvitamin D and 30-day mortality in patients with severe sepsis and septic shock. *Am J Crit Care* 2014;23:e72-e79. doi:10.4037/ajcc2014723
25. Alves FS, Freitas FGR, Bafi AT, Azevedo LCP, Machado FR. Serum concentrations of vitamin D and organ dysfunction in patients with severe sepsis and septic shock. *Rev Bras Ter Intensiva* 2015;27:376-382. doi:10.5935/0103-507X.20150063
26. Ginde AA, Camargo CA Jr, Shapiro NI. Vitamin D insufficiency and sepsis severity in emergency department patients with suspected infection. *Acad Emerg Med* 2011;18:551-554. doi:10.1111/j.1553-2712.2011.01047.x
27. Shojaei M, Sabzeghabaei A, Valaei Barhagh H, Soltani S. The correlation between serum level of vitamin D and outcome of sepsis patients; a cross-sectional study. *Arch Acad Emerg Med* 2019;7:e1.
28. De Pascale G, Vallecoccia MS, Schiattarella A, et al. Clinical and microbiological outcome in septic patients with extremely low 25-hydroxyvitamin D levels at initiation of critical care. *Clin Microbiol Infect* 2016;22:456.e7-456.e13. doi:10.1016/j.cmi.2015.12.015
29. Malinverni S, Ochogavia Q, Lecrenier S, et al. Severe vitamin D deficiency in patients admitted to the emergency department with severe sepsis is associated with an increased 90-day mortality. *Emerg Med J* 2023;40:36-41. doi:10.1136/emermed-2021-211973
30. Cecchi A, Bonizzoli M, Douar S, et al. Vitamin D deficiency in septic patients at ICU admission is not a mortality predictor. *Minerva Anestesiol* 2011;77:1184-1189.
31. Ala-Kokko TI, Mutt SJ, Nisula S, et al; FINNAKI Study Group. Vitamin D deficiency at admission is not associated with 90-day mortality in patients with severe sepsis or septic shock: Observational FINNAKI cohort study. *Ann Med* 2016;48:67-75. doi:10.3109/07853890.2015.1134807
32. Li Y, Ding S. Serum 25-Hydroxyvitamin D and the risk of mortality in adult patients with Sepsis: a meta-analysis. *BMC Infect Dis* 2020;20:189. doi:10.1186/s12879-020-4879-1
33. Huish SA, Jenkinson C, Dunn JA, Meredith DJ, Bland R, Hewison M. Low serum 1,25(OH)2D3 in end-stage renal disease: is reduced 1α-hydroxylase the only problem? *Endocr Connect* 2021;10:1291-1298. doi:10.1530/EC-21-

0372

34. Lagishetty V, Chun RF, Liu NQ, Lisse TS, Adams JS, Hewison M. 1alpha-hydroxylase and innate immune responses to 25-hydroxyvitamin D in colonic cell lines. *J Steroid Biochem Mol Biol* 2010;121:228-233. doi:10.1016/j.jsbmb.2010.02.004
35. Nguyen HB, Eshete B, Lau KHW, Sai A, Villarin M, Baylink D. Serum 1,25-dihydroxyvitamin D: an outcome prognosticator in human sepsis. *PLoS One* 2013;8:e64348. doi:10.1371/journal.pone.0064348
36. Parekh D, Patel JM, Scott A, et al. Vitamin D deficiency in human and murine sepsis. *Crit Care Med* 2017;45:282-289. doi:10.1097/CCM.0000000000002095
37. Møller S, Laigaard F, Olgaard K, Hemmingsen C. Effect of 1,25-dihydroxy-vitamin D3 in experimental sepsis. *Int J Med Sci* 2007;4:190-195. doi:10.7150/ijms.4.190
38. Cutuli SL, Cascarano L, Tanzarella ES, et al. Vitamin D status and potential therapeutic options in critically ill patients: a narrative review of the clinical evidence. *Diagnostics (Basel)* 2022;12:2719. doi:10.3390/diagnostics12112719
39. Miroliaee AE, Salamzadeh J, Shokouhi S, et al. Effect of vitamin D supplementation on procalcitonin as prognostic biomarker in patients with ventilator associated pneumonia complicated with vitamin D deficiency. *Iran J Pharm Res* 2017;16:1254-1263.
40. Putzu A, Belletti A, Cassina T, et al. Vitamin D and outcomes in adult critically ill patients. A systematic review and meta-analysis of randomized trials. *J Crit Care* 2017;38:109-114. doi:10.1016/j.jcrc.2016.10.029
41. Langlois PL, Szwec C, D'Aragon F, Heyland DK, Manzanares W. Vitamin D supplementation in the critically ill: a systematic review and meta-analysis. *Clin Nutr* 2018;37:1238-1246. doi:10.1016/j.clnu.2017.05.006
42. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network; Ginde AA, Brower RG, Caterino JM, et al. Early high-dose vitamin D_3 for critically ill, vitamin D-deficient patients. *N Engl J Med* 2019;381:2529-2540. doi:10.1056/NEJMoa1911124
43. Amrein K, Schnedl C, Holl A, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. *JAMA* 2014;312:1520-1530. doi:10.1001/jama.2014.13204
44. Sosnowski K, Lin F, Mitchell ML, White H. Early rehabilitation in the intensive care unit: an integrative literature review. *Aust Crit Care* 2015;28:216-225. doi:10.1016/j.aucc.2015.05.002
45. Martucci G, McNally D, Parekh D, et al. Trying to identify who may benefit most from future vitamin D intervention trials: a post hoc analysis from the VITDAL-ICU study excluding the early deaths. *Crit Care* 2019;23:200. doi:10.1186/s13054-019-2472-z
46. Gao Z, Xie J, Li C, Liu L, Yang Y. High dose vitamin D3 supplementation is not associated with lower mortality in critically ill patients: a meta-analysis of randomized control trials. *Front Nutr* 2022;9:762316. doi:10.3389/fnut.2022.762316
47. Singh S, Sarkar S, Gupta K, Rout A. Vitamin D supplementation in critically ill patients: a meta-analysis of randomized controlled trials. *Cureus* 2022;14:e24625. doi:10.7759/cureus.24625
48. Menger J, Lee ZY, Notz Q, et al. Administration of vitamin D and its metabolites in critically ill adult patients: an updated systematic review with meta-analysis of randomized controlled trials. *Crit Care* 2022;26:268. doi:10.1186/s13054-022-04139-1
49. Ding F, Zang B, Fu J, Ji K. Effect of vitamin D_3 on the severity and prognosis of patients with sepsis: a prospective randomized double-blind placebo study. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2017;29:106-110. doi:10.3760/cma.j.issn.2095-4352.2017.02.003 [In Chinese]
50. Quraishi SA, De Pascale G, Needleman JS, et al. Effect of cholecalciferol supplementation on vitamin D status and cathelicidin levels in sepsis: a randomized, placebo-controlled trial. *Crit Care Med* 2015;43:1928-1937. doi:10.1097/CCM.0000000000001148
51. Amrein K, Sourij H, Wagner G, et al. Short-term effects of high-dose oral vitamin D3 in critically ill vitamin D deficient patients: a randomized, double-blind, placebo-controlled pilot study. *Crit Care* 2011;15:R104. doi:10.1186/cc10120
52. Sistanizad M, Kouchek M, Miri M, et al. High dose vitamin D improves total serum antioxidant capacity and ICU outcome in critically ill patients—a randomized, double-blind clinical trial. *Eur J Integr Med* 2021;42:101271. doi:10.1016/j.eujim.2020.101271
53. Trochoutsou AI, Kloukina V, Samitas K, Xanthou G. Vitamin-D in the immune system: genomic and non-genomic actions. *Mini-Rev Med Chem* 2015;15:953-963. doi:10.2174/1389557515666150519110830
54. Amrein K, Parekh D, Westphal S, et al; VITDALIZE Collaboration Group. Effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients with severe vitamin D deficiency: a study protocol of a multicentre, placebo-controlled double-blind phase III RCT (the VITDALIZE study). *BMJ Open* 2019;9:e031083. doi:10.1136/bmjopen-2019-031083
55. Duplancic D, Cesarik M, Poljak NK, et al. The influence of selective vitamin D receptor activator paricalcitol on cardiovascular system and cardiorenal protection. *Clin Interv Aging* 2013;8:149-156. doi:10.2147/CIA.S38349