Vitamin D, Hospital-Acquired Infections and Mortality in Critically Ill Patients: Emerging Evidence

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Introduction

Hospital-acquired infections (HAIs) represent a major cause of morbidity and mortality worldwide. With a reported incidence of 22 new episodes per 100,000 admissions, this equates to approximately 2 million new cases of HAI each year, and is the cause of nearly 100,000 deaths annually in the United States alone [1]. Catheter-associated urinary tract infections (CAUTIs) are the most common cause of HAIs, followed by surgical site infections (SSIs), hospital-acquired pneumonia (HAP), and hospital-acquired bloodstream infections (HABSIs). Additional healthcare expenditure due to HAIs in the United States is estimated at between $28 and $45 billion annually, and is mainly driven by an increase in hospital length of stay (LOS).

Current HAI reduction strategies principally include behavioral interventions (e. g., removal of unnecessary devices), increased staff education (directed towards medical and nursing providers), reduction of microbial transmission through infection control measures (e. g., use of bundle kits for placement of central venous catheters), improvements to hand hygiene, and the adoption of antibiotic stewardship programs. And although hospitalized patients are known to exhibit varying degrees of immune dysfunction, few modifiable risk factors have been identified to improve this state [2]. Recently, however, sub-optimal vitamin D status has been

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Table 1 Main investigations on vitamin D, hospital-acquired infections and mortality in the critically ill patient setting

First author	Year	Design of the study	Sample size	Results
Vitamin D and sepsis in hospitalized patients				
Ginde [9]	2011	Prospective cohort study	81 septic patients admitted from the ED	25(OH)D < 30 ng/ml (n = 64) was associated with severity of sepsis (p = 0.005)
Braun [19]	2011	Retrospective cohort study	2,399 hospital admitted patients (1,160 subgroup who had blood cultures taken)	25(OH)D < 15 ng/ml was associated with HABSI (p = 0.03) occurrence and mortality (p < 0.001)
Cecchi [13]	2011	Prospective cohort study	170 ICU patients (92 with severe sepsis/septic shock)	Lower 25(OH)D levels in septic patients. No association with mortality in multivariable analysis
Flynn [17]	2012	Prospective cohort study	66 ICU patients	Hypovitaminosis D (74%) was associated with a trend to higher infection/sepsis rate (p = 0.09)
Nair [10]	2013	Prospective cohort study	100 ICU patients (26 with sepsis)	25(OH)D admission levels correlated with higher SAPS II, APACHE II scores (p < 0.001; p = 0.02) and fewer hospital-free days (OR 3.15; 95% CI 1.18–8.43)
Lange [14]	2013	Retrospective cohort study	5,628 hospital admitted patients	25(OH)D ≤ 15 ng/ml associated with increased odds of sepsis (OR, 1.29; 95% CI 1.06–1.57; p = 0.01)
Nguyen [15]	2013	Prospective cohort study	91 septic hospital admitted patients	Low $1,25(OH)_2D$ levels associated with increased 30-day mortality (p < 0.01)
Quraishi [20]	2013	Retrospective cohort study	2,135 hospitalized patients	25(OH)D < 10 ng/ml associated with significantly increased odds of HABSI occurrence
Moromizato [16]	2014	Retrospective cohort study	3,386 ICU patients	Preadmission 25(OH)D level an independent predictor of sepsis development in ICU (p = 0.009)
Amrein [18]	2014	Retrospective cohort study	655 ICU patients	Death prevalent in septic patients with vitamin D deficiency

Table 1 (Continued)

First author	Year	Design of the study	Sample size	Results
Vitamin D and SSI and CDI				
Quraishi [26]	2013	Retrospective cohort study	770 gastric bypass surgery patients	Patients with 25(OH)D < 30 ng/ml at higher risk of HAI [OR 3.05 (95% CI 1.34–6.94)] and SSI [OR 4.14 (95% CI 1.16–14.83)]
Zittermann [27]	2016	Prospective cohort study	3,340 cardiac surgical patients	$1,25(OH)_2D$ levels independent risk factors for post-surgical infections (OR 2.57, 95% CI 1.47–4.49)
Quraishi [28]	2014	Retrospective cohort study	5,047 patients admitted to the hospital	25(OH)D levels < 10 ng/ml and 10–19.9 ng/ml increased CDI risk (OR 4.96; 95% CI 1.84–13.38 and OR 3.36; 95% CI 1.28–8.85)
Wang [30]	2014	Prospective cohort study	62 hospitalized patients with CDI	Normal 25(OH)D levels predicted CDI resolution ($p = 0.028$)
Van der Wilden [32]	2015	Prospective cohort study	100 hospitalized patients with CDI	$25(OH)D_3$ levels significantly correlated with disease severity (OR 0.92; CI 0.87–0.98; $p = 0.008$); 1 ng/ml increase in $25(OH)D_3$ decreased by 8% the risk of severe CDI
Vitamin D and in-hospital mortality				
McKinney [41]	2011	Retrospective cohort study	136 ICU patients	Risk of death significantly higher in ICU patients with vitamin D deficiency (RR 1.81)
Venkatram [42]	2011	Retrospective cohort study	437 ICU patients	Hospital mortality higher in patients with 25(OH)D deficiency ($p = 0.01$)
Arnson [45]	2012	Prospective cohort study	130 ICU patients	Shorter survival curves in patients with 25(OH)D < 20 ng/ml ($p < 0.05$)
Remmelts [36]	2012	Prospective cohort study	272 hospitalized patients	25(OH)D < 20 ng/ml independent predictor of 30-day mortality (AUC 0.69; 95% CI 0.71–0.94)
Braun [43]	2012	Retrospective cohort study	1,325 ICU patients	25(OH)D < 15 ng/ml associated with increased mortality ($p = 0.01$)
Higgins [46]	2012	Prospective cohort study	196 ICU patients	Higher levels of 25(OH)D were associated with a shorter time-to-alive ICU discharge (HR 2.11; 95% CI, 1.27–3.51)

Table 1 (Continued)

First author	Year	Design of the study	Sample size	Results
Matthews [47]	2012	Prospective cohort study	258 ICU patients	Severe/moderate deficiency status (< 26 ng/ml) was associated with significantly increased ICU costs (p = 0.027/p = 0.047)
Aygencel [44]	2013	Prospective cohort study	201 ICU patients	25(OH)D < 20 ng/ml was associated with increased mortality rate (43% vs 26 %; p = 0.027)
Lange [14]	2013	Retrospective cohort study	26,603 hospitalized patients	25(OH)D < 15 ng/ml and 25(OH)D 15–30 ng/ml were associated with increased all cause 30-day mortality (p < 0.001; p = 0.003)
Amrein [40]	2013	Retrospective cohort study	24,094 hospitalized patients	25(OH)D levels < 20 and ≥ 60 ng/ml before hospitalization associated with increased odds of 90-day mortality (U shaped relationship)
Quraishi [4]	2014	Prospective cohort study	100 ICU patients	Significant association of 25(OH)D with readmission (OR per 1 ng/ml, 0.84; 95% CI, 0.74–0.95) and mortality (OR per 1 ng/ml, 0.84; 95% CI 0.73–0.97)
Amrein [51]	2014	Randomized controlled trial	492 ICU patients	Lower mortality associated with vitamin D supplementation in patients with severe vitamin D deficiency (p = 0.04)
De Pascale [48]	2016	Retrospective cohort study	107 ICU septic patients	Extremely low 25(OH)D level independent predictor of sepsis-related mortality (p = 0.01)

25(OH)D: 25-hydroxyvitamin D; *ED*: emergency department; *HABSI*: hospital-acquire bloodstream infection; *ICU*: intensive care unit; *SAPS II*: Simplified Acute Physiology Score II; *APACHE II*: Acute Physiology and Chronic Health Evaluation II; *SSI*: skin and soft tissue infection; *CDI*: *Clostridium difficile* infection; *OR*: odds ratio; *CI*: confidence interval

investigated as a potential risk factor for HAIs and other undesirable clinical outcomes [3].

Indeed, growing evidence suggests that low vitamin D status, as characterized by serum 25-hydroxyvitamin D [25(OH)D] levels < 20 ng/m, increases the risk of cardiovascular disease, cancer, and pulmonary ailments in community dwelling individuals. There is now also increasing evidence of a strong relationship between hypovitaminosis D and increased morbidity as well as higher mortality in hospitalized patients (Table 1). This may be due to the central role that vitamin D plays in regulating innate and adaptive immune responses [4]. As such, the objective of this chapter is to provide a comprehensive account of the emerging evidence regarding the relationship of vitamin D status with HAIs and mortality in the critical care setting.

Vitamin D as an Immune Regulator

Vitamin D production and function is dependent on a complex regulatory system. It is derived from endogenous or exogenous prehormones, requiring extensive tissue modification, which includes an active intermediate molecule [25(OH)D], and is potentially influenced by numerous modulators, such as parathyroid hormone (PTH), calcium, phosphorus, and fibroblast growth factor-23. Calcitriol or 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] is the most biologically active metabolite of the vitamin D pathway. However, plasma levels of $1,25(OH)_2D$ are not only 500–1,000 times lower than those of 25(OH)D, but its half-life is also significantly shorter than the monohydroxylated form. As such, and under normal circumstances, 25(OH)D levels are used to represent total body vitamin D status. Both 25(OH)D and $1,25(OH)_2D$ are largely protein-bound to vitamin D binding protein (DBP) and, much less so (~ 10%), to albumin, while less than 1% of each molecule is found unbound in the circulation. Since the binding affinity of vitamin D metabolites to albumin is significantly lower than it is to DBP, it is postulated that during times of acute need, only the unbound and albumin-bound 25(OH)D and/or $1,25(OH)_2D$ is biologically active, and therefore referred to as the bioavailable fraction of vitamin D [3]. Epithelial, mucosal and innate immune cells, such as leukocytes, monocytes and macrophages, all of which represent the first barrier against infections, express the vitamin D receptor (VDR) and produce 1-α-hydroxylase, which facilitates conversion of 25(OH)D to $1,25(OH)_2D$ for paracrine and autocrine use within the target cells. Stimulation of the VDR through production of $1,25(OH)_2D$ can attenuate the proliferation and differentiation of both T and B lymphocytes, which likely improves outcome in autoimmune diseases. Furthermore, vitamin D metabolites activate Toll-like receptors (TLRs) in order to stimulate innate immunity and upregulate the production of potent antimicrobial peptides, such as cathelicidin and β-defensin 2 [3]. LL-37, the only know human cathelicidin, expresses a wide-range of antimicrobial activity against pathogens, including Gram-positive and Gram-negative bacteria, fungi, mycobacteria and viruses. LL-37 is not only expressed systemically by cells of the immune system, but is also produced

by epithelial cells at barrier sites including skin, respiratory tract, and gastrointestinal mucosa. Recent evidence suggests that LL-37 production is optimized with 25(OH)D levels of ~ 30–35 ng/ml.

Bloodstream Infections

Bloodstream infections (BSIs) represent a major concern among all causes of HAIs. It is estimated that the incidence of BSIs is 0.6 cases per 100 admissions across all units, and 9.7 per 100 admissions in the intensive care unit (ICU), with attributable LOS and hospital costs of approximately 10 days and €5,000 (US ~ $5,500), respectively [1]. To-date, most preventive strategies are focused on the control of environmental factors, such as hand hygiene, skin decontamination, antiseptic-impregnated catheters, and non-pharmacological bundles. And, although immune dysfunction is recognized as a key element for susceptibility to infection, few modifiable immunomodulatory factors have been identified to reduce HABSIs.

Low serum 25(OH)D levels may be an important risk factor for HABSI development. A prospective study looking at vitamin D status in 49 critically ill patients and 21 healthy controls found that 25(OH)D and LL-37 concentrations were significantly lower in ICU patients than in controls, with a positive correlation between the two [5]. Moreover, a retrospective cohort analysis of acute care patients hospitalized in non-federal US hospitals with a diagnosis of sepsis during a 24 year period found that the incidence of sepsis and mortality rate increased by 16.5 and 40% respectively during the winter. Indeed, low vitamin D status, due to reduced exposure to ultraviolet B radiation, which is necessary for endogenous 25(OH)D production, has been proposed as a possible underlying cause of such observations [6]. Similarly, in a prospective review of 106 French ICU patients, spring admission, low albumin levels, and high Simplified Acute Physiology Score (SAPS II) were independent predictors of low 25(OH)D levels [7]. Furthermore, preclinical data support the relationship between sepsis incidence or severity and vitamin D status. In a mouse study, DBP levels were shown to correlate with disease severity and the administration of vitamin D3 improved survival rates by 40% [8].

Prospective studies have also investigated the relationship between vitamin D status and sepsis. A pilot study assessed 25(OH)D levels in 81 patients admitted to an emergency department with suspected infection. Subjects with 25(OH)D levels < 75 nmol/l (23.5 ng/ml) were more likely to develop severe sepsis within 24 h of presentation compared to subjects with normal values [9]. These findings are further supported by another study, which found that the degree of hypovitaminosis D in critically ill patients was associated with higher SAPS II, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and fewer hospital-free days [10]. Conversely, a recent randomized controlled trial (RCT), which included 67 critically ill septic patients found that a single intravenous administration of 2 μg of calcitriol did not improve mortality rates or blood cathelicidin levels after 48 h but it did increase plasma $1,25(OH)_2D$ and anti-microbial protein mRNA levels [11]. Nevertheless, a case-control study that included 240 patients with severe sep-

sis found no significant differences in outcomes between patients with normal or low vitamin D levels. However, this investigation only evaluated samples taken the morning after admission, and the mean serum level for the top quartile was 58.3 nmol/l (23.3 ng/ml), therefore still below an optimal value [12]. Interestingly, an Italian study found that the median 25(OH)D levels at admission for 172 ICU patients were lower in the severe sepsis and septic shock group than in trauma patients (10.1 ng/ml vs. 18.4 ng/ml): the univariate analysis revealed that, after adjusting for age, sex and SAPS II score, low vitamin D status was associated with a higher mortality rate [13].

Retrospective studies have also found a strong correlation between sepsis and vitamin D levels. An analysis of 5,628 patients reported that pre-hospital 25(OH)D levels ≤ 15 ng/ml were associated with a 1.3-fold increased risk of developing a community-acquired BSI requiring hospitalization compared to patients with levels >15 ng/ml [14]. Similarly, all 91 outpatients admitted to the emergency department of a large US hospital with sepsis met vitamin D deficiency or insufficiency criteria, and, in this population, low $1,25(OH)_2D$ levels were associated with increased 30-day mortality and PTH insensitivity [15]. A two-center study analyzed 3,386 critically ill patients admitted to ICUs and verified that deficient vitamin D levels three days prior and seven days after ICU admission were strong independent predictors of sepsis [16]; similar results have been observed in surgical ICU patients with vitamin D levels <20 ng/ml [17]. Conversely, a recent cohort study of 655 critically ill patients did not find any association between 25(OH)D levels and LOS, but all 20 patients who died of sepsis had vitamin D levels less than 30 ng/ml [18].

Even though a growing body of evidence supports a strong relationship between low vitamin D status and sepsis, few data are available regarding nosocomial bacteremia. The results of an observational study that analyzed 2,399 patients admitted to two university hospitals in Boston showed that, for the 1,160 subjects who had blood cultures, hypovitaminosis D was significantly associated with a higher risk of BSI development (OR 1.64; CI 1.05–2.55; $p = 0.03$) [19].

Furthermore, in a retrospective analysis of 2,135 patients, the odds of developing a HABSI in the 323 patients with 25(OH)D levels <10 ng/ml was 2.3-fold higher than in patients with levels ≥ 30 ng/ml despite adjusting for age, sex, race, Deyo-Charlson Comorbidity index and admission cause [20]. And finally, a recent meta-analysis of 14 observational reports found that 25(OH)D <20 ng/ml was significantly associated with an increased risk of sepsis in critically ill patients (RR 1.46, 95% CI 1.27 to 1.68) [21].

Although definitive data from large RCTs are lacking, the available observational evidence and preliminary RCTs suggest a potential beneficial effect of vitamin D on sepsis outcomes in ICU patients.

Surgical Site Infections

SSIs are a leading cause of morbidity and mortality during the 30 days following surgery. It is estimated that up to 40% of all patients and around 15% of hospitalized patients may develop an SSI following an invasive procedure. Surgical stress, pain, and exposure to general anesthesia are only a few example of the myriad of factors that can affect immune regulation in the perioperative period. And immunocompetence as well as barrier site (skin or anastomosis) integrity are known risk factors for developing SSIs. Therefore, due to its immunomodulatory effects, vitamin D may be involved in the mechanisms that are involved in attenuating post-operative immunoparalysis and that may promote wound protection as well as repair.

Suboptimal vitamin D status before surgery may be a highly prevalent issue of concern. An analysis of patients undergoing bariatric surgery during a five year period found that 84% of 127 patients had low 25(OH)D baseline levels and that this deficiency was significantly correlated with preoperative body mass index and PTH levels [22]. Similar results were documented in a review of 379 obese individuals undergoing bariatric surgery between 2002 and 2004, which identified low vitamin D status in 68% of patients [23]. On the other hand, in a retrospective review of 723 patients undergoing orthopedic surgery, preoperative 25(OH)D < 32 ng/ml was present in almost half of all patients, while levels < 20 ng/ml were observed in 40% of individuals in this cohort [24].

There is a growing body of literature that has investigated the association of vitamin D status with post-surgical health. A prospective analysis in Germany of 190 patients who came into an orthopedic clinic for either total hip, knee, or shoulder prosthesis due to aseptic loosening of the joint or periprosthetic infection, demonstrated that 64, 52, and 86% of patients, respectively, had 25(OH)D levels < 20 ng/ml. Moreover, the mean 25(OH)D level of the 43 patients with joint infections was significantly lower than that of patients with aseptic loosening [25]. Recent evidence also suggests that surgical stress may be associated with a significant reduction in circulating 25(OH)D levels when compared with preoperative values. Moreover, the derangement in perioperative 25(OH)D levels may be sustained for up to 3 months after surgery.

A retrospective analysis of the association between preoperative 25(OH)D levels and HAIs following Roux-en-Y gastric bypass surgery was performed at a major Boston teaching hospital [26]. During the five-year study period, 770 patients underwent surgery and had their 25(OH)D levels checked within 30 days before surgery. Forty-one cases of HAI were diagnosed, with 20 cases identified as SSIs and the other 21 were either urinary tract infections (UTIs), pneumonia, or bacteremia. Using a propensity score matching approach, subjects with baseline 25(OH)D levels < 30 ng/ml demonstrated a 3-fold and 4-fold increased risk of HAIs and SSI development, respectively, compared to patients with levels ≥ 30 ng/ml (OR 3.05; CI, 1.34–6.94). The validity of these findings has recently been bolstered in a cohort of 3,340 consecutive patients undergoing cardiac surgery. In their analysis, the study investigators found that low $1,25(OH)_2D$ levels were independently associated with

an increased risk of post operative-infection [27]. So, although limited, emerging data support the potential beneficial effect of optimizing vitamin D status in the perioperative setting.

Clostridium Difficile Infections

C. difficile is the major cause of nosocomial diarrhea in North America. During the last decade, the incidence of hospital-acquired *C. difficile* infection (HACDI) has increased dramatically, with more than 300,000 new cases and almost 15,000 deaths being reported annually [1].

Vitamin D is thought to be involved in innate gastrointestinal immune defenses by promoting the maturation of T cell populations, and protection of macrophages from the deleterious effects of *C. difficile* toxins. Furthermore, VDR activation within the gastrointestinal tract is thought to upregulate macrophage and epithelial LL-37 as well as β-defensin expression, which attenuates interleukin (IL)-1β release.

A recent retrospective cohort study investigating CDIs in 568 adults admitted to two Boston teaching hospitals found that only 13% of patients had 25(OH)D $\geq$ 30 ng/ml [28]. After adjusting for age, sex, race, patient type, and the Deyo-Charlson Comorbidity index, 25(OH)D levels < 10 ng/ml were strongly associated with HACDI occurrence, with the odds of infection being 3-fold higher than those of patients with levels $\geq$ 30 ng/ml. Another recent analysis looked at the association between CDI and vitamin D status in 3,188 patients who had inflammatory bowel disease and at least one 25(OH)D test on record at two US teaching hospitals. The 35 patients in this cohort who developed CDI had a mean 25(OH)D level of 20.4, which was significantly lower than in non-CDI patients [29].

Prospective studies on this topic have recently been conducted as well. An analysis of data from 62 hospitalized patients with *C. difficile*-associated diarrhea found that 25(OH)D levels > 21 ng/ml were significantly associated with higher *C. difficile* disease resolution; indeed, in these patients, low vitamin D status was associated with a higher risk of recurrence and an almost 6-fold increased risk of death compared to patients with more optimal 25(OH)D levels [30]. Vitamin D status may also be a predictor of CDI severity. A recent study enrolled 100 patients with confirmed CDI while admitted to a large teaching hospital in Boston between 2011 and 2013. Multivariable regression analysis demonstrated that 25(OH)D_3 levels were significantly associated with disease severity and each 1 ng/ml increase in 25(OH)D_3 was observed to decrease the risk of severe CDI by 8% (OR 0.92; CI 0.87–0.98). However, no association was observed between total 25(OH)D or 25(OH)D_2 levels, supporting the hypothesis that vitamin D_3 is the biological driver of vitamin D-related immune function [32]. Similarly, a longer course of CDI-associated diarrhea has been observed in patients with low vitamin D status compared to a matched group with more optimal 25(OH)D levels [31]. And finally, in a recent meta-analysis of 8 observational studies, including both community and nosocomial CDIs, patients with lower vitamin D status were shown to have significantly higher odds

of developing severe CDI compared with those with more optimal 25(OH)D levels [33]. Although, at present, there are no RCTs that have investigated the effect of vitamin D supplementation in patients with CDI, within the given limits of observational cohort studies there is a strong signal that vitamin D optimization in patients affected by or at high risk for CDIs may be clinically relevant.

Other Nosocomial Infections

CAUTIs are the most common HAIs worldwide, accounting for almost 50% of all nosocomial infectious complications. Nearly 25% of patients with bacteriuria develop CAUTI, followed, in 4% of cases, by bacteremia. These episodes are responsible for an estimated health care-related cost of between $676 and $2,836 per patient. Preliminary investigations have shown a relationship between vitamin D status and UTIs. In a study of 92 patients diagnosed with a UTI, a significant relationship between VDR gene polymorphism and infection was observed, and a significant increase in LL-37 expression after a three-month period of vitamin D supplementation was observed in bladder biopsies of patients infected with *Escherichia coli* [34]. Additionally, a significant association between hypovitaminosis D and recurrent UTIs was observed in premenopausal women. Although previous studies demonstrated an upregulation of LL-37 with chronic UTI [34], increased β-defensin 2 expression may be more profound in the acute setting. To date, no RCTs have investigated whether vitamin D supplementation may reduce the incidence, severity, or duration of CAUTI.

HAP represents a leading cause of morbidity and mortality in ICU patients. In the critically ill, nosocomial pneumonias, including ventilator-associated pneumonia (VAP), are responsible for increased ICU LOS, patient-related resource utilization and mortality. Vitamin D significantly contributes to innate immune function in respiratory mucosa and many recent studies have identified hypovitaminosis D as a determining risk factor for pulmonary infections. A retrospective analysis of 16,975 individuals with documented 25(OH)D levels from the third National Health and Nutrition Examination Survey (NHANES) revealed that patients with levels < 30 ng/ml had a 56% higher chance of developing community-acquired pneumonia (CAP) [35]. Similarly, a prospective cohort study including 272 hospitalized patients with CAP observed that, after controlling for commonly used biomarkers and prognostic scores, vitamin D deficiency was independently associated with 30-day mortality [36]. Interestingly, although there are no published investigations about the potential role of vitamin D as a risk indicator and prognostic marker of HAP, vitamin D levels < 50 nm/l have been frequently observed in hospitalized critically ill patients with acute respiratory distress syndrome (ARDS) [37].

New data relating vitamin D deficiency and other infection types are also emerging. A large retrospective population study observed that, after adjusting for potential confounding variables, vitamin D status was associated with the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal carriage. Similarly, in a prospective observation involving 201 critically ill patients, hypovitaminosis D

and invasive mechanical ventilation were the two independent risk factors for *Acinetobacter baumannii* infections [38]. A French study analyzed the vitamin D levels of 88 patients with cirrhosis who attended a liver clinic, finding a 56.8% rate of severe 25(OH)D deficiency, defined as < 10 ng/ml. These subjects were more likely to be hospitalized due to a severe infection than those with a normal vitamin D status [39].

Mortality and Critical Care Outcomes

It is well know that vitamin D deficiency is associated with all-cause mortality in the general population, mainly due to its relationship with chronic conditions including cardiovascular disease and cancer. Recent evidence supports its role as a major determinant of poor outcome in hospitalized patients, especially in the ICU setting. A retrospective cohort study of 24,915 hospitalized adult patients with mean and median pre-hospital serum 25(OH)D levels of 27.9 and 26 ng/ml, respectively, found that 13% of the enrolled patients were ICU admitted [40]. In a cohort study of patients with pre-hospital admission 25(OH)D levels, those with levels ≤ 15 ng/ml had a 1.45 greater odds of 30-day in-hospital mortality compared to those with levels > 15 ng/ml, after adjusting for major potential influencing covariates [14]. Furthermore, in a retrospective study of 136 veterans, ICU survivors had a significantly lower rate of suboptimal vitamin D status compared to non-survivors, and also had a shorter ICU LOS [41]. Another cohort study of 523 critically ill patients admitted to a medical ICU demonstrated a significant relationship between low vitamin D status and mortality [42], as did another large observational study from Boston, which included 1,325 study patients. In the latter study, low pre-hospital 25(OH)D levels were an independent risk factor for 30-day mortality (OR 1.85; CI 1.25–2.98) [43].

Prospective data from a Turkish cohort demonstrated that among 139 adults admitted to a medical ICU, the median serum 25(OH)D level was 14.9 ng/ml; 69% of these patients had 25(OH)D levels < 20 ng/ml [44] and had more comorbidities, needed more invasive procedures and had a higher incidence of septic shock. However, no difference in mortality was observed. However, in patients with 25(OH)D levels < 20 ng/ml, a higher mortality rate and a shorter survival course (15.3 days vs. 24.2 days) was observed compared to those with 25(OH)D ≥ 20 ng/ml in a cohort of 130 critically ill patients admitted to a mixed ICU [45]. Similarly, in another analysis of 196 patients admitted to a medical/surgical ICU, low 25(OH)D levels were associated with greater ICU LOS and a trend towards increased risk of ICU-acquired infections [46]. Additionally, among 100 critically ill patients enrolled in a multicenter prospective Australian study, the observed rate of 25(OH)D < 30 and < 20 ng/ml was 54% and 24%, respectively, confirming a significant relationship between hypovitaminosis and both worse disease severity and fewer hospital-free days [10]. Although there are fewer data on just critically ill surgical patients, a prospective study which assessed the vitamin D status of 258 patients admitted to a surgical ICU reported a severe/moderate vitamin D deficiency status in 91.8% of cases. Low

vitamin D status in these patients was associated with higher mortality (11.9 vs. 0%) and greater health care costs ($51,413 ± $75,123 vs. $20,414 ± $25,714), compared to patients with more optimal 25(OH)D levels [47]. More recently, another prospective cohort study of 100 patients in two surgical ICUs of a single institution demonstrated that 25(OH)D levels upon admission were inversely associated with LOS, 90-day readmission, and 90-day mortality rate [4].

Finally a recent observational study analyzed the vitamin D profile of 107 critically ill patients with severe sepsis and septic shock. At ICU admission, vitamin D deficiency (≤ 20 ng/ml) was observed in 93.5% of the patients and 57 showed levels < 7 ng/ml. Severe vitamin D deficiency was associated with lower microbiological eradication and significantly higher sepsis-related mortality [48].

Future Directions

Although emerging data suggest a relationship between low vitamin D status and an increased risk of infection, little is known about optimal 25(OH)D levels for immune function during acute stress and critical illness. 25(OH)D levels around 35 ng/ml are thought to optimize vitamin D-dependent cathelicidin expression, while patients with levels ≥ 60 ng/ml have been shown to be at higher risk of 90-day mortality compared to patients with levels between 30–50 ng/ml [40]. Usually, adults need a daily supplementation of 1,500–2,000 IU of vitamin D to maintain blood levels above 30 ng/ml and oral intakes up to 5,000 IU a day have been observed to be absolutely safe [40].

Recent data have demonstrated that critically ill patients undergoing very high supplementation regimens ($> 200{,}000$ UI in a single oral dose) had their vitamin D deficiency rapidly corrected without increasing risk of hypocalcemia or hypercalciuria [49, 50], but a large randomized clinical trial enrolling 492 vitamin D deficient ICU patients found that oral vitamin D (540,000 IU bolus followed by 90,000 IU monthly doses) increased 25(OH)D levels without improving ICU and hospital LOS and mortality rates. However, such supplementation did improve 6-month mortality rates in severely deficient patients with serum 25(OH)D levels ≤ 12 ng/ml [51].

Single intramuscular or intravenous vitamin D administration has also been observed to effectively correct hypovitaminosis in critically ill patients [11]. Hence, although a strong relationship seems to link vitamin D and immune system function, there is limited and conflicting evidence supporting its use as adjunctive therapy in high-risk patients for severe systemic infections, such as hospitalized critically ill subjects. Investigations in this research field have to carefully consider multiple possible biases (such as baseline vitamin D status, dosages administered, and plasmatic levels obtained), which can influence the appropriateness of final observations.

Conclusion

Preclinical research and observational studies highlight the key role of vitamin D for optimal function of the human immune system. The incidence and prognosis of HAIs may benefit from hypovitaminosis D correction, especially in the critically ill setting where low 25(OH)D levels appear to significantly influence outcome. However, evidence supporting vitamin D supplementation as a tool to improve morbidity and mortality is still lacking. Further studies aimed at defining target populations where functional vitamin D insufficiency is detrimental and to provide new insights regarding optimal administration regimens are needed in order to definitively determine the antimicrobial properties of this intriguing molecule.

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References

1. Klevens RM, Edwards JR, Richards CL Jr et al (2007) Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep 122:160–166
2. De Pascale G, Cutuli SL, Pennisi MA, Antonelli M (2013) The role of mannose-binding lectin in severe sepsis and septic shock. Mediators Inflamm 2013:625083
3. Quraishi SA, Camargo CA Jr (2012) Vitamin D in acute stress and critical illness. Curr Opin Clin Nutr Metab Care 15:625–634
4. Quraishi SA, Bittner EA, Blum L, McCarthy C, Bhan I, Camargo CA Jr (2014) Prospective study of vitamin D status at initiation of care in critically ill surgical patients and risk of 90-day mortality. Crit Care Med 42:1365–1371
5. Jeng L, Yamshchikov AV, Judd SE et al (2009) Alterations in vitamin D status and antimicrobial peptide levels in patients in the intensive care unit with sepsis. J Transl Med 7:28
6. Danai PA, Sinha S, Moss M, Haber MJ, Martin GS (2007) Seasonal variation in the epidemiology of sepsis. Crit Care Med 35:410–415
7. Lucidarme O, Messai E, Mazzoni T, Arcade M, du Cheyron D (2010) Incidence and risk factors of vitamin D deficiency in critically ill patients: results from a prospective observational study. Intensive Care Med 36:1609–1611
8. Horiuchi H, Nagata I, Komoriya K (1991) Protective effect of vitamin D3 analogues on endotoxin shock in mice. Agents Actions 33:343–348
9. Ginde AA, Camargo CA Jr, Shapiro NI (2011) Vitamin D insufficiency and sepsis severity in emergency department patients with suspected infection. Acad Emerg Med 18:551–554
10. Nair P, Lee P, Reynolds C et al (2013) Significant perturbation of vitamin D-parathyroid-calcium axis and adverse clinical outcomes in critically ill patients. Intensive Care Med 39:267–274
11. Leaf DE, Raed A, Donnino MW, Ginde AA, Waikar SS (2014) Randomized controlled trial of calcitriol in severe sepsis. Am J Respir Crit Care Med 190:533–541
12. Barnett N, Zhao Z, Koyama T et al (2014) Vitamin D deficiency and risk of acute lung injury in severe sepsis and severe trauma: a case-control study. Ann Intensive Care 4:5

13. Cecchi A, Bonizzoli M, Douar S et al (2011) Vitamin D deficiency in septic patients at ICU admission is not a mortality predictor. Minerva Anestesiol 77:1184–1189
14. Lange N, Litonjua AA, Gibbons FK, Giovannucci E, Christopher KB (2013) Pre-hospital vitamin D concentration, mortality, and bloodstream infection in a hospitalized patient population. Am J Med 126:e19–27
15. Nguyen HB, Eshete B, Lau KH, Sai A, Villarin M, Baylink D (2013) Serum 1,25-dihydroxyvitamin D: an outcome prognosticator in human sepsis. PLoS One 8:e64348
16. Moromizato T, Litonjua AA, Braun AB, Gibbons FK, Giovannucci E, Christopher KB (2014) Association of low serum 25-hydroxyvitamin d levels and sepsis in the critically ill. Crit Care Med 42:97–107
17. Flynn L, Zimmerman LH, McNorton K et al (2012) Effects of vitamin D deficiency in critically ill surgical patients. Am J Surg 203:379–382
18. Amrein K, Zajic P, Schnedl C et al (2014) Vitamin D status and its association with season, hospital and sepsis mortality in critical illness. Crit Care 18:R47
19. Braun A, Chang D, Mahadevappa K et al (2011) Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. Crit Care Med 39:671–677
20. Quraishi SA, Litonjua AA, Moromizato T et al (2013) Association between prehospital vitamin D status and hospital-acquired bloodstream infections. Am J Clin Nutr 98:952–959
21. de Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A (2014) Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Crit Care 18:660
22. Fish E, Beverstein G, Olson D, Reinhardt S, Garren M, Gould J (2010) Vitamin D status of morbidly obese bariatric surgery patients. J Surg Res 164:198–202
23. Flancbaum L, Belsley S, Drake V, Colarusso T, Tayler E (2006) Preoperative nutritional status of patients undergoing Roux-en-Y gastric bypass for morbid obesity. J Gastrointest Surg 10:1033–1037
24. Bogunovic L, Kim AD, Beamer BS, Nguyen J, Lane JM (2010) Hypovitaminosis D in patients scheduled to undergo orthopaedic surgery: a single-center analysis. J Bone Joint Surg Am 92(13):2300–2304
25. Maier GS, Horas K, Seeger JB, Roth KE, Kurth AA, Maus U (2015) Vitamin D insufficiency in the elderly orthopaedic patient: an epidemic phenomenon. Int Orthop 39:787–792
26. Quraishi SA, Bittner EA, Blum L, Hutter MM, Camargo CA Jr (2014) Association between preoperative 25-hydroxyvitamin D level and hospital-acquired infections following Roux-en-Y gastric bypass surgery. JAMA Surg 149:112–118
27. Zittermann A, Kuhn J, Ernst JB et al (2016) Circulating 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations and postoperative infections in cardiac surgical patients: The CALCITOP-Study. PLoS One 11:e0158532
28. Quraishi SA, Litonjua AA, Moromizato T et al (2015) Association between prehospital vitamin D status and hospital-acquired Clostridium difficile infections. JPEN Parenter Enteral Nutr 39:47–55
29. Ananthakrishnan AN, Cagan A, Gainer VS et al (2014) Higher plasma vitamin D is associated with reduced risk of Clostridium difficile infection in patients with inflammatory bowel diseases. Aliment Pharmacol Ther 39:1136–1142
30. Wang WJ, Gray S, Sison C et al (2014) Low vitamin D level is an independent predictor of poor outcomes in Clostridium difficile-associated diarrhea. Therap Adv Gastroenterol 7:14–19
31. Wilden GM van der, Fagenholz P et al (2015) Vitamin D status and severity of Clostridium difficile infections: a prospective cohort study in hospitalized adults. JPEN J Parenter Enteral Nutr 39:465–470
32. Wong KK, Lee R, Watkins RR, Haller N (2016) Prolonged Clostridium difficile infection may be associated with vitamin D deficiency. J Parenter Enteral Nutr 40:682–687
33. Furuya-Kanamori L, Wangdi K, Yakob L et al (2015) 25-hydroxyvitamin D concentrations and Clostridium difficile infection: A meta-analysis. JPEN J Parenter Enteral Nutr Dec 23, Epub ahead of print

34. Hertting O, Holm Å, Lüthje P et al (2010) Vitamin D induction of the human antimicrobial peptide cathelicidin in the urinary bladder. PLoS One 14:e15580
35. Quraishi SA, Bittner EA, Christopher KB, Camargo CA Jr (2013) Vitamin D status and community-acquired pneumonia: results from the third National Health and Nutrition Examination Survey. PLoS One 8:e81120
36. Remmelts HH, van de Garde EM et al (2012) Addition of vitamin D status to prognostic scores improves the prediction of outcome in community-acquired pneumonia. Clin Infect Dis 55:1488–1494
37. Dancer RC, Parekh D, Lax S et al (2015) Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax 70:617–624
38. Türkoğlu M, Aygencel G, Dizbay M et al (2013) Is vitamin D deficiency associated with development of Acinetobacter baumannii infections in critically ill patients? J Crit Care 28:735–740
39. Anty R, Tonohouan M, Ferrari-Panaia P et al (2014) Low levels of 25-hydroxy vitamin D are independently associated with the risk of bacterial infection in cirrhotic patients. Clin Transl Gastroenterol 5:e56
40. Amrein K, Quraishi SA, Litonjua AA et al (2014) Evidence for a U-shaped relationship between pre-hospital vitamin D status and mortality: a cohort study. J Clin Endocrinol Metab 99:1461–1469
41. McKinney JD, Bailey BA, Garrett LH, Peiris P, Manning T, Peiris AN (2011) Relationship between vitamin D status and ICU outcomes in veterans. J Am Med Dir Assoc 12:208–211
42. Venkatram S, Chilimuri S, Adrish M, Salako A, Patel M, Diaz-Fuentes G (2011) Vitamin D deficiency is associated with mortality in the medical intensive care unit. Crit Care 15:R292
43. Braun AB, Litonjua AA, Gibbons FK, Litonjua AA, Giovannucci E, Christopher KB (2012) Low serum 25-hydroxyvitamin D at critical care initiation is associated with increased mortality. Crit Care Med 40:179
44. Aygencel G, Turkoglu M, Tuncel AF, Candır BA, Bildacı YD, Pasaoglu H (2013) Is vitamin d insufficiency associated with mortality of critically ill patients? Crit Care Res Pract 2013:856747
45. Arnson Y, Gringauz I, Itzhaky D, Amital H (2012) Vitamin D deficiency is associated with poor outcomes and increased mortality in severely ill patients. QJM 105:633–639
46. Higgins DM, Wischmeyer PE, Queensland KM, Sillau SH, Sufit AJ, Heyland DK (2012) Relationship of vitamin D deficiency to clinical outcomes in critically ill patients. JPEN J Parenter Enteral Nutr 36:713–720
47. Matthews LR, Ahmed Y, Wilson KL, Griggs DD, Danner OK (2012) Worsening severity of vitamin D deficiency is associated with increased LOS, surgical intensive care unit cost, and mortality rate in surgical intensive care unit patients. Am J Surg 204:37–43
48. De Pascale G, Vallecoccia MS, Schiattarella A et al (2016) Clinical and microbiological outcome in septic patients with extremely low 25-hydroxyvitamin D levels at initiation of critical care. Clin Microbiol Infect 22:456
49. Quraishi SA, De Pascale G, Needleman JS et al (2015) Effect of cholecalciferol supplementation on vitamin D Status and cathelicidin levels in sepsis: a randomized, placebo-controlled trial. Crit Care Med 43:1928–1937
50. Amrein K, Sourij H, Wagner G et al (2011) 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 15:R104
51. Amrein K, Schnedl C, Holl A et al (2014) 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 312:1520–1530