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Vitamin D's potential to reduce the risk of hospital-acquired infections

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Health care–associated and hospital-acquired infections are two entities associated with increased morbidity and mortality. They are highly costly and constitute a great burden to the health care system. Vitamin D deficiency (< 20 ng/ml) is prevalent and may be a key contributor to both acute and chronic ill health. Vitamin D deficiency is associated with decreased innate immunity and increased risk for infections. Vitamin D can positively influence a wide variety of microbial infections.

Herein we discuss hospital-acquired infections, such as pneumonia, bacteremias, urinary tract and surgical site infections, and the potential role vitamin D may play in ameliorating them. We also discuss how vitamin D might positively influence these infections and help contain health care costs. Pending further studies, we think it is prudent to check vitamin D status at hospital admission and to take immediate steps to address existing insufficient 25-hydroxyvitamin D levels.

Introduction

There is increasing evidence that vitamin D deficiency plays an important role in worsening outcomes and increasing the susceptibility to infections. Vitamin D has potential benefits on innate immunity and potentiates antimicrobial actions through a variety of mechanisms. Vitamin D has potential antimicrobial actions against different organisms, such as bacteria, viruses and fungi.

It is also well known that hospital acquired infections constitute a major cause of hospital morbidity and mortality. Viewing the widespread lack of testing of 25-hydroxyvitamin D [25(OH)D] levels in the inpatient setting, and the possible beneficial effects of getting sufficient levels, we raise in this article the potential association between vitamin D deficiency and the risk of acquisition of unnecessary infections during a hospital stay.

Burden of Hospital-Acquired Infections

Hospital-acquired infections (HAIs) are a leading cause of death in the US health care arena, with an overall estimated annual incidence of 1.7 million cases[1] and 100,000 deaths.[2] As a result, HAIs have given rise to state laws, legislative proposals at the federal level, public-private initiatives, and work at the hospital system and individual hospital level.[2] They constitute a substantial cause of morbidity and mortality. Pneumonia was the most likely disease, followed by bacteremias, urinary tract infections, surgical site infections and others.[3] On the basis of published medical and economic literature, HAIs in US hospitals generate an estimated $28.4 billion–$45 billion in excess health care costs annually.[4]

Similarly, 12.7% of admitted patients developed HAIs, doubling the cost of these patients' hospital stays. The totals for 159 patients were $1.48–$3.34 million in medical costs and $5.27 million for premature death, and excess length of stay (LOS) totaled 844–1,373 hospital days.[5] Patients with sepsis had a nearly 6-fold higher odds of death than patients without an HAI. Patients with other HAIs had a 1.5- to 1.9-fold higher odds of mortality than control subjects. Patients with HAIs had costs that were approximately 2- to 2.5-fold higher than those of patients without HAIs. The median LOS was approximately 2-fold higher in patients with HAIs than in patients without HAIs.[6] For example, results from a population-based data set indicated that mortality and LOS are increased among inflammatory bowel disease patients who develop HAIs. Most HAIs were from catheter-associated urinary tract infections (UTIs).[7] HAIs increase morbidity and mortality in intensive-care units (ICUs) not only for adults (including the elderly) but also for newborn infants.[8]

Multiple challenges stand against the implementation of HAI reduction plans: poor adherence, insufficient resources, staffing problems, lack of culture change, no impetus to change, and issues related to staff and patient education.[9] The rates of hospital-acquired bacterial infection can be reduced by restricting the admission of patients colonized with resistant bacteria, increasing the rate of patient turnover, reducing transmission by infection control measures and the use of second-line drugs for which there is no resistance.[10] Many simple measures can decrease infection rates, such as adequate hand hygiene[11] and, most recently, vitamin D supplementation.

Antimicrobial Role of Vitamin D

Vitamin D modulates the immune system[12] and appears to have systemic antimicrobial effects[13] that may be crucial in a variety of

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both acute and chronic illness. Moreover, vitamin D deficiency may predispose patients to hypocalcemia, which by itself impairs normal lymphocyte and neutrophil function.[14] It also decreases the barrier protective function of cells.[15] Vitamin 1,25-D_3 inhibits proliferation of T helper 1(Th1) cells [consequently impairing production of IL-2, tumor necrosis factor α and interferon (IFN)], as well as T helper 17 (Th17) cells, skewing cytokine production toward a T helper 2 (Th2) phenotype.[16] Most cells, such as B and T lymphocytes, monocytes, and dendritic cells, have specific vitamin D receptors (VDRs).[16] Vitamin D exerts its immunomodulatory effects on these cell lines through its effects on the VDR.[17] Vitamin D tends to favor a mononuclear phenotype, increasing VDR expression on monocytes and macrophages.[18,19] Vitamin D increases the oxidative burst of macrophages[20] and facilitates neutrophilic motility and phagocytic function.[21]

Vitamin D reduces local and systemic inflammatory responses as a result of modulating cytokine responses and reducing Toll-like receptor activation.[22] It directly affects T-cell activation and the phenotype and function of antigen-presenting cells, especially dendritic cells.[23] Furthermore, vitamin D stimulates the expression of potent antimicrobial peptides, such as cathelicidin and β-defensin 2.[24]

Cathelicidins are a family of peptides thought to provide an innate defensive barrier against a variety of potential microbial pathogens, such as gram-positive and gram-negative bacteria, fungi, and mycobacteria, at multiple entry sites, including skin and mucosal linings of the respiratory and gastrointestinal systems,[24] as well as viruses.[25] These antimicrobial peptides are expressed on epithelial surfaces and in neutrophils, are inducible in keratinocytes in response to infection, and act as natural antibiotics. In earlier studies, cathelicidins (LL-37 and CRAMP) were expressed at select epithelial interfaces and may kill bacteria such as group A Streptococcus.[26,27] Studies in mice showed that deletion of the cathelicidin gene, *Cnlp*, results in increased susceptibility to group A Streptococcus infection. Keratinocytes inhibit the growth of *S. aureus*, due partially to their ability to synthesize and activate cathelicidin.[28] The human cathelicidin, hCAP18, is a component of the innate immune system and has broad antimicrobial activity conferred by its C-terminal fragment, LL-37. hCAP18 is produced in leukocytes and is induced in barrier organs upon inflammation and infection; hCAP18 also works in the reepithelialization of skin wounds.[29] To resist innate immunity, bacteria can develop enzymes that inactivate cathelicidins. Thus, streptococcal cysteine protease SpeB-mediated inactivation of LL-37 is noted in patients with severe group A Streptococcus tissue infections.[30] However, addition of cathelicidins by combining synthetic cathelicidin peptides in vitro, by producing human keratinocytes that overexpress cathelicidins in culture, showed increased resistance to infections with group A Streptococcus.[31] In case of prolonged deficiency of both dietary vitamin D and calcium, vitamin D deficiency may predispose to hypocalcemia, which impairs normal lymphocyte and neutrophil function and potentially increases the risk of acquiring infectious diseases.[32] Vitamin D-deficient patients are susceptible to increased nosocomial infections, such as pneumonia, sepsis and central line infections.[16,33]

Neutrophils, macrophages, lymphocytes, monocytes and natural killer cells increase the expression of these antimicrobial peptides with 25(OH)D stimulation.[34] Human β-defensin 2 (HBD-2) is beneficial in multidrug-resistant microbes in vitro.[35] Human β-defensin 3 (HBD-3) is an antimicrobial peptide that exhibits broad-spectrum antimicrobial activity against gram-positive/negative bacteria and fungi.[36] It could be more potent than HBD-2 in *S. aureus* skin infections.[37] Moreover, the bacterial protein flagellin stimulates the mucosal surface innate immunity by production of antimicrobial peptides and may generate cytoprotection and control infection in the cornea and other mucosal tissues.[38] Enhanced antimicrobial peptide production may also improve skin lesions in psoriasis and atopic dermatitis.[39]

Use of Vitamin D in Infectious Diseases

In a previous publication, we outlined the most important actions of vitamin D against many infections, whether they are bacterial, mycobacterial, fungal, parasitic, or viral.[40] We also found that vitamin D deficiency was intimately linked to adverse health outcomes and costs in veterans with staphylococcal and *Clostridium difficile (C. difficile)* infections. Vitamin D-deficient patients with *C. difficile* or staphylococcal infections had costs more than five times higher than those of nondeficient patients. The total length of hospital stay was four times greater in the vitamin D-deficient group. Also, the total number of hospitalizations was significantly greater in vitamin D-deficient patients.[41] Similarly, vitamin D-deficient patients with MRSA and *Pseudomonas aeruginosa* infections had higher costs and service utilization than patients who were not vitamin D deficient.[42] In a retrospective study by McKinney and colleagues, ICU survivors had a significantly lower rate of vitamin D deficiency than did nonsurvivors (28% vs. 53%). The risk of death was significantly higher in ICU patients with vitamin D deficiency.[43] Most recently, Higgins et al. conducted a prospective study to evaluate the burden of vitamin D deficiency in intensive care unit patients. Serum 25(OH)D was checked upon admission and at 10 d after admission and the patients were followed up at 28 d. Twenty-six percent were deficient and 56% were insufficient. 25(OH)D status was not significantly associated with 28-d all-cause mortality. However, higher levels of 25(OH)D were associated with a shorter time-to-alive ICU discharge. 25(OH)D-deficient patients showed a trend toward a higher infection rate.[44] Vitamin D therefore appears to be important for patients with critical illness. On the basis of US epidemiologic studies, Grant hypothesized that solar UVB light and vitamin D could reduce the risk of septicemia.[45] Grant also stated that supplementation with vitamin D to mothers and infants may reduce the risk of sepsis in premature infants.[46] One study by Jeng and colleagues in critically ill patients pointed at the important correlation between 25(OH)D levels, vitamin D-binding protein, and LL-37 levels. These patients had significantly lower plasma 25(OH)D concentrations and LL-37 levels than did healthy control subjects. Vitamin D-binding protein levels in plasma were significantly lower in critically ill subjects with sepsis than in critically ill subjects without sepsis.[47] Therapy with vitamin D in animal models of sepsis improves blood

coagulation parameters in disseminated intravascular coagulation and modulates levels of systemic inflammatory cytokines, including tumor necrosis factor α and interleukin 6.[48]

Vitamin D deficiency is also more prevalent in blacks than in whites.[49,50] Severe sepsis occurs more often and leads to more deaths in black than in white individuals. Racial differences in severe sepsis are explained by both a higher infection rate and a higher risk of acute organ dysfunction in black than in white individuals.[51]

Currently, prescribing traditional antimicrobials for infectious processes is customary in medicine. The current use of antimicrobials in the United States costs billions of dollars, and the overuse of antibiotics persists and contributes to the emergence of resistant organisms.[52] Vitamin D is likely to emerge as a powerful and hitherto unrecognized antimicrobial agent. Evidence is mounting that vitamin D could help to manage infectious illnesses. But does vitamin D deficiency cause infections? This question remains. Hill proposed one way to determine causality in a biological system,[53] on the basis of nine criteria: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy. The more criteria that are elicited, the better the case for causality. Some examples of applying Hill's criteria include the relationship between vitamin D as a risk-reduction factor for several types of cancer[54] and that of vitamin D deficiency and periodontal disease.[55] Below we discuss the most common HAIs and the beneficial role of vitamin D. **Table 1** summarizes the effects of vitamin D on each entity.

Bacteremias and Central Vascular Catheter-Associated Bloodstream Infections

Patients with health care-associated, community-acquired bacteremia have more malignancies, open wounds at admission, and intravascular catheter-related infections.[56] Most pneumococcal bloodstream infections (BSIs) are community acquired, although HAIs are common in neutropenic patients.[57] Critically ill patients who develop ICU-acquired BSIs suffer excess morbidity and mortality and incur significantly increased health care costs.[58] According to the latest *News and Numbers* from the Agency for Healthcare Research and Quality, septicemia was the single most expensive condition treated in US hospitals, at nearly $15.4 billion in 2009, including community- and hospital-acquired cases. The federal agency also found that the number of hospital stays principally for septicemia more than doubled between 2000 and 2009, making it the sixth most common principal reason for hospitalization in 2009. Also, the in-hospital death rate for septicemia was 16% in 2009, more than eight times as high as for all other hospital stays.[59]

Streptococcus pneumoniae is a common cause of community-acquired pneumonia and bacteremia. White and colleagues confirmed that the wintertime predominance of invasive pneumococcal disease in Philadelphia is related to extended periods of low UV radiation. They suggested that the mechanism of action of diminished sunlight exposure on disease occurrence may be due to direct effects on pathogen survival or host immune function via altered $1,25(OH)_2D$ production.[60]

In dialysis patients, vitamin D deficiency was among several pathophysiologic factors that enhance the risk of infections in this population. Twenty to 30% of dialysis patients develop infection, and 20–30% of these die from their infection. Sepsis and bacteremia are significantly more frequent, and their mortality is 50 times higher than in the healthy population.[61]

In a study by Lee and colleagues, 17% of intensive care unit patients had undetectable levels of 25-hydroxyvitamin D [25(OH)D].[32] In a different study, 20% of critically ill patients with bacterial sepsis had hypocalcemia, and their mortality rate

Table 1. Effects of vitamin D on HAIs

HAI	Effect	References
Intensive care unit infections	Higher levels of 25(OH)D were associated with a shorter time-to-alive ICU discharge. 25(OH)D-deficient patients had higher infection rate	44
Bacteremia	Increased prevalence of pneumococcal sepsis in wintertime	60
Bacteremia, dialysis patients	Increased risk of infections, sepsis and bacteremia in deficiency	61
Bacterial sepsis	66% higher mortality rate for low vs. high serum 25(OH)D	62
Community acquired pneumonia	Higher 30-d mortality in case of severe deficiency	68
Pneumonia in Children	Higher oxygen supplements and ventilator need in deficiency	69, 70
Pneumonia	Supplementation with 1000–2000 IU/d for five days—no effect	74
Pneumonia associated with influenza	Case-fatality rate was significantly reduced in regions with higher solar UVB doses	79
Clostridium difficile	Vitamin D protects macrophages against death Deficiency was associated with higher costs	86 41
Catheter-associated urinary tract infections	VDR ApaI polymorphism seems to be protective. Tt and tt genotypes have higher risk of UTI. Vitamin D_3 supplementation increased cathelicidin production in bladders infected with uropathogenic *Escherichia coli*.	90–92
Surgical site infections	50,000 IU dose eliminated wound infections	Donald Miller (Personal communication)
Virulent organisms such as MRSA	*S. aureus* colonization decreased by 6.6% for each 5-nmol/l increase in 25(OH)D	105

was significantly higher (50%) than that of normocalcemic patients with sepsis (29%).[62] Vitamin D deficiency in the obese may have a role in the pathogenesis of endotoxemia and adipose inflammation.[63]

Health Care-Associated Pneumonia and Hospital-Acquired Pneumonia

Health care-associated pneumonia (HCAP) usually develops in patients in outpatient facilities, such as nursing homes, long-term care facilities, and dialysis centers. HCAP should be dealt with as if it is hospital-acquired pneumonia (HAP) and should be treated as such until final cultures are available. Analysis of multi-institutional clinical data showed that mortality associated with HCAP is higher than that with community-acquired pneumonia.[64] Postoperative HAP is a major risk associated with surgery. In one study, 10.7% of patients with HAP after intra-abdominal surgery died before discharge. HAP was independently associated with a 4.13-fold increase in risk to be discharged to a skilled nursing facility. The mean length of hospital stay of these patients was significantly greater than that of intra-abdominal surgery patients who did not develop HAP. HAP was independently associated with a 75% mean increase in total hospital charges.[65] In children younger than 1 y and those with chronic medical conditions, hospital-acquired febrile respiratory illness is caused mainly by viruses such as respiratory syncytial virus and is associated with increased mortality.[66]

Vitamin D promotes lung and bone health.[67] Upon evaluating the associations between mortality and serum 25(OH)D in patients with community-acquired pneumonia, Leow and colleagues verified that severe 25(OH)D deficiency was common and associated with a higher 30-d mortality rate than that of patients with sufficient 25(OH)D during winter.[68] Similar findings were noted in children with acute lower respiratory infection. Patients needing more supplementary oxygen and ventilator management were those with vitamin D deficiency.[69] Also, in a case-control study in Nigerian children with pneumonia, those with hypovitaminosis D and hypocalcemia had more complications and worse outcomes than those without deficiency.[70] Moreover, rickets was a significant predictor of reduced success in treating severe pneumonia in Yemen.[71] In ICU-admitted veterans, a longer stay was significantly linked to lower vitamin D status.[43] Two recent reviews describe the role of vitamin D and susceptibility to chronic lung diseases and thus risk for superimposed infections.[72,73]

Given the relationship between 25(OH)D levels and community-acquired pneumonia, we think that the association is likely to be even stronger for HAIs. However, in one randomized, double-blind, placebo-controlled trial in India that involved children admitted for pneumonia, supplementation with oral vitamin D of 1,000–2,000 IU per day for 5 d was not beneficial in resolving severe pneumonia.[74] The dose and especially the duration of vitamin D treatment may have been insufficient to influence outcome. Cannell and colleagues have advocated much higher short-term doses for acute illness.[75]

Influenza was associated with a higher tendency to develop superimposed bacterial pneumonia, and prevention may avoid the higher risk of pneumonia, especially in elderly and chronic lung disease patients. Whether vitamin D should be implemented as a mandatory vitamin to prevent pandemic influenza is the question.[76] Juzeniene et al. studied pandemic and nonpandemic influenzas in Sweden, Norway, the United States, Singapore, and Japan. The higher exposure to UVB radiation in summer and consequently higher 25(OH)D levels protect against influenza.[77] Hayes hypothesizes that influenza pandemics are associated with solar control of 25(OH)D levels in humans, which increase or decrease with solar cycle–dependent UV radiation.[78] Studying the 1918–1919 influenza pandemic, Grant and Giovannucci determined that vitamin D, by producing antimicrobial peptides and reducing production of proinflammatory cytokines, decreases the development of pneumonia after infection with influenza virus.[79] Also one randomized controlled trial involving Japanese schoolchildren found a relative risk of influenza of 0.36 in those taking 1,200 IU/day compared with those taking 200 IU/day.[80] However, Shaman et al. studied levels of 25(OH)D to see if it can be used to simulate influenza rates. They found it unlikely that seasonal variations in vitamin D levels principally determine the seasonality of influenza in temperate regions.[81]

We believe that this finding also applies to patients in the hospital, especially those infected with the influenza virus, and the subsequent development of HAP.

Clostridium difficile Infections

Clostridium difficile is the most common cause of nosocomial infectious diarrhea in the United States. *C. difficile*-associated disease (CDAD) can be severe and fatal. *C. difficile* infection (CDI) is a major cause of hospital-acquired diarrhea and is most commonly associated with changes in normal intestinal flora caused by administration of antibiotics. In Massachusetts, between 1999 and 2003, CDAD management consumed 55,380 inpatient-days and cost $51.2 million. Based on this study, a conservative estimate of the annual US cost for CDAD management was expected to be $3.2 billion.[82] In one institution, over a 5-y period, the economic burden of CDAD was increasing to the point that its associated medical expenditures approached $1 million per year.[83] An analysis by the Centers for Disease Control and Prevention revealed that, in the United States, CDI continues to increase, with more than 250,000 US hospitalizations in 2005 associated with it.[84]

Vitamin D has been found to play a protective role in the gut. Vitamin D and the VDR are required for the development and function of two regulatory populations of T cells: the iNKT cells and CD4/CD8αα intraepithelial lymphocytes (IEL). Protective immune responses that depend on iNKT cells or CD8αα IEL are therefore impaired in the vitamin D or VDR deficient host and the mice are more susceptible to immune-mediated diseases in the gut.[85] Also, vitamin D protects macrophages against death induced by *Cdif* toxin (TcdA/B)-induced intestinal injury.[86] In one study undertaken in Weill Cornell College of Medicine and New York Hospital Queens, 30 d clearance rates were 53% in those with normal serum levels of 25(OH)D vs. 26% in those with levels below 21 ng/dL. Mortality rates were also higher in the

patients with low vitamin D, at 56% compared with 33% for those with serum 25(OH)D levels of 21 ng/dL or above.[87] We discussed previously the health care costs of patients with CDI associated with vitamin D deficiency. In the outpatient setting, vitamin D deficiency in patients with *C. difficile* and staphylococcal infections were associated with significantly increased total outpatient costs and fee-based consultation.

In addition the total number of hospitalizations was also significantly greater in the vitamin D-deficient group. In the inpatient setting, vitamin D-deficient patients had higher laboratory, pharmacy, and radiology costs. These deficient patients had five times higher costs than the non-deficient patients, manifested by four times greater length of hospital stay and more hospitalizations.[41]

Catheter-Associated Urinary Tract Infections

Almost 60% of patients having a foley catheter in the hospital do not need it. Twenty-six percent of patients using indwelling catheters for 2–10 d get bacteriuria. Among those, symptoms of urinary tract infections (UTIs) develop in an estimated 24%, and bacteremia in 3.6%. Each episode of UTI is expected to cost an additional $676, and catheter-related bacteremia at least $2,836.[88] Changes in reimbursement policies have focused attention on the use of indwelling catheters in the critical care unit as well as their role in hospital-acquired UTIs. Implementation of an evidence-based prevention program can significantly reduce both the prevalence of indwelling catheterization and the incidence of hospital-acquired, catheter-associated UTIs.[89] One review discussed the role of vitamin D in the prevention of infections, including UTIs.[90] A study evaluated the different vitamin D receptor polymorphisms in children with UTIs and those with a history of UTI. The ApaI polymorphism was significantly increased in the control group and considered a protective factor. Comparing with the TaqI, the study found that both the Tt and tt genotypes carried minimal increased risk of UTI.[91] To prove the activity of vitamin D in protecting against UTIs, Hertting and colleagues demonstrated a significant increase in the production of cathelicidin after vitamin D_3 supplementation in bladders infected with uropathogenic *Escherichia coli*. The authors recommended that vitamin D be considered as a potential preventive measure for UTIs.[92]

Surgical Site Infections

The first report of a group A Streptococcus hospital outbreak was reported in an acute care facility in Texas. The wound care team was the means of transmission: a member of this team was colonized with the matching type.[93] Surgical site infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are increasing significantly and are independently associated with higher mortality, increased length of stay and higher cost.[94]

In a personal communication with Seattle cardiothoracic surgeon Donald Miller M.D., he indicated that the post-pericardiotomy syndrome occurring in veterans after coronary artery bypass surgery virtually disappeared, as did sternotomy wound infections, after a preoperative dose of 50,000 IU of cholecalciferol.

Vitamin D enhances antimicrobial peptide production in the skin. Deficiency in antimicrobial peptide production contributes to the increased susceptibility of *S. aureus* skin infections in patients with atopic dermatitis.[95] Antimicrobial peptides may contribute to host defense through wound repair[96] and clearance of bacteria at various barrier sites.[97] Applying topical vitamin D would result in faster recovery from many skin disorders, both infectious and noninfectious, including wounds, bacterial and viral infections, diabetic ulcers, and chronic skin ulcers. Arnold and van de Kerkhof investigated the efficacy of MC903, a vitamin D_3 analog, in reducing hyperproliferation as determined by levels of ornithine decarboxylase in 15 patients with chronic plaque psoriasis. Eight of 11 patients treated with MC903 showed clinical improvement.[98]

Several other studies showed beneficial outcomes in skin and soft tissue in the presence of vitamin D. For example, one study compared outcomes of periodontal surgery and teriparatide administration in vitamin D-sufficient and vitamin D-insufficient individuals. Placebo patients with baseline vitamin D deficiency had significantly less clinical attachment and probing depth reduction than vitamin D-sufficient individuals. At 1 y, infrabony defect resolution was greater in teriparatide-treated vitamin D-sufficient individuals.[99] In an animal study, incidence of injection site lesions was lowest among animals given vitamin AD_3, a water emulsifiable solution to be used as a supplemental source of Vitamins A and D_3 in cattle (as calves, at both branding and weaning times) and was highest in cattle given injections of 5 mL of clostridial products at branding or of long-acting oxytetracycline antibiotic at weaning.[100]

Infections due to Virulent Organisms, such as MRSA

In one hospital, most MRSA infections were health care associated: 58.4% were community-onset infections, 26.6% were hospital-onset infections, and 13.7% were community-associated infections, and the rest could not be classified. The incidence rates were highest among persons aged 65 y and older, blacks, and males.[101] Hospital-acquired MRSA and community-acquired MRSA are important causes of pneumonia and present diagnostic and therapeutic challenges.[102]

Nasal colonization with *S. aureus* is a significant risk factor for ICU-acquired *S. aureus* infections, and strategies to control these infections should target both MSSA (methicillin-susceptible *S. aureus*) and MRSA colonization.[103] A secondary data analysis of the National Health and Nutrition Examination Survey, 2001–2004, showed that vitamin D deficiency was associated with an increased risk of MRSA nasal carriage.[104] To support this finding, the Tromsø Staph and Skin Study 2007–2008 demonstrated that in nonsmoking men, the probability of *S. aureus* colonization and carriage, respectively, decreased by 6.6% and 6.7% for each 5-nmol/L increase in serum 25(OH)D concentration. This study also established serum 25(OH)D thresholds of greater than 59 nmol/L and at least 75 nmol/L for ~30% and ~50% reduction in *S. aureus* colonization and carriage,

respectively.[105] Vitamin D supplementation to reach a serum 25 (OH)D above 75 nmol/L may reduce the incidence of MSSA and MRSA infection and thus may be a significant synergistic step in preventing HAIs.

Appropriate Dose of Vitamin D

Vitamin D deficiency is associated with increased mortality rates.[106] A meta-analysis of 11 prospective studies of serum 25(OH)D at time of enrollment found a significantly reduced mortality rate for those with serum 25(OH)D concentrations of 75 nmol/L compared with those with less than 42 nmol/L.[107] Another recent paper estimated that doubling worldwide population mean serum 25(OH)D concentrations, from 50–55 nmol/L to 100–105 nmol/L, would reduce mortality rates by 7–17% and increase life expectancy by 2 y.[108] Also, a recent publication of a meta-analysis of 12 prospective studies showed that a 20nmol/l increase in 25(OH)D levels was associated with an 8% lower mortality in the general elderly population.[109]

The optimal serum 25(OH)D concentration for bacterial and viral immunity is still a controversial matter. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine gives guidelines for the daily vitamin D needed supplementation, based on a review of randomized controlled trials that they deemed of high quality, finding strong evidence only for beneficial effects for bones.[110] They recommended a daily dose of 600 IU of vitamin D. They also considered a serum level of 16 ng/mL to meet the needs for almost half the population. This report suggested that vitamin D deficiency is overdiagnosed. However, a 600-IU daily dose is inadequate to achieve the health-related goals we have described.[111] And because the response to vitamin D supplementation varies among patients, many patients need higher doses.[112] Norman and colleagues[113] addressed the current public health needs of vitamin D. Recently, the Endocrine Society released *Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline*, which recommended doses of vitamin D supplementation for each age group. Adults require at least 1,500–2,000 IU of vitamin D per day to maintain a blood level of 25(OH)D above 75 nmol/L. This dosage is similar to the requirements for those aged 50–70 y and for pregnant women.[110] Moreover, results in the literature on severe respiratory infections support these findings. In an observational study, individuals with serum 25(OH)D concentrations greater than 95 nmol/L had low rates of acute viral respiratory tract infections, whereas those with lower concentrations had a 50% chance of developing such infections during a half-year observational period. In a 2009 Paris meeting, a panel of vitamin D researchers endorsed a serum 25(OH)D concentration of 75–100 nmol/L.[115]Sabetta et al. demonstrated that maintenance of a vitamin D serum concentration of 38 ng/mL or higher should significantly reduce the incidence of acute viral respiratory tract infections, including influenza, at least during the fall and winter in temperate zones.[116]

Conclusion

For HAIs, pointing to vitamin D deficiency as the sole risk factor is difficult. Patients admitted to the hospital are sicker and thus are more prone to acquire pathogens and manifest illnesses. However, vitamin D deficiency can increase this probability by decreasing the host innate defense mechanisms. We have suggested the use of vitamin D in the management of acute illness in elderly patients and those with an underlying chronic illness.[117] This review aims to show the potential benefits of vitamin D in infection. Given the prevalence of vitamin D deficiency, we believe that intensive vitamin D supplementation in patients before and during hospital stays could improve health outcomes. Vitamin D is inexpensive, and adequate supplementation can be achieved at minimal cost. Vitamin D use could reduce inappropriate antibiotic prescription and boost therapeutic response when combined with appropriate antibiotic use. Although prospective double-blind studies are needed to confirm the antimicrobial effects of vitamin D, the existing evidence for an antimicrobial effect by vitamin D is compelling. We recommend that vitamin D deficiency be taken into greater consideration as a risk factor for immunodeficiency and increased susceptibility to infections. To note that most recently, Cannell announced that it has become possible to prescribe vitamin D_3, as 50,000 IU once weekly, and it can also be prescribed as once every 2 weeks.[118]

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