



DEFICIENCY IN 25-HYDROXYVITAMIN D AND 30-DAY MORTALITY IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK

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Background Vitamin D has immunomodulating properties.

Objective To determine if vitamin D deficiency within 30 days of admission to the intensive care unit in patients with sepsis might be associated with increased all-cause 30-day mortality.

Methods In a retrospective cohort study at a large, tertiary, urban, academic medical center, records of patients who had 25-hydroxyvitamin D levels measured within 30 days of admission for severe sepsis or septic shock from June 2006 to April 2011 were examined. Patients were considered deficient in vitamin D if its serum concentration was 15 ng/mL or less. The primary outcome of interest was 30-day mortality.

Results Among the 121 patients in the sample, 65 (54%) were vitamin D deficient. Baseline demographics were similar between vitamin D deficient and nondeficient groups, except that the vitamin D deficient group had more African Americans ($P = .01$). All-cause 30-day mortality was significantly higher in patients deficient in vitamin D (37% vs 20%; $P = .04$) and remained higher at 90 days (51% vs 25%, $P = .005$). In multivariate analysis, age (odds ratio, 1.04; 95% CI 1.01-1.07; $P = .01$) and vitamin D deficiency (odds ratio, 2.7; 95% CI, 1.39-18.8; $P = .02$) were independently associated with increased 30-day mortality.

Conclusion Patients deficient in vitamin D within 30 days of hospital admission for severe sepsis or septic shock may be at increased risk for all-cause 30-day mortality. (*American Journal of Critical Care*. 2014;23:e72-e79)

Vitamin D is a fat-soluble vitamin. Cells throughout the body, including the heart, brain, colon, and immune system, have vitamin D receptors,^{1,2} and it plays an important role as an immunomodulator. The receptors are nuclear receptors expressed on the surface of many immune cells, including T lymphocytes, neutrophils, and antigen-presenting cells, and have activity in gene regulation.³ When vitamin D is converted to its active form, 1,25-dihydroxyvitamin D, within these cells, it induces modulation of both innate and adaptive immune responses.²⁻⁴ Vitamin D deficiency has been implicated in multiple chronic disease states, particularly cardiovascular diseases,⁵ atherosclerosis,⁶ diabetes mellitus,⁷ hypertension,⁸ malignant neoplasms,⁹ and multiple sclerosis.^{3,10} It has also been associated with infectious diseases such as tuberculosis^{11,12} and seasonal influenza.¹³

Recent studies have indicated that vitamin D deficiency may be associated with worse outcomes in critically ill patients. Vitamin D deficiency (serum level of 25-hydroxyvitamin D \leq 15 ng/mL; to convert to nanomoles per liter, multiply by 2.496) has been reported in 27% to 50% of intensive care unit (ICU) patients, and vitamin D insufficiency (15-30 ng/mL) has been reported in 38% of critically ill patients.^{14,15} In a small cohort of ICU patients, 17% had undetectable levels of vitamin D.¹⁶ In 2 recent studies,^{14,15} a serum level of 25-hydroxyvitamin D less than 15 ng/mL in the year preceding hospital admission and within 7 days of ICU admission was independently associated with increased mortality. Furthermore, these studies indicated that 25-hydroxyvitamin D deficiency (defined as a serum level $<$ 15 ng/mL) before hospital admission was a significant predictor of sepsis in the critically ill, and patients with sepsis whose 25-hydroxyvitamin D level before admission was less than 30 ng/mL had increased risk for mortality after the ICU admission.

Sepsis is a common indication for ICU admission and is associated with marked morbidity and mortality.¹⁷⁻¹⁹ Other than early goal-directed therapy, few interventions have decreased mortality in patients with sepsis.²⁰ The primary objective of our study was to evaluate the effect of vitamin D deficiency on 30-day mortality in patients with severe sepsis or septic shock.

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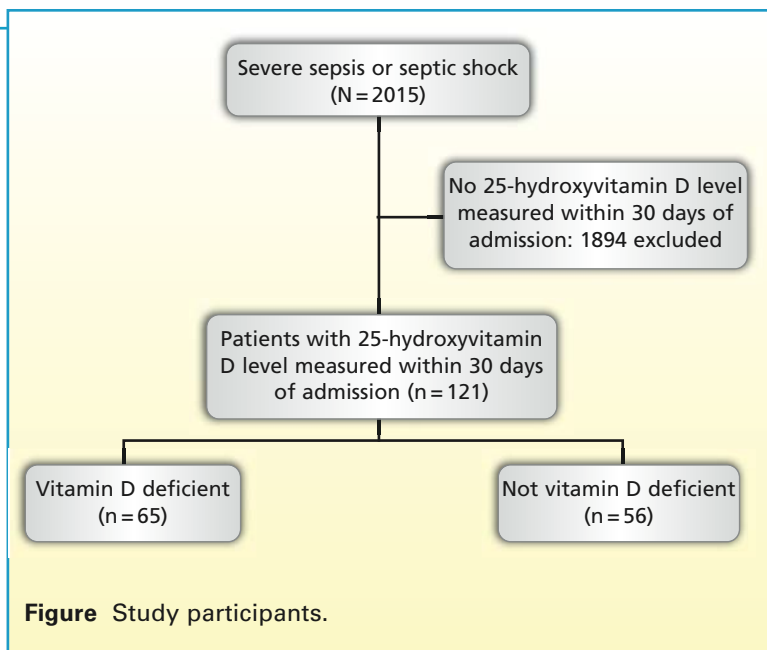
Methods

This study was a retrospective cohort investigation conducted at Henry Ford Hospital, a large, urban, academic tertiary care center in Detroit, Michigan. Patients were identified from a computerized database of patients with sepsis, and data were collected via the hospital's electronic records. All patients with sepsis in the ICU from June 2006 to April 2011 who had the serum level of 25-hydroxyvitamin D measured within 30 days of admission were included in the study. Sepsis was treated in accordance with current evidence-based practice guidelines at the discretion of the attending physician and defined according to the Surviving Sepsis Campaign.¹⁷ Blood samples for measurement of 25-hydroxyvitamin D levels were obtained at the discretion of a physician before or during ICU admission. If 25-hydroxyvitamin D levels were measured more than once within 30 days of admission, the measurement obtained closest to the date of diagnosis of sepsis was used. Although the Institute of Medicine and the Endocrine Society clinical practice guideline²¹ recently suggested a serum level of 25-hydroxyvitamin D less than 20 ng/mL as the cutoff for vitamin D deficiency, for this study, deficiency was defined as 15 ng/mL or less on the basis of previous studies.^{14,15} Levels of 25-hydroxyvitamin D were determined by using a LIAISON analyzer (DiaSorin). The study was approved by the institutional review board of the hospital, and a waiver of informed consent was granted because the study was a retrospective investigation.

Data Collection

The following data were retrieved: sex, race, age, baseline score on the Acute Physiology and Chronic

Vitamin D deficiency before hospital admission was predictive of sepsis in critically ill patients.



Health Evaluation II, baseline score on the Sequential Organ Failure Assessment, temperature, serum levels of 25-hydroxyvitamin D, and history of diabetes, hypertension, or end-stage renal disease. Other clinically relevant data collected included source of infection, use of vasopressors, and total amounts of fluids and antibiotics administered within 6 hours of diagnosis of sepsis. Data on vitamin D supplementation were collected by chart review of prescription history of cholecalciferol or ergocalciferol before admission.

Outcomes and Definitions

The hypothesis was that vitamin D deficiency within 30 days of hospitalization for sepsis is associated with increased all-cause 30-day mortality. The primary end point was all-cause 30-day mortality. Secondary end points included hospital and 90-day mortality and hospital and ICU length of stay. Patients with in-hospital mortality or those who left against medical advice were excluded from the length-of-stay analysis. When mortality data were not apparent from hospital records or the patient was lost to follow-up at 90 days, the Social Security Death Index was used to determine date of death.

Statistical Analysis

Categorical variables were analyzed by using χ^2 analysis or the 2-sided Fisher exact test. Continuous variables were analyzed by using the independent samples *t* test or the nonparametric Mann-Whitney test, as appropriate. A multivariate logistic regression analysis was conducted to determine factors independently associated with 30-day mortality. Variables with $P < .20$ in the univariate analysis were examined

in the multivariate logistic regression analysis. Statistical analysis was performed by using SPSS software, version 20.0 (IBM SPSS).

Results

Overall, 2015 patients were admitted for severe sepsis or septic shock during the study period. The mean age was 62 (SD, 28) years, 53% were men, 61% were African American, 27% were white, 46% had severe sepsis, and 54% had septic shock. Of these patients, 121 (6%) had a 25-hydroxyvitamin D level measured within 30 days of admission, and 65 (54%) of the 121 were vitamin D deficient (see Figure). Baseline characteristics of study patients were similar to those of the overall population, with a mean age of 63 (SD, 17) years, 49% men, 63% African American, 30% white, 49% severe sepsis, and 51% septic shock. The mean serum level of 25-hydroxyvitamin D for the study cohort was 17 (SD, 11) ng/mL, and 65 patients (54%) were classified as vitamin D deficient (≤ 15 ng/mL).

Baseline characteristics are given in Table 1. African-American patients differed significantly ($P = .01$) in vitamin D levels; 77% were vitamin D deficient and 46% were not. Among white patients, 45% were not deficient in vitamin D, and 17% were ($P = .05$). Mean 25-hydroxyvitamin D levels were 9.1 (SD, 2.7) ng/mL in vitamin D deficient patients and 27 (SD, 7.6) ng/mL in those who were not deficient ($P < .001$). The majority of patients in both groups were admitted to the medical ICU (89% vs 88%; $P = .77$). Sepsis associated with bacteremia occurred significantly more often ($P = .001$) in vitamin D deficient patients (19%) than in nondeficient patients (0%). Sepsis associated with pneumonia occurred significantly more often ($P = .01$) in patients who were not deficient (46%) than in patients who were deficient (25%).

Clinical Outcomes

All-cause 30-day mortality (Table 2) was significantly higher ($P = .04$) in patients deficient in vitamin D (37%) within 30 days of admission for severe sepsis or septic shock than in patients who were not deficient (20%). In addition, all-cause 90-day mortality was significantly higher ($P = .005$) in patients deficient in vitamin D (51%) than in patients who were not deficient (25%); however, the 2 groups did not differ in hospital mortality (25% for vitamin D deficient patients vs 21% for nondeficient patients; $P = .68$).

Length-of-stay analysis (Table 2) included 95 patients (26 patients were excluded from analysis because of hospital mortality; no patients left

Table 1
Baseline characteristics

Characteristic ^a	Vitamin D deficient (n = 65)	Not vitamin D deficient (n = 56)	P	30-Day mortality (n = 35)	No mortality (n = 86)	P
Age, mean (SD), yr	65.6 (17.2)	64.5 (16.6)	.53	69.4 (15.6)	61.1 (16.9)	.01
Male sex	30 (46)	29 (52)	.54	17 (49)	42 (49)	>.99
Race						
African American	50 (77)	26 (46)	.01	25 (71)	51 (59)	.21
White	11 (17)	25 (45)	.05	8 (23)	28 (33)	.29
Other	4 (6)	5 (9)	.60	2 (6)	7 (8)	.65
25-hydroxyvitamin D, ^b mean (SD), ng/mL	9.1 (2.7)	27 (7.6)	<.01	15 (10.1)	18.4 (10.6)	.12
APACHE II score, mean (SD)	18.8 (7.9)	17.1 (6.9)	.20	19.8 (9.1)	17.3 (6.6)	.14
SOFA score, mean (SD)	6.5 (4)	5.7 (2.8)	.20	6.2 (3.3)	6.1 (3.7)	.94
Comorbid conditions						
Diabetes mellitus	28 (43)	25 (45)	.86	17 (49)	36 (42)	.50
Hypertension	41 (63)	34 (61)	.79	22 (63)	53 (62)	.90
End-stage renal disease	18 (28)	13 (23)	.57	7 (20)	24 (28)	.37
Septic shock	36 (55)	26 (46)	.33	19 (54)	43 (50)	.67
Type of intensive care unit						
Medical	58 (89)	49 (88)	.77	32 (91)	75 (87)	.51
Surgical	5 (8)	5 (9)	>.99	2 (6)	8 (9)	.52
Neurological	1 (2)	0 (0)	>.99	0 (0)	1 (1)	>.99
Cardiac	1 (2)	1 (2)	>.99	1 (3)	1 (1)	.49
Source of infection						
Abdominal	6 (9)	7 (12)	.56	5 (14)	8 (9)	.52
Blood	12 (18)	0 (0)	<.01	4 (11)	8 (9)	.74
Meningitis	1 (2)	0 (0)	>.99	0 (0)	1 (1)	>.99
Pulmonary	16 (25)	26 (46)	.01	10 (29)	32 (37)	.37
Urinary tract	19 (29)	21 (38)	.34	13 (37)	27 (31)	.54
Other/unknown	11 (17)	2 (4)	.02	3 (9)	10 (12)	.76
Antibiotics within 6 hours	59 (91)	52 (93)	.68	33 (94)	78 (91)	.72
Total fluids, ^c L	4.8 (3.8)	4.3 (3.9)	.51	4.3 (4.1)	4.7 (3.7)	.59
Vasopressor use	36 (55)	26 (46)	.33	19 (54)	43 (50)	.67

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

^a Unless otherwise indicated, data in the table are expressed as number (percentage). Because of rounding, percentages may not total 100.

^b To convert to nanomoles per liter, multiply by 2.249.

^c Within 6 hours of recognition of sepsis.

against medical advice). ICU length of stay was significantly longer ($P = .02$) in vitamin D deficient patients (mean [SD], 13 [17] days) than in those who were not deficient (mean [SD], 7 [7] days). Mean hospital length of stay did not differ significantly ($P = .20$) between the 2 groups: 22 (SD, 19) days for patients deficient in vitamin D and 18 (SD, 14) days for patients not deficient in the vitamin.

A univariate analysis was used to compare patients with mortality at 30 days to those alive at 30 days (Table 1). Patients who experienced mortality at 30 days (mean age, 70 years) were significantly older ($P = .01$) than patients who were alive at 30 days (mean age, 61 years). No other differences between

Table 2
Clinical outcomes

Outcome	Vitamin D deficient (n = 65)	Not vitamin D deficient (n = 56)	P
Mortality, No. (%) of patients			
Hospital	16 (25)	12 (21)	.68
30-Day	24 (37)	11 (20)	.04
90-Day	33 (51)	14 (25)	.005
Length of stay, ^a mean (SD), days			
Intensive care unit	13 (17)	7 (7)	.02
Hospital	22 (19)	18 (14)	.20

^a Length-of-stay analysis includes 95 patients.

Table 3
Multivariate analysis

Variable ^a	P	Odds ratio	95% CI
Age	.01	1.04	1.01-1.07
Vitamin D deficiency	.02	2.70	1.39-18.80

^a Only variables with *P* values less than .20 from Table 1 were used.

the 2 groups were significant. However, patients with 30-day mortality tended to be African American (71% died vs 59% lived; *P* = .21), have lower serum levels of 25-hydroxyvitamin D (mean [SD]: died, 15 [10.1] ng/mL vs lived, 18.4 [10.6] ng/mL; *P* = .12), and have higher baseline scores on the Acute Physiology and Chronic Health Evaluation II (mean [SD]: died, 19.8 [9.1] vs lived, 17.3 [6.6]; *P* = .14).

Vitamin D Supplementation

Overall, 24 patients (20%) received vitamin D supplementation before admission; among these, 7 patients (11%) were in the vitamin D deficient group and 17 (30%) were in the nondeficient group (*P* = .01). The percentage of patients taking ergocalciferol was significantly higher (*P* = .05) among patients who were not vitamin D deficient (20%) than among patients who were deficient (8%), but supplementation with cholecalciferol did not differ between the 2 groups (2% of each group; *P* > .99).

Hospital mortality was significantly lower (*P* = .01) among patients who had supplementation (4%) than among those who did not (28%). Similarly, 90-day mortality was significantly lower (*P* = .02) among patients who received supplementation (17%) than among those who did not

(44%). The 2 groups did not differ significantly (*P* = .07) in 30-day mortality: mortality was 13% for those receiving supplementation and 33% for those who did not. ICU length of stay was significantly shorter (*P* < .01) for patients given vitamin D supplementation (mean [SD], 7 [7] days) than for those given no supplementation (mean [SD], 11 [4] days), but hospital length of stay did not differ significantly (*P* = .06) between the 2 groups: mean (SD), 16 (10) days for patients given supplementation and 21 (18) days for those not given supplementation.

Multivariate Analysis

Factors with *P* < .20 in the univariate analysis were analyzed in a multivariate regression analysis. The variables included in this analysis were age,

African American race, vitamin D deficiency, score on the Acute Physiology and Chronic Health Evaluation II, pulmonary source of sepsis, and any vitamin D supplementation. Age (odds ratio, 1.04; 95% CI, 1.01-1.07; *P* = .01) and vitamin D deficiency (odds ratio, 2.70; 95% CI, 1.39-18.80; *P* = .02) were independently associated with increased 30-day mortality (Table 3).

Discussion

Our results indicate that vitamin D deficiency within 30 days of hospitalization for severe sepsis or septic shock was significantly associated with increased all-cause 30-day mortality, and the difference remained significant after accounting for confounders. Furthermore, mortality may be decreased by ensuring adequate vitamin D concentrations through supplementation with ergocalciferol or cholecalciferol within 30 days of hospitalization. This finding has important implications because sepsis is a leading cause of mortality in critically ill patients.^{18,19}

The mechanism through which vitamin D deficiency is associated with increased mortality in patients with sepsis may be related to its immunological effects. Studies^{22,23} suggest that vitamin D can regulate adaptive and innate immune responses. Receptors for vitamin D are nuclear receptors that are expressed on many immune cells, including activated B and T cells, macrophages, and other antigen-presenting cells. Upregulation of vitamin D receptors occurs in response to infectious processes.²³ Upon binding to its receptors, vitamin D is converted to its active form.^{22,22} Vitamin D plays a role in B-cell homeostasis by inhibiting the differentiation of plasma cells and class-switched memory cells.²² After antigenic activation, vitamin D receptors are upregulated on the surface of T cells. Vitamin D is intricately involved with T-cell proliferation and phenotype selection, which ultimately result in a reduction in the production of inflammatory cytokines.²⁴

In contrast to its effects in the adaptive immune system, the favorable effects of vitamin D in the innate immune response are mainly directed at macrophage activity.²⁵ Activated vitamin D stimulates differentiation of precursor monocytes to more mature phagocytic macrophages.^{26,27} These macrophages detect lipopolysaccharide components of bacteria through the activity of toll-like receptors. This interaction leads to the production of cathelicidin, a peptide with strong bactericidal properties, which disrupts bacterial cell membranes.^{3,25} Furthermore, binding of toll-like receptors increases expression of vitamin D receptors on the surface of macrophages. Through this mechanism, vitamin D

Hospital mortality was significantly lower among patients who received vitamin D supplementation.

is a direct regulator of innate immune responses.²⁸ These immunological properties attenuate the inflammatory and immune responses associated with sepsis.

Previous studies^{14,15,29} have shown that vitamin D deficiency is associated with increased mortality in critically ill patients. In 2399 patients, vitamin D deficiency up to 365 days before admission was a significant predictor of both short- and long-term mortality and of blood cultures positive for growth of microorganisms.¹⁵ Significantly more ($P < .01$) patients in the vitamin D deficient group (30.3%) had a diagnosis of sepsis at admission than did patients who had insufficient (24%) or sufficient (19.4%) levels of the vitamin.¹⁵ In a study¹⁴ of 1325 patients, vitamin D deficiency within 7 days of ICU admission was a significant predictor of all-cause mortality. In that study¹⁴ the incidence of sepsis was significantly greater ($P < .01$) in patients with vitamin D deficiency (37.3%) than in patients with insufficient (28.6%) or sufficient (22.1%) levels of the vitamin.

Furthermore, a higher prevalence of vitamin D deficiency has been noted in patients with critical illness and sepsis.^{29,30} A study³¹ of 80 patients who came to the emergency department because of suspected infection indicated that patients with serum levels of 25-hydroxyvitamin D less than 30 ng/mL had a higher incidence of severe sepsis within 24 hours than did patients with higher serum levels. Additionally, a recent retrospective cohort study³² of more than 3000 patients indicated that risk for sepsis was 1.6-fold higher in critically ill patients with serum levels of 25-hydroxyvitamin D less than 15 ng/mL compared with patients in the cohort with 25-hydroxyvitamin D concentrations of 30 ng/mL or higher. Finally, in the cohort with sepsis ($n = 568$), the multivariable-adjusted risk for 90-day mortality was 1.6-fold higher in those with serum levels of 25-hydroxyvitamin D levels less than 30 ng/mL than in patients whose preadmission level of 25-hydroxyvitamin D was greater than 30 ng/mL.³²

Correlation between vitamin D sufficiency and decreased mortality has not been observed in all studies. In 2 studies^{33,34} of critically ill patients with smaller sample sizes, vitamin D deficiency was associated with longer length of stay and a trend toward higher rates of infection and sepsis; however, the increase in mortality did not differ significantly between patients who were deficient in vitamin D and patients who were not. In a study³⁵ of 170 patients, 92 with sepsis and 72 with trauma, patients with sepsis had significantly lower mean serum levels of 25-hydroxyvitamin D on admission. The mortality rate in patients with sepsis correlated with

levels of vitamin D at admission but was not significant after multivariate adjustment.

Vitamin D deficiency is associated with increased incidence of infectious diseases. According to the National Health and Nutrition Examination Survey,³⁶ levels of 25-hydroxyvitamin D are inversely associated with occurrence of upper respiratory infections. Patients with serum levels of 25-hydroxyvitamin D less than 10 ng/mL had 55% higher odds of an upper respiratory tract infection ($P < .001$) than did patients with levels greater than 30 ng/mL. Evidence³⁷ also indicates that vitamin D status has an effect on influenza and invasive pneumococcal disease. According to Cannell et al,³⁸ the seasonality of influenza may be in part due to seasonal impairments of the innate immune system caused by fluctuations in 25-hydroxyvitamin D levels. In addition, supplementation with vitamin D can prevent seasonal influenza¹³ and acute respiratory infections in children.³⁹ An investigation⁴⁰ based on data from the National Hospital Discharge Survey showed that the seasonal incidence of sepsis increased 16.5% in the winter ($P < .05$), especially sepsis due to respiratory infections. Although 25-hydroxyvitamin D levels were not assessed in that study,⁴⁰ vitamin D deficiency through decreased sun exposure in winter months may play a role.

Finally, vitamin D deficiency has also been linked to tuberculosis.^{11,12} A meta-analysis⁴¹ indicated that 25-hydroxyvitamin D levels were 0.68 standard deviations lower in people with tuberculosis than in control patients. Vitamin D supplementation can also attenuate inflammation and accelerate sputum smear conversion in patients with tuberculosis.⁴² These findings on vitamin D and infectious diseases support the immunomodulating role of vitamin D in the pathophysiology of sepsis.^{11,12,41,42}

The United States Endocrine Society²¹ recommends identification of vitamin D deficiency and treatment of the deficiency with vitamin D supplementation. In our study, patients who had supplementation with ergocalciferol or cholecalciferol before admission had significantly lower hospital and 90-day mortality than did patients who were not receiving supplementation. However, in the multivariate analysis, supplementation did not retain significance. These data are inconclusive; further studies are needed to determine if the risk for mortality in patients with sepsis can be modified by ensuring adequate levels of 25-hydroxyvitamin D.

Vitamin D deficiency is associated with increased all-cause 30-day mortality.

In our study, the incidence of vitamin D deficiency was significantly higher in African Americans than in the other patients. This finding is consistent with the results of other studies^{43,44} and may be related to increased skin pigmentation, which reduces the skin's ability to synthesize activated vitamin D.⁴⁵ The number of African American patients in this study is reflective of the hospital's urban Detroit population. According to data from the National Health and Nutrition Examination Survey, non-Hispanic blacks and Mexican Americans are more likely to be at risk for vitamin D deficiency than are other races after adjustments are made for season and age.⁴⁶ However, we attempted to control for confounding baseline characteristics by using multivariate analysis, in which African American race was not associated with increased incidence of 30-day mortality.

Our study has several limitations. First, it was observational and retrospective, so controlling for the presence of all potential confounding factors might not have been possible, a situation that may have influenced the results. We attempted to account for confounders by performing a multivariate regression analysis. Selection bias might also exist. The study group had blood samples obtained for measurement of 25-hydroxyvitamin D levels at the discretion of any physician within 30 days of admission for sepsis, and the reason for each measurement was not ascertained. The number of samples for measurement of 25-hydroxyvitamin D levels each year did increase during the study period (16 in 2006 and 32 in 2010), perhaps because of increased awareness of consensus guideline recommendations and the benefit of correcting vitamin D deficiency.²¹

Another limiting factor is that the immunoassay used for detecting 25-hydroxyvitamin D in the study depends on vitamin D binding protein, which is decreased in septic states.⁴⁷ Furthermore, a small study⁴⁸ of cardiovascular surgery patients indicated that intravenous fluid replacement results in hemodilution, which lowers serum concentration of 25-hydroxyvitamin D by 35% for up to 24 hours. However, in our study, only 9 patients (7%) had 25-hydroxyvitamin D levels measured within 24 hours of the start of sepsis, thus limiting subtherapeutic 25-hydroxyvitamin D concentrations due to decreased vitamin D binding protein and fluid shifts. Additionally, our study was limited by a small sample size and inclusion of patients at single hospital. Of the 2015 patients with severe sepsis or septic shock included in our registry, only 121 (6%) had a 25-hydroxyvitamin D level determined within 30 days of admission. This number was lower than

anticipated. Despite this limitation, the demographics of our sample were comparable to those of the overall population of patients with sepsis, indicating that our sample was representative of the overall population. Finally, this study is limited because we were unable to collect some data that may have had an impact on serum concentrations of 25-hydroxyvitamin D and vitamin D binding protein, including markers of liver function (ie, albumin, transaminases) and markers of inflammation (eg, C-reactive protein).

Conclusion

Patients deficient in vitamin D within 30 days of hospital admission for severe sepsis or septic shock had increased all-cause 30-day mortality. Risk of mortality may be potentially modifiable by ensuring adequate levels of 25-hydroxyvitamin D. Further evaluation in a larger sample of patients or through randomized controlled trials is necessary to further explore our results.

FINANCIAL DISCLOSURES

None reported.

eLetters

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