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Report

Solar ultraviolet-B irradiance and vitamin D may reduce the risk of septicemia

William B. Grant

Sunlight, Nutrition and Health Research Center (SUNARC); San Francisco, California USA

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The primary features of the epidemiology of septicemia in the United States include highest rates in winter and the Northeast, lowest in fall and in the West; higher rates among African Americans than white Americans; a rapid increase in incidence with age; comorbidity with several chronic and infectious diseases; and a rapid increase in incidence rate starting in the early 1980s. This article reviews the literature on the epidemiology of septicemia in the United States, along with the roles of solar ultraviolet-B (UVB) and vitamin D3 related to the more important features. Solar UVB doses in summer are highest in the Southwest and lowest in the Northeast. Serum 25-hydroxyvitamin D [25(OH)D] levels are highest in summer, lowest in winter. African Americans have much lower 25(OH)D levels than those of white Americans. Serum 25(OH)D levels decline rapidly with advancing age. The risk of diseases comorbid with septicemia are generally inversely correlated with serum 25(OH)D levels. Sun-avoidance messages may have led to lower population levels of 25(OH)D, although prevalence of antibiotic-resistant bacteria may have increased. Previous reports have shown that 1,25-dihydroxyvitamin D upregulates human cathelicidin, LL-37, which has antimicrobial as well as antiendotoxin activity. The general agreement between the epidemiology of septicemia in the United States and the variations of solar UVB and the effects of vitamin D supports the hypothesis that both play important roles in reducing the risk of septicemia. Further study is warranted to evaluate this hypothesis.

Introduction

Septicemia (or sepsis) is a systemic inflammatory response syndrome in response to the presence of pathogenic organisms or their toxins in the blood or tissues.[1] Septicemia is often caused by infection by bacteria such as *Staphylococcus aureus*,[2] sometimes preceded by or occurring in conjunction with viral infections[3] and, to a lesser extent, fungal infections.[4] It is a relatively common and often deadly disease. In the United States, there were 4.07 million cases of septicemia from 1995 to 2000, of which 730,000 died.[5] In 1995, the average costs per case were $22,100, with annual total costs of $16.7 billion.[6] Rates of severe septicemia have increased since then,[7] whereas the mortality rates decreased, probably because of improved care.[8]

There are five well-characterized features associated with the epidemiology of septicemia in the United States:

- Rates are highest in winter and lowest in fall.[9]
- Rates are generally highest in the Northeast and lowest in the West.[9]
- African Americans have higher incidence rates than those of white Americans.[10,11]
- There is a rapid increase in incidence with age.[10]
- Several infectious and chronic diseases are associated with an increased risk for septicemia.[10,12,13]

This article presents the hypothesis that low serum 25-hydroxyvitamin D [25(OH)D] is a risk factor for incidence of and death from septicemia and reviews the epidemiology of septicemia in the United States in support of this hypothesis.

Results

Table 1 lists the more important features of the epidemiology of septicemia in the United States taken from the literature. Most of these features relate to serum 25(OH)D in a way that generally supports the vitamin D/septicemia hypothesis.

Table 2 gives the regional and seasonal variations in incidence rates of septicemia based on graphical data in Figure 2 of Danai et al.[9] Incidence rates are highest in the Northeast and lowest in the West. Winter is the season of highest rates except for the South, whereas fall is the season of lowest rates.

Table 3 expresses the relationship between the role of sex and ethnic background on risk of septicemia for various types of cancer, based on data in Table 3 of Danai et al.[10]

Discussion

Solar UVB and vitamin D. A review of the epidemiological features associated with septicemia and UVB doses in the United States indicates that vitamin D variations may explain much of the epidemiology of septicemia in the United States. The hypothesis examined here is that vitamin D, through induction by 1,25-dihydroxyvitamin D [(1,25(OH)2D)] of human cathelicidin, LL-37, reduces the risk of septicemia. LL-37 is the cleaved antimicrobial 37-residue,

Correspondence to: William B. Grant; Sunlight, Nutrition and Health Research Center (SUNARC); P.O. Box 641603; San Francisco, California 94164-1603 USA; Tel.: 1.415.409.1980; Email: wbgrant@infionline.net

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Table 1 **Characteristics of septicemia epidemiology in the united states**

Feature	Finding	Reference
Seasonality	Peak in winter, 17.7% higher in winter than in fall	9
	40% increase in septicemia linked to respiratory infections in winter compared with that in fall	9
Geographic variation	Highest rate in the Northeast, lowest in West	9
Trends	Incidence rates were relatively constant from 1979 to 1982 (20 cases/100,000/year), then doubled by 1985 and rose by another 20 cases/100,000/year in the mid-1990s	9
Racial disparity	Lowest hospitalization rates for whites, higher for African Americans and other races in the United States	5, 10, 11
Sex	For 1979–2001, males made up 53.2% of cases of septicemia with cancer but only 47.9% of septicemia without cancer	5
Age dependence	Death rate increases with age (RR per decile, 1.32 [95% CI, 1.31–1.34])	10
Comorbidity, death rates	Cancers (RR, 2.15 [95% CI, 2.04–2.26])	10
	HIV (RR, 2.40 [95% CI, 2.10–2.73])	10
	Pulmonary infection (RR, 1.66 [95% CI, 1.58–1.74])	10
	Cirrhosis (RR = 1.59 [95% CI, 1.42–1.77])	10
	Congestive heart failure (RR, 1.38 [95% CI, 1.31–1.45])	10
	(HR = 3.38 [95% CI, 2.67–4.29])	12
	Peripheral vascular disease (HR = 1.96 [95% CI, 1.53–2.53])	12
	COPD (HR = 1.64 (95% CI, 1.22–2.19])	12
	Diabetes (OR = 4.6 [95% CI, 1.2–18.1]; p = 0.03)	13
High body mass index	Increased risk for death for those with bacteriemia.	14
Sex differences	Males have about a 20% higher incidence rate than females in the United States	5
Urban/rural	Higher in urban regions, lower in rural regions	11

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; RR, relative risk.

COOH-terminal peptide of hCAP18 (human cationic antimicrobial protein with a molecular mass of 18 kD).[15] 1,25(OH)2D is directly correlated with serum 25(OH)D levels,[16] and 25(OH)D levels are directly related to vitamin D from both oral intake and photoproduction caused by UVB irradiance.

Mookherjee et al.,[17] reviewed cathelicidin's antisepticemia properties. They ascribed some benefit to the anti-infective properties of cathelicidins. Although vitamin D provides immune protection against *Mycobacterium tuberculosis*,[18] the mechanisms of action have only recently been uncovered.[19] Vitamin D also offers protection against respiratory diseases caused by viral infections.[20,21] They attributed the primary effect in reducing the risk of septicemia to other effects of cathelicidins, including lower endotoxin and proinflammatory cytokine tumor necrosis factor α levels in plasma, as well as reduced endotoxic shock and death.[22]

Next, the UVB-vitamin D hypothesis in light of knowledge about septicemia epidemiology in the United States is examined.

Seasonality. The season of lowest rate for incidence of septicemia in general was fall, rather than summer, the time when serum 25(OH)D levels are lowest.[9] However, case fatality rates were lowest in summer.[9] From 1979 to 2003, septicemia incidence rates in the United States were 17.7% higher in winter than in fall, whereas septicemia case fatality rates were 13% higher in winter than in summer.[9] Serum 25(OH)D levels are much higher in the summer than the winter,[23] indicating that solar UVB is an important source of vitamin D in the United States.

Geographic location. The annual incidence rates by location, lowest in the West and highest in the Northeast (Table 2), are well correlated with summertime solar UVB doses in the United States.[24]

Table 2 **Regional and seasonal variation of septicemia incidence rates in the united states, 1979–2003[a]**

Region	Winter	Spring	Summer	Fall	Winter/Fall
Northeast	65	57	55	50	1.30
Midwest	53	47	47	47	1.14
South	47	49	47	44	1.08
West	42	39	38	36	1.16
NE/W	1.55	1.46	1.44	1.39	

[a]Data are cases/100,000/year.

UVB doses east of the Rocky Mountains are generally comparable to those at much higher latitudes from the Rocky Mountains to the west coast because of two important factors: surface elevation is generally higher in the West, and the stratospheric ozone layer is lower in the west as the prevailing westerly winds push the tropopause higher as the air masses prepare to cross the Rocky Mountains. In winter, latitude is a better index of solar UVB dose. The half-life residence time of vitamin D in the body is 1–2 months, so vitamin D produced in summer or fall will not last through winter. Although wintertime UVB doses have a variation that is more related to latitude than the summertime UVB distribution, lower summertime UVB could predispose people to comorbid diseases that would lead to septicemia in winter.

Trends. Although there are probably several reasons why septicemia rates have risen rapidly since the early 1980s, a reason connected with solar UVB and vitamin D relates to the introduction

Table 3 **Incidence of septicemia among patients with cancer, 1979–2001[10]**

Cancer	Male/female (risk ratio, 95% CI)	African American/white (risk ratio, 95% CI)	Smoking as a risk factor	Vitamin D as a risk factor
Lung	1.17 (1.10–1.23)	1.28 (1.16–1.40)	Yes	Yes
Gastrointestinal	0.84 (0.73–0.94)	1.24 (0.90–1.58)	No	Yes
Urinary tract	0.74 (0.58–0.91)	1.70 (0.97–2.42)	Yes	Yes
Leukemia	0.89 (0.76–1.03)	2.94 (2.11–3.77)	No	No
Lymphoma	1.13 (0.98–1.27)	1.28 (0.98–1.58)	No	No
Breast		2.28 (1.10–3.47)	No	Yes
Prostate		1.25 (0.84–1.65)	No	Yes
Female reproductive tract		1.68 (1.08–2.28)	-[a]	Yes

CI, confidence interval. [a]Cervical cancer, yes; endometrial and ovarian cancer, no.

of widespread use of sunscreen in the United States. In Australia, the sun protection campaign began in 1980.[25] It seems reasonable that a similar effort began in the United States near the same time. Changes in melanoma and nonmelanoma skin cancer (NMSC) mortality rates between 1950–1969 and 1970–1994 suggest that the sun-protection message has had a definite effect on health.[26] Melanoma is linked to UVA (320–400 nm) irradiance, whereas NMSC is linked to UVB (280–320 nm). On the basis of data in *The Atlas of Cancer Mortality Rates in the United States*,[27] NMSC mortality rates decreased by 31% for males and 47% for females, whereas melanoma mortality rates increased by 89% for males and 42% for females. Melanoma rates rose monotonically since 1950–1954 while NMSC rates decreased until 1970–1974 then stabilized or increased slightly. Sunscreen sold in the United States until 2007 had strong blocking effect against UVB radiation but exhibited only weak blocking against UVA radiation. However, it is also likely that the increased prevalence of antibiotic-resistant bacteria explains most of the trend.

Racial disparities. On the basis of data for all those admitted to hospitals and diagnosed with septicemia in New Jersey in 2002, African Americans were 4.3 times more likely to be diagnosed with septicemia than white Americans for those aged 35–44 years and about 1.7 times as high for those older than 75 years.[28] The high ratio in middle ages may be related to human immunodeficiency virus (HIV) infection.[29] However, such is not the case for those older than 75 years.

Martin et al.[5] examined trends for racial disparities in septicemia from 1979 to 2000. Because HIV and AIDS had not reached the United States before 1980, one can use the racial disparity data for the first few years of those data to estimate the black-white differences apart from the effect of HIV. For 1979–1985, the ratio of black to white incidence rates varied from ~1.7 to ~2.1, with a mean value of ~1.9.

There are several published reports comparing serum 25(OH)D levels for black and white Americans. In northern states in winter, for those aged 20–40 years, the ratio of black to white 25(OH)D levels is 0.50.[23] For those aged 72–79 years, the ratio is 0.68 for males and 0.76 for females.[30] In the southern states in winter, for those older than 60 years, the ratio was 0.84 for males and 0.73 for females.[31] Thus, the ratio of serum 25(OH)D levels for blacks and whites in winter in northern states was close to the inverse of that for the ratio of incidence rates for septicemia for the two races in cases when HIV was not a factor. A recent study also found that African-American women required high doses of vitamin D in order to raise their serum 25(OH)D levels.[32]

African Americans have higher septicemia risk ratios than white Americans for all types of cancer, with the ratios being statistically significant for four and marginally nonsignificant for two cancers. African Americans have higher cancer rates than those of white Americans, which has been attributed partly to lower serum 25(OH)D levels on the basis of solar UVB doses[33] and a vitamin D index.[34]

Reduction of 25(OH)D with age. Serum 25(OH)D levels decrease with age because the rate of photoproduction of vitamin D from UVB decreases with age. Concentrations of 7-dehydrocholesterol, which UVB converts into pre-vitamin D, decrease with age by 10%–20% per decade.[35] Healthy young and elderly subjects given a whole-body irradiation of one minimal erythemal dose of simulated sunlight had serum 25(OH)D levels measured for several days thereafter. One day after the irradiation, the young experienced mean increases of 28 ng/mL (range, 18–38 ng/mL), whereas the elderly experienced mean increases of 6 ng/mL (range, 4–9 ng/mL).[36] Also, people probably spend less time in the sun as they age. Oral vitamin D intake also declines with age.[37]

Body mass index. High body mass index is associated with lower serum 25(OH)D levels.[38] Foods associated with increased body mass index, such as fat, meat and simple carbohydrates,[39] generally do not have vitamin D, and heavier people are less likely to spend time outdoors.

Sex differences. Females make up a larger fraction of septicemia cases for those without cancer, whereas males do when cancer is included.[5] Smoking is an important risk factor for many types of cancer,[40] and males smoke more than females do. Elderly males have higher serum 25(OH)D levels than those of elderly females in the United States.[30,31] Thus, the sex differences omitting cancer could be related to serum 25(OH)D and 1,25(OH)2D levels.

Comorbid diseases. Various diseases are substantially correlated with elevated septicemia death rates as listed in Table 1. These comorbidities strongly suggest that immunological factors are involved. Because risk of many diseases increases with age, such factors could include factors that decline with increasing age.[41,42] However, this report focuses on how these comorbidities could be related to vitamin D status.

Cancer. The death rate from septicemia for those with cancer is more than twice that for control subjects.[10] Low 25(OH)D level has been found for about 15 types of cancer,[40,43-49] and survival rates are higher for those with higher 25(OH)D levels[50] or those whose cancer is discovered in summer or fall, when 25(OH)D levels are higher.[51] For two of the three vitamin D-sensitive cancers (Table 3), males have a lower risk of septicemia than that for females; for lung cancer, smoking is a more important risk than vitamin D is a risk-reduction factor.

A study in Boston found that 48% of breast cancer patients seen in summer had 25(OH)D levels less than 20 ng/mL, compared with 12% of the control subjects.[52] Two recent papers reviewed the mechanisms whereby vitamin D reduces the risk of cancer.[53,54] Dose-response relations have been estimated for cancer rates for males in the United States (1500 IU of vitamin D per day, 29% reduction)[44] and colorectal cancer (1500 IU/day, 50% reduction in incidence).[46] A recent study of breast cancer in Germany found an odds ratio of 0.31 (95% confidence interval (CI), 0.24–0.42), for those with serum 25(OH)D >30 ng/mL compared to those with serum 25(OH) D <12 ng/mL.[48] Cancer patients who develop septicemia are likely to have been staying indoors and have lower 25(OH)D levels.

Respiratory diseases from viral infections. The annual solar UVB cycle seems in part to explain the seasonal variation in influenza rates.[20] The action of solar UVB appears to be mediated through vitamin D, probably through production of the antimicrobial peptide LL-37.[55]

Experimental support for this hypothesis was quickly supplied through a post-hoc analysis of incidence rates of influenza and common colds in a prospective, double-blind trial of supplemental vitamin D for prevention of bone disease in 208 African American postmenopausal women living in or near Mineola, New York. Self-reported cases of colds and influenza were 40% as high for those taking 800 IU of vitamin D per day during two years and 10% as high for those taking 2000 IU of vitamin D per day for one year, compared with those taking the placebo over a three year period.[21]

HIV. Although those with HIV or AIDS have compromised immune systems, they are also particularly prone to low 1,25(OH)2D levels. A study of 54 HIV-infected patients found that 29 (54%) of the patients had serum levels of 1,25-(OH)2D below the lower reference limit, and 18 of these had undetectable levels.[56] The authors pointed out that markedly depressed serum 1,25(OH)2D levels are also present in certain other disorders characterized by immunological hyperactivity.

Cirrhosis. Cirrhosis of the liver is associated with a statistically significantly increased risk of septicemia.[10] In cirrhosis, there is widespread disruption of normal liver structure. 25(OH)D levels are low in patients with liver disease[57] because the liver is where vitamin D is transformed to 25(OH)D through the addition of a hydroxyl radical.

Congestive heart failure (CHF). Low serum 25(OH)D and 1,25-dihydroxyvitamin D [1,25(OH2)D] are risk factors for CHF. One study in Germany found low 1,25(OH2)D associated with poorer outcome in end-stage CHF.[58] Another study in Germany found a hazard ratios for death due to CHF of 2.84 (95% CI, 1.20–6.74) when comparing patients with severe vitamin D deficiency [25(OH)D <10 ng/mL)] with persons in the optimal range [25(OH) D ≥30 ng/mL].[59] In a study of African-Americans, serum 25(OH) D ≤30 ng/mL was found in 96% and 90% with protracted or short-term decompensated HF, where it was of moderate to marked severity (<20 ng/mL) in 83% and 76%, respectively.[60]

Peripheral vascular disease. Peripheral arterial disease is also linked to low serum 25(OH)D.[61]

Chronic obstructive pulmonary disease (COPD). Those in the NHANES III study with lower serum 25(OH)D levels were found to have poorer pulmonary function.[62]

Confounding factors. There is the possibility that factors other than serum 25(OH)D and 1,25(OH)2D could affect the risk of incidence of and mortality from septicemia. Such factors could include seasonal changes in temperature and air quality, access to medical care, and prevalence of diseases that reduce immune system response such as HIV. While the epidemiological studies that form the basis for this study did not account for such factors, it is not thought that they significantly affected the associations reported. Seasonal temperature effects would generally have a latitudinal effect, which does not agree with the observed geographical variation.[9] Also, the higher incidence of and lower survival with cancer by African-Americans compared to white Americans has been found dependent on serum 25(OH)D levels[33,34,63] in addition to any other reasons for disparities.

Vitamin D benefits and risks. Vitamin D has many health benefits[64,65] and few adverse effects.[66] Those with higher 25(OH)D levels upon admission to hospitals have shorter lengths of stay.[67] A meta-analysis of vitamin D supplements on mortality rates found that relative risk for mortality from any cause was 093 (95% CI, 0.87–99) for a mean dose of 528 IU of vitamin D per day over a mean period of 5.7 years for people older than 47 years at enrollment.[68] A more recent study in the United States found a 26% increased rate of all-cause mortality (mortality rate ratio, 1.26; 95% CI, 1.08–1.46) for serum 25(OH)D <17.8 ng/mL compared to >32.1 ng/mL.[69]

The emerging scientific consensus is that recommended vitamin D oral intake levels in the absence of solar UVB should be above 30 ng/mL,[44,46,47] with above 40 ng/mL providing more benefits.[49] In the absence of solar UVB, this would take a daily oral intake of about 4000 IU/day. This is similar to what is estimated as the daily body utilization of vitamin D.[70] However, the mean serum 25(OH)D level in the United States is near 30 ng/mL,[33] so an extra 1000–2000 IU/day should bring most people to 30–40 ng/mL or higher, as found in one supplementation study.[49]

Vitamin D toxicity appears when more than 20,000 IU/day is consumed over a prolonged period.[66] Hypercalcaemia can develop in those with granulomatous diseases such as sarcoidosis[71] and Crohn's disease[72] due to extra-renal production of 1,25(OH)2D and calcium metabolism dysregulation.[73] Also, those with lymphoma should be careful due to the same reason.[74] In addition, higher levels of serum 25(OH)D and 1,25(OH)2D may increase the risk of adverse effects from infections such as *Toxoplasma gondii*[75] and intracellular protozoan *Leishmania major*.[76]

As discussed by Mookherjee et al.[17] whereas LL-37 is a potent antiendotoxin, it has limitations as an antisepsis therapeutic agent because of known adverse effects such as cytotoxicity and the induction of mast cell degranulation and release of histamine from mast cells. Thus, until cathelicidin analogs are developed, vitamin D from oral intake or photoproduction will remain the most important source of LL-37. This situation is similar to that for cancer, where the form of vitamin D effective in fighting cancer is 1,25(OH)2D.

However, high doses of 1,25(OH)2D can lead to calcium metabolism dysregulation, so 1,25(OH)2D analogs are being developed.[77] Meanwhile, those with higher natural vitamin D levels have reduced risk of cancer[43,44,46-49] and increased chance for survival.[50,51]

Alternative explanations for associations. Although vitamin D appears to explain many of the epidemiological features of septicemia, other factors surely contribute. As one ages, the immune system ages due to other factors than low 25(OH)D levels. Cold temperature can also increase the incidence of respiratory infections and septicemia,[78,79] which could explain some of the seasonality of infectious disease. On the other hand, cancer incidence rates are generally independent of season, although survival rates can depend on season, as discussed earlier.[50,51]

Hypothesis testing. This report presents a hypothesis based on an analysis of characteristics of septicemia with respect to characteristics of vitamin D. One test of the hypothesis would be to measure serum 25(OH)D in those diagnosed both with and without septicemia. Another would be to treat vitamin D deficiency in patients preparing to enter a hospital for an operation and compare their septicemia rates with those of control subjects. A third way would be to use pharmacological doses of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) for those diagnosed with septicemia and compare outcomes with those of control subjects undergoing standard treatment.

Data and Methods

This analysis is based on several recent reports on the epidemiology of septicemia in the United States and on the relation of solar UVB and vitamin D to the diseases or conditions associated with various features of the epidemiology of septicemia. The U.S. National Institute of Medicine's and the National Institutes of Health's Pubmed system (www.pubmed.gov) was searched for relevant papers. The cited reports selected are representative, not exhaustive.

Summary and Conclusion

The epidemiological features of septicemia, including seasonality, racial disparity, increased rate with age, and several clinically significant comorbidities, are similar to the epidemiology of vitamin D deficiency. The hypothesis that higher levels of 25(OH)D reduces the incidence and improve the prognosis of septicemia should be easy to test.

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