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Research Paper

Vitamin D deficiency in pediatric critical illness☆

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ABSTRACT

Introduction: The potential role for vitamin D in infection has been well described in adults. The objective of our study was to determine the prevalence of vitamin D insufficiency and to evaluate the relationship between vitamin D status and markers of innate immunity and infection in critically ill children.
Hypothesis: Vitamin D deficiency is highly prevalent in children with critical illness and correlates with the severity of illness and dysfunction in innate immunity.
Methods: We performed a prospective clinical observational study with both case and control groups in the pediatric intensive care unit (PICU). Vitamin D status was defined as vitamin D sufficient (25-hydroxyvitamin D (25(OH)D $\geq$ 20 ng/mL), vitamin D insufficient (25(OH)D 10–20 ng/mL), and vitamin D deficient (25(OH)D <10 ng/mL). Vitamin D status, severity of illness scores, and cathelicidin, and other clinical data were collected.
Results: Sixty-one PICU patients and 46 control patients were enrolled. Over 60% of the PICU cases were found to be vitamin D insufficient while less than 1/3 of the controls were insufficient ($p < 0.0001$). No significant correlation was seen between plasma 25(OH)D and any severity of illness scores. Cases with asthma had a significantly lower median level 25(OH)D (16.9 ng/mL) than cases without asthma (18.7 ng/mL). Over 50% of patients hospitalized during the fall and winter were considered vitamin D deficient or insufficient whereas in the sunnier seasons (spring and summer) the prevalence of vitamin D deficiency/insufficiency decreased to about 30% ($p = 0.003$).
Conclusions: Vitamin D deficiency is common in the pediatric critical care population. Significant seasonal differences were noted even in the critically ill. The role of vitamin D in certain diseases like asthma in critically ill children merit further study.

Introduction

Vitamin D plays an important role, not only for bone health, but also in the immune system [1]. Both *in vitro* and clinical studies have demonstrated that vitamin D is important for the innate and adaptive immune response [2–6]. In adults, vitamin D insufficiency is common in patients who are hospitalized or have a severe infectious process and is associated with increased mortality [7–11]. Vitamin D enhances the anti-microbial response of monocytes of adults suggesting a protective role of vitamin D in infection. Particularly, anti-microbial peptides such as human cathelicidin antimicrobial peptide (hCAP18) and β-defensin are up-regulated in response to vitamin D therapy [12]. In adult patients with sepsis, plasma LL-37, the active cathelicidin protein cleaved from hCAP18, is positively correlated to vitamin D status [7,13].

Similar links between vitamin D status and the immune system have been shown in pediatric populations. For example, children with cystic fibrosis, who suffer from chronic respiratory infections, have a high prevalence of vitamin D insufficiency that is associated with increased risk of pulmonary exacerbations [14,15]. Two

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randomized controlled trials conducted in children demonstrated that vitamin D supplementation reduced the risk of influenza and recurrent pneumonia [15,16]. Given the potential role of vitamin D in infection, achieving optimal vitamin D status may be important in children with infection.

Many children are admitted to a pediatric intensive care unit (PICU) with serious infections or with a high chance of acquiring nosocomial infection once admitted [17]. Severe blood stream infections alone account for significant morbidity and mortality. Of the 636,842 patients children admitted to 43 Children's Hospital Association (CHA) hospitals between 2004 and 2012 the prevalence of severe sepsis was 7.7% (49,153) with an associated mortality rate of 14.4% [18]. Adequate nutritional support has been a mainstay in pediatric intensive care unit (PICU) management with research showing improved outcomes and fewer ICU patient days [19]. However, there have been few studies to investigate the prevalence of vitamin D deficiency in critically ill children. Madden et al. found that 40% of children admitted to the pediatric intensive care unit had vitamin D deficiency [20]. A more recent study found that a subset of children with pneumonia or bronchiolitis requiring PICU care had a higher prevalence of vitamin D deficiency compared to children without respiratory symptoms [21]. There may, therefore, be an important role for vitamin D in the prevention and/or treatment of infections in critically ill children.

The purpose of this study was to examine vitamin D status in children admitted to our pediatric intensive care unit. We also evaluated the relationship between vitamin D status and markers of innate immunity and infection. Our hypothesis was that vitamin D deficiency was highly prevalent in children with critical illness and correlated with the severity of illness and dysfunction in innate immunity.

Methods

We performed a prospective clinical observational study with both case and control groups in the pediatric intensive care unit (PICU) at Children's Healthcare of Atlanta at Egleston between January 2010 and March 2012. This study was approved by the Institutional Review Boards of Emory University and Children's Healthcare of Atlanta. Informed consent was obtained from each patient's guardian.

PICU and control patient definition

Patients were recruited from among children 0–18 years of age with a weight of 6 kg or more admitted to the PICU within the last 48 h. PICU patients were excluded if they had the following issues: chronic renal disease, gastrointestinal malabsorption conditions, post-operative state following an elective surgery, or trauma as related to possible abuse. Control patients were recruited among children in the magnetic resonance imaging (MRI) suite. Only those patients undergoing MRI for the following were considered: new onset headache without other neurological complaint, new onset seizure without other neurological complaint and not on antiepileptic drugs, patients with history of cardiac surgery with four chamber cardiac anatomy (i.e. VSD, coarctation of the aorta), and isolated limb complaints without concern for neoplastic or rheumatologic condition. Additional inclusion criteria for control patients were: requirement of intravenous (IV) access for sedation or contrast, 0–18 years of age, and weight greater than or equal to 6 kg. Controls were excluded if they were on medications, developmentally delayed, had a severe or chronic illness-defined as any condition causing significant physical or mental disability (including chronic renal disease), abnormal cardiac anatomy (i.e. single ventricle physiology), or gastrointestinal malabsorption.

Protocol

Blood draws from critically ill children were performed on the first day of enrollment and the fifth day after enrollment to allow for trending over the time period. Control children only had one blood draw at the time of enrollment. Patient demographic information was obtained from their medical record and included: age, gender, ethnic group, admission diagnosis, and history of chronic disease. Clinical information collected included length of hospital stay, exposure to advance life support systems, duration of mechanical ventilation, length of PICU stay (LOS), amount/duration of medication used, development of rebound hypotension or secondary infections, and duration of shock.

Determination of severity of illness

Septic shock was defined and classified according to the American College of Critical Care Medicine (ACCM) definitions of cardiovascular support [22]. Severity of illness scores calculated were Pediatric Risk of Mortality score III (PRISM III) [23], calculated risk of mortality, and pediatric logistic organ dysfunction (PELOD) score [24].

Determination of vitamin D deficiency

Vitamin D status was assessed by measurement of plasma 25-hydroxyvitamin D (25(OH)D). Vitamin D status was defined as vitamin D sufficient (25(OH)D $\geq$20 ng/mL), vitamin D insufficient (25(OH)D 10–20 ng/mL), and vitamin D deficient (25(OH)D $<$10 ng/mL). These categories are consistent with definitions used to define vitamin D status reporting vitamin D status in children participating in the National Health and Nutrition Examination Survey (NHANES) [25].

Vitamin D and cathelicidin (LL-37) assays

Blood was collected from case and control patient populations on the day of enrollment in EDTA tubes. After centrifugation for plasma separation, plasma was stored at -80 °C. Samples were batch processed for 25(OH)D concentrations using the Immunodiagnostic Systems iSYS automated ELISA system (Fountain Hills, AZ). This method has a lower limit of detection of 4 ng/mL, and correlates well with the gold-standard, liquid chromatography-tandem mass spectrometry [26]. The laboratory participates in the vitamin D external quality assessment scheme (DEQAS) to ensure accuracy of the measurement of 25(OH)D concentrations, and has a laboratory inter-assay CV of 10.1–13.0% and intra-assay CV of 1.8–4.0% for measurement of 25(OH)D. Cathelicidin (LL-37) concentrations were determined in plasma by ELISA (Hycult Biotech, Uden, Netherlands) as previously reported [27].

Power calculation

Prior to initiating this study, power calculations were performed using current available data regarding prevalence of vitamin D deficiency [28] and data from several clinical studies that examined the prevalence of vitamin D deficiency in various populations of hospitalized patients, both adult and pediatric [7,21,29]. In order to detect a difference of 20% in vitamin D levels between cases and controls, we calculated a sample size of 50 patients per group was required to achieve a power of 0.80 using a 2 sided alpha of 0.05. A convenience sample of 120 patients, 60 patients each for cases and controls was selected to account for any errors in sample processing or withdrawal from study participation.

Table 1
Demographics of cases and controls

Variable	Level	Controls ($N = 46$)	PICU ($N = 61$)	p-Value
Age, mean ± SD		7.6 ± 4.5	11.5 ± 5.1	<0.001
Gender[a], N (%)	Male	16 (45.7%)	34 (56.7%)	0.39
	Female	19 (54.3%)	26 (43.3%)	
Race, N (%)	African American	20 (43.5%)	39 (63.9%)	0.01[b]
	White	22 (47.8%)	16 (26.2%)	
	Native Hawaiian/Other Pacific Islander	0 (0.0%)	1 (1.6%)	
	Asian	0 (0.0%)	2 (3.3%)	
	Multiracial	1 (2.2%)	3 (4.9%)	
	Other	3 (6.5%)	0 (0%)	
Weight (lbs), mean ± SD		–	45.2 ± 22.7	–
Mechanical ventilation, N (%)	Yes	–	31 (50.8%)	–
PRISM III score, median (IQR)		–	10 (7–15)	–
Total SOFA, median (IQR)		–	7 (2–10)	–
Total PELOD, median (IQR)		–	20 (7–15)	–
Cathelicidin (LL-37)[a], median (IQR)		57.8 (35.3–125.9)	56.3 (41.3–79.8)	0.66
25-hydroxyvitamin D (ng/mL)				
Mean (SD)		39.6 (21.8)	23.6 (17.0)	<0.0001[b]
Median (IQR)		39.8 (20.1–56.9)	18.5 (12.4–26.8)	<0.0001[b]
Vitamin D status by category	Sufficient (≥20 ng/mL)	35 (76.1%)	24 (39.3%)	<0.001[b,c]
	Insufficient (10–20 ng/mL)	11 (23.9%)	27 (44.3%)	
	Deficient (<10 ng/mL))	0 (0.0%)	10 (16.4%)	

SOFA, Sequential Organ Failure Assessment score; PELOD, Pediatric logistic organ dysfunction; PRISM III, Pediatric Risk of Mortality III.
[a] Indicates missing data. Data are incomplete for some patients.
[b] Statistically significant differences ($p < 0.05$).
[c] p-Value is based on Cochran–Armitage test for trend.

Statistical analysis

All statistical analyses were performed using SAS 9.2 (Cary, NC). Statistical significance was assessed using a significance level of 0.05 unless otherwise noted. Appropriate descriptive statistics (e.g., frequencies and percentages, means and standard deviations, or medians and interquartile ranges) were calculated for cases and controls. Univariate tests for normality were used to determine if a parametric test was appropriate. If normality was rejected, a nonparametric test was used instead. Demographic data for the healthy controls were compared to PICU patients using t-tests or Wilcoxon rank sum tests and Chi-square tests. Similar tests were used to compare plasma 25(OH)D concentrations among subgroups based on comorbidities such as asthma, septic shock, etc. Plasma 25(OH)D levels were categorized to determine if insufficiency was related to severity of illness, diagnosis, race, or season of hospital visit. The Cochran–Armitage test for trend was used to test for an association between two ordinal variables (e.g., group and vitamin D group).

To determine whether plasma 25(OH)D levels were correlated with severity of illness scores and LL37, Spearman's rank correlation and associated 95% confidence intervals were used. The Kruskal–Wallis test was used to determine if severity of illness scores differed across vitamin D subgroups. To control for multiple comparisons, pairwise comparisons between vitamin D subgroups were made using a significance level of $(0.05/4) = 0.0125$.

Results

Subject demographics

Sixty-one PICU patients and 46 control patients were enrolled over a 17-month period. A comparison of demographic characteristics and lab values between cases and controls can be found in Table 1. PICU patients were older than controls (11.5 years of age vs. 7.6 years of age; $p < 0.001$). The distribution of race was not the same in the two groups ($p = 0.011$); PICU had a higher proportion of African Americans while the controls had a much higher proportion of Caucasians (63.9% vs. 43.5%, $p = 0.035$). There were no gender differences between the groups ($p = 0.40$). Table 2 contains the comparison of plasma 25(OH)D levels between cases and controls separately for Caucasians and African Americans. There was no difference in plasma 25(OH)D concentrations between cases and controls for African Americans; however in the Caucasian subgroup, cases had a significantly lower median plasma 25(OH)D level than controls ($p = 0.002$). After adjusting for race, plasma 25(OH)D concentrations of the cases were significantly lower than in the controls (median; 23.6 vs. 39.8 ng/mL; $p < 0.001$). When plasma 25(OH)D levels were categorized into sufficient, insufficient, and deficient, a significant association ($p < 0.0001$) was found between group (PICU, control) and vitamin D status; over 60% of the PICU cases were found to be vitamin D insufficient while less than 1/3 of control were insufficient.

Relationship between vitamin D status and markers of critical illness

No significant correlations were found between plasma 25(OH)D and any of the lab values, including the anti-microbial peptide, LL-37, or between 25(OH)D and any of the severity of illness scores (Table 3). None of the vitamin D status subgroups were significantly different from one another for any of the severity of illness scores (Table 4); although, SOFA showed a trend ($p = 0.12$). Table 5 provides the median and range of plasma 25(OH)D concentration for each risk subgroup. Caucasians had the highest median plasma 25(OH)D levels (20.6 ng/mL) followed by African Americans (17.1 ng/mL) then "other" (16.2 ng/mL). Cases with asthma had a

Table 2
Comparison of plasma 25-hydroxyvitamin D (ng/mL) between cases and controls within race groups

Race group	Case/Control	N	Median (IQR)	p-Value
Caucasians	Control	22	48.0 (22.7–68.2)	0.002
	Case	16	20.6 (19.0–25.7)	
African Americans	Control	20	20.3 (15.2–43.6)	0.12
	Case	39	17.1 (10.1–29.7)	

Table 3
Correlations and associated 95% confidence interval of plasma 25-hydroxyvitamin D concentrations with lab value and severity of illness scores

Outcome	Category	Variable	Groups	*N*	Spearman correlation	95% CI LCL	95% CI UCL	*p*-Value
Vitamin D (25(OH)D)	Lab values	LL37	Cases and Controls	92	0.154	−0.054	0.347	0.14
			Cases	56	0.115	−0.153	0.366	0.40
			Controls	36	0.195	−0.146	0.490	0.26
			Asthma Only	13	−0.159	−0.649	0.435	0.61
			Sepsis only	13	0.302	−0.310	0.725	0.32
	Severity of illness	Total PELOD	Cases	61	0.089	−0.166	0.333	0.49
		PRISM III score	Cases	61	0.044	−0.210	0.293	0.73
		Total SOFA	Cases	61	0.219	−0.307	0.445	0.09
		Total PELOD	Asthma only	13	−0.172	−0.656	0.424	0.58
		PRISM III score	Asthma only	13	0.088	−0.490	0.607	0.78
		Total SOFA	Asthma only	13	−0.208	−0.676	0.395	0.50
		Total PELOD	Sepsis only	15	−0.106	−0.584	0.432	0.71
		PRISM III score	Sepsis only	15	−0.088	−0.572	0.447	0.76
		Total SOFA	Sepsis only	15	0.014	−0.522	0.502	0.96
LL37	Severity of illness	Total PELOD	Cases	56	−0.101	−0.354	0.167	0.46
		PRISM III score	Cases	56	−0.111	−0.362	0.158	0.42
		Total SOFA	Cases	56	−0.088	−0.342	0.180	0.52
		Total PELOD	Asthma only	13	0.235	−0.372	0.691	0.34
		PRISM III score	Asthma only	13	0.384	−0.227	0.765	0.20
		Total SOFA	Asthma only	13	0.038	−0.525	0.576	0.90
		Total PELOD	Sepsis only	13	−0.201	−0.672	0.401	0.52
		PRISM III score	Sepsis only	13	−0.061	−0.590	0.509	0.85
		Total SOFA	Sepsis only	13	−0.257	−0.702	0.352	0.41

SOFA, Sequential Organ Failure Assessment score; PELOD, Pediatric logistic organ dysfunction; PRISM III, Pediatric Risk of Mortality III.

significantly lower median level plasma 25(OH)D (16.9 ng/mL) than cases without asthma (18.7 ng/mL). Table 6 contains the comparison of race and season between vitamin D subgroups using the combined sample of cases and controls. Over fifty-percent of patients hospitalized during the fall and winter were considered vitamin D deficient or insufficient whereas in the sunnier seasons (spring and summer) almost 70% of patients were considered vitamin D sufficient ($p = 0.003$).

Discussion

The evolving understanding of vitamin D as an immunomodulator holds great attraction as both a potential target for treatment and prevention of disease states. In this study, pediatric critical care patients had a greater burden of vitamin D deficiency than healthy children, with an increased risk among those with asthma. Plasma 25(OH)D levels, however, did not have any direct correlation to illness severity scoring. Significant seasonal variation as well as ethnic differences in vitamin D was noted in vitamin D status in these critically ill children.

The association between vitamin D and infections has been suggested for over a century. Simple observations regarding the high burden of respiratory infections in children with rickets were made by medical practitioners of the late 1800s [29]. Additionally, the placement of tuberculosis patients in sunnier climates to improve exposure to UV light was noted to improve the clinical state of these patients. These findings have been revisited in modern research. Several studies in children have found significant associations in between vitamin D deficient states and respiratory illness. In a study of pediatric hospital admissions in Ethiopia, children with clinical evidence of rickets were 13-fold more likely to present with pneumonia than those without rickets [29]. In a Canadian study, children admitted to intensive care for lower respiratory infections had higher rates of vitamin D deficiency [21]. In an adult study, patients with tuberculosis showed faster response to multi-drug therapy if they were given vitamin D supplementation [6].

Vitamin D may play an important role in the induction of the anti-microbial response to pathogens in humans. Macrophages from vitamin D insufficient persons are not able to optimally up-regulate production of the active cathelicidin protein, LL-37 [32]. When 25(OH)D is added to vitamin D deficient sera, the production of LL-37 in response to an infectious signal is restored [5]. In a study of adults admitted to the ICU, Jeng et al., demonstrated that vitamin D status positively correlated with plasma LL-37 concentrations [7]. We, however, did not find a relationship between vitamin D status

Table 4
Median and ranges for each severity of illness score by vitamin D subgroup

Severity score median (IQR)	Vitamin D sufficient (≥20 ng/mL) (*N* = 24)	Vitamin D insufficient (10–20 ng/mL) (*N* = 27)	Vitamin D deficient (<10 ng/mL) (*N* = 10)	*p*-Value[a]
Total PELOD	21.0 (11.0–30.5)	20.0 (1.0–32.0)	11.5 (1.0–30.0)	0.59
PRISM III score	10.5 (7.5–15.5)	10.0 (6.0–15.0)	9.5 (7.0–15.0)	0.89
Total SOFA	8.0 (5.0–10.0)	4.0 (1.0–10.0)	4.5 (1.0–8.0)	0.12

SOFA, Sequential Organ Failure Assessment score; PELOD, Pediatric logistic organ dysfunction; PRISM III, Pediatric Risk of Mortality III.
[a] *p*-Value is from the Kruskal–Wallis test.

Table 5
Comparison of plasma 25-hydroxyvitamin D (ng/mL) levels among risk subgroups in cases only

Subgroup	Level	*N*	Median (IQR)	*p*-Value
Race	White	16	20.6 (19.0–25.7)	0.01[a,b]
	AA	39	17.1 (10.1–29.7)	
	Other	6	16.2 (13.8–19.2)	
Season	Spring	12	25.7 (15.2–36.5)	0.09[b]
	Summer	17	20.8 (17.2–33.4)	
	Fall	8	19.0 (17.7–20.6)	
	Winter	24	16.4 (9.3–19.3)	
Asthma[c]	No	37	18.7 (14.0–24.6)	0.048[a]
	Yes	13	16.9 (9.6–17.7)	
Shock	No	26	17.5 (11.0–22.0)	0.63
	Yes	29	17.3 (12.4–33.4)	
Sepsis	No	46	18.6 (12.1–26.8)	0.76
	Yes	15	18.4 (13.8–29.7)	

[a] Significant at 0.05 level of statistical significance.
[b] *p*-Value obtained from median one-way analysis.
[c] Indicates missing data.

Table 6
Comparison of vitamin D subgroups with race and season for combined cases and controls

Subgroup	Level	Vitamin D sufficient ($N = 59$)	Vitamin D insufficient ($N = 38$)	Vitamin D deficient ($N = 10$)	p-Value
Race	White	29 (76.3%)	9 (23.7%)	0 (0.0%)	0.01[b]
	AA	25 (42.4%)	25 (42.4%)	9 (15.3%)	
	Other	5 (8.5%)	4 (10.5%)	1 (10.0%)	
Season	Spring	16 (69.6%)	6 (26.1%)	1 (4.3%)	0.003[b,d]
	Summer	18 (69.2%)	8 (30.8%)	0 (0.0%)	
	Fall	5 (45.5%)	5 (45.5%)	1 (9.1%)	
	Winter	20 (40.8%)	19 (38.8%)	10 (20.4%)	
Asthma[a,c]	No	15 (40.5%)	18 (48.7%)	4 (10.8%)	0.02[b,d]
	Yes	1 (7.7%)	8 (61.5%)	4 (30.8%)	
Shock and/or sepsis[c]	No	11 (35.5%)	16 (51.6%)	4 (12.9%)	0.97[d]
	Yes	13 (43.3%)	11 (36.7%)	6 (20.0%)	

[a] Indicates missing data.
[b] Significant at 0.05 level of statistical significance.
[c] Only for cases.
[d] p-Value is based on Cochran–Armitage test for trend.

and cathelicidin in our critically-ill pediatric cohort. These findings likely reflect the heterogeneity of disease of the overall study population. In a sub-set of patients with sepsis ($n = 15$) there was no statistically significant relationship between plasma 25(OH)D and LL-37. It is also possible that blood levels of LL-37 do not accurately reflect the monocyte responses to infection. Adams et al. demonstrated no change in circulating cathelicidin (hCAP18) concentrations in adults receiving oral vitamin D supplementation. However, the ex vivo harvested and cultured monocytes had enhanced hCAP18 expression in response to 25-hydroxyvitamin D. This suggests that enhanced cathelicidin action might only be detected locally by cells of the immune system. Alternative biomarkers of innate immunity and markers monocyte action and function should be explored to determine the impact of vitamin D on enhancing innate immunity [32].

A prominent finding was the difference in racial background between cases and controls. Sixty-four percent of case patients self-identified as African-American. This racial distribution was similar to our general hospital and PICU admissions in the same time period. The greater representation of African-American cases may influence differences in vitamin D status between cases and controls given the well-established fact of greater burden of hypovitaminosis D in the African-American population at large [33,34]. However, our findings of lower plasma 25(OH)D concentrations in critically ill pediatric patients remained after adjusting for race. Recently, it has been suggested that differences in vitamin D status among black and white Americans may be partially influenced by differences in concentration of the vitamin D binding protein and differences in the frequency of vitamin D binding protein polymorphisms [35]. Although African Americans have lower total 25(OH)D concentrations compared to Whites, bioavailable 25(OH)D concentrations may not differ. Future similar studies in critically ill pediatric patients should measure vitamin D binding protein and assess bioavailable 25(OH)D.

Significantly lower plasma 25(OH)D levels in critically ill asthmatic children has been clearly identified as a subset of patients worthy of further study. It is well known that there is a significant innate immunologic role in asthma [30,31]. While the mechanisms for potential benefit to achieve higher plasma 25(OH)D levels is unclear from this data, further study is certainly warranted in these children.

One limitation of our study could be our control children. Children undergoing sedated MRI are more than likely to have health complaints indicating the need for scans. The control subjects were carefully screened for any chronic conditions or suggestion of severe systemic disease before being enrolled. Additional limitations are PICU patient population is heterogenous in terms of diagnosis and severity of disease. Where possible we explored high risk subsets with similar disease processes. As demonstrated, asthma patients admitted to the ICU had significantly poorer vitamin D status then other patients. This is in line other publications that demonstrate higher rates of vitamin D deficiency in patients affected by asthma [35,36]. Certainly several arguments exist as to whether this is an issue of cosegregation of findings as related to lifestyle (i.e. asthmatic patients are less active and have decreased sunlight exposure) or if it may be a contributing factor to the severity of the illness.

In conclusion, we found a very high prevalence of profound vitamin D deficiency in the pediatric critical care population. In an era of increasing bacterial antibiotic resistance and limited development of new antibiotics, augmentation of immune function by adjunctive therapies holds great promise for our patients. With regard to chronic inflammatory conditions such as asthma, immunomodulation beyond current immunosuppressive approaches would be a great addition. Vitamin D potentially could be developed as a safe and effective additive therapy in critically ill pediatric patients. Multicenter trials should be performed to examine the safety, feasibility, and effectiveness of vitamin D supplementation/repletion in this at-risk population.

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