The Association of Vitamin D Status With Pediatric Critical Illness

AUTHORS: J. Dayre McNally, MD, PhD,a,b Kusum Menon, MD, MSc,a,b Pranesh Chakraborty, MD,b,c Lawrence Fisher, BSc, ART,b,c Kathryn A. Williams, MSc,b Osama Y. Al-Dirbashi, PhD,b,c Dermot R. Doherty, MD, MB, BCH, BAO,a,b,d,e on behalf of the Canadian Critical Care Trials Group

aDivision of Critical Care, Department of Pediatrics, and bDepartment of Anesthesia, Faculty of Medicine, University of Ottawa, Children’s Hospital of Eastern Ontario, Canada; cResearch Institute and dOntario Newborn Screening Laboratory, Children’s Hospital of Eastern Ontario, Canada; and eUniversity College, Dublin, Ireland

KEY WORDS
vitamin D, pediatrics, risk factors, length of stay, critically ill children

ABBRévIATIONS
25(OH)D—25-hydroxyvitamin D
AIP—Adrenal Insufficiency in Pediatric Critical Illness Study
ALRI—acute lower respiratory infection
CI—confidence interval
IQR—interquartile range
OR—odds ratio
PRISMA—Pediatric Risk of Mortality III

Drs Al-Dirbashi, Chakraborty, and Mr Fisher: acquisition of data, critical revision of the manuscript for important intellectual content, final approval of version to be published; Dr Doherty: study conception and design, analysis and interpretation of data, drafting the article, final approval of version to be published; Dr McNally: study conception and design, analysis and interpretation of data, drafting the article, final approval of version to be published; Dr Menon: study conception and design, analysis, acquisition of data, analysis and interpretation of data, drafting the article, final approval of version to be published; Dr McNally: study conception and design, analysis and interpretation of data, drafting the article, final approval of version to be published; and Ms Williams: analysis and interpretation of data, drafting the article, final approval of version to be published.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-3328
doi:10.1542/peds.2011-3328

Accepted for publication May 30, 2012
Address correspondence to James D. McNally, MD, PhD, Children’s Hospital of Eastern Ontario, 401 Smyth Rd, Ottawa, Ontario K1S 3H2, Canada. E-mail: dmcnally@cheo.on.ca

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This study was supported by the Canadian Institutes of Health Research and Children’s Hospital of Eastern Ontario Research Institute. Research fellowship funding to JDM was provided by the Children’s Hospital of Eastern Ontario Popham Foundation.

COMPANION PAPER: A companion to this article can be found on page 421, and 557 online at www.pediatrics.org/cgi/doi/10.1542/peds.2011-3328.

abstract

OBJECTIVES: Vitamin D is a pleiotropic hormone important for the proper functioning of multiple organ systems. Adult critical care studies have suggested vitamin D as a modifiable risk factor. No studies have investigated the prevalence, risk factors, or role in pediatric critical illness.

WHAT’S KNOWN ON THIS SUBJECT: Vitamin D is a pleiotropic hormone important for proper functioning of multiple organs. Adult critical care studies have suggested vitamin D deficiency as a modifiable risk factor. No studies have investigated the prevalence, risk factors, or role in pediatric critical illness.

WHAT THIS STUDY ADDS: This study provides evidence that the majority of critically ill children have vitamin D deficiency at the time of PICU admission, and that lower levels are associated with hypocalcemia, catecholamine administration, significant fluid bolus requirements, and longer PICU admissions.

RESULTS: The prevalence of 25(OH)D <50 nmol/L was 69% (95% confidence interval, 64–74), and 23% (95% confidence interval, 19–28) for 25(OH)D between 50 to 75 nmol/L. Lower levels were associated with hypocalcemia, catecholamine utilization, and significant fluid bolus administration. Vitamin D deficiency was independently associated with a longer PICU length of stay (β+1.92 days, \( P = .03 \)) and increasing severity of illness as determined by the Pediatric Risk of Mortality score with every additional point increasing the likelihood of being vitamin D deficient by 8% (\( P = .005 \)).

CONCLUSIONS: This study provides evidence that vitamin D deficiency is both common among critically ill children and associated with greater severity of critical illness. Further research will determine whether targeted vitamin D supplementation or rapid restoration will improve outcome. Pediatrics 2012;130:429–436
In Canada each year, 10,000 children are admitted to PICUs, resulting in ~40,000 patient days. The identification of previously unrecognized modifiable risk factors could help guide new preventative or therapeutic strategies for pediatric critical illness. Vitamin D supplementation may represent a novel strategy to modulate pediatric critical illness occurrence, intensity, duration, and associated chronic morbidities. Although poor nutritional status is recognized as a risk factor for adverse outcomes in critical illness, there are no published studies investigating the potential role of vitamin D deficiency in pediatric critical illness.

Vitamin D, a nutrient derived from both diet and sunlight, has been increasingly recognized as pivotal to good health. A pleiotropic hormone, vitamin D has been increasingly implicated in the proper functioning of multiple organs, with deficiency states associated with cardiovascular disease, asthma, multiple sclerosis, diabetes, acute lower respiratory infection (ALRI), and cancer. It was recently hypothesized that vitamin D deficiency could also contribute to or prolong critical care pathophysiology. A number of adult-based critical care studies support this idea, reporting high deficiency rates and associations between lower 25-hydroxyvitamin D (25(OH)D) levels, higher illness severity scores, and longer ICU length of stay. Furthermore, a recent adult publication demonstrated lower premorbid 25(OH)D concentration as a predictor of ICU-related mortality.

The objective of this study was to determine the prevalence of vitamin D deficiency among critically ill children by using biological samples secured from a recently completed prospective multicenter trial investigating adrenal insufficiency. Secondary objectives included establishing the risk factors for vitamin D deficiency and exploring relationships with clinically important outcomes. We hypothesized that vitamin D deficiency would be common in critically ill children.

METHODS

This study was a secondary analysis of data and biological samples collected as part of the Adrenal Insufficiency in Pediatric Critical Illness Study (AIP), a prospective cohort study conducted in 7 tertiary-care PICUs (latitude range: 43°N to 53°N) in Canada. Briefly, patients were eligible if they were newborn to 17 years of age, had arterial or central venous catheters, and could be enrolled within 24 hours of admission. AIP excluded premature infants; patients with known or suspected adrenal, pituitary or hypothalamic disease; those who received systemic steroids for >10 days in the previous month or more than 1 dose of systemic steroids within 24 hours of admission (except dexamethasone); those expected to have care withdrawn; those transferred from another ICU; or those whose primary physician refused. From June 2005 to July 2008, 4090 patients were admitted to the participating PICUs. Of these, 1707 (42%) met eligibility criteria, and 434 of 2383 eligible patients (18%) were excluded for steroid criteria. The AIP authors compared eligible patients who could not be consented with the final participants, and no significant difference in the Pediatric Risk of Mortality Score III (PRISM) scores (6 [interquartile range (IQR) 3 to 10] vs 6 [IQR 3 to 9]; P = .81) or age (P = .72) was evident. Research ethics board approval for the vitamin D substudy was obtained from 6 centers, representing 337 of the original 389 study participants. In AIP, blood samples were collected within 24 hours of admission, and again on day 2. Of the potential 337 study participants, day 1 and 2 serum was used for 321 and 5 patients, respectively. Supplemental Fig 2 provides a patient flow diagram.

Total serum 25(OH)D, the metabolic precursor to calcitriol, is considered the best indicator of body stores and vitamin D axis activity. The Ontario Newborn Screening Laboratory calculated total 25(OH)D from samples by using a published liquid chromatography-mass spectrometry procedure measuring both 25(OH)D2 and 25(OH)D3. Vitamin D deficiency and insufficiency were defined as 25(OH)D concentrations <50 nmol/L and between 50 and 75 nmol/L.

Demographic, clinical, and laboratory data were available in a computerized database. Variables used as measures of illness severity, organ dysfunction, and clinical course included PRISM, catecholamine administration, fluid bolus requirements, mechanical ventilation duration, PICU length of stay, and mortality. Both albumin and lowest pH-corrected ionized calcium levels during admission were obtained from the principal investigators center. Hypocalcaemia was defined as an ionized value <1.1 mmol/L. Examples of conditions used to classify participants with preexisting illness included developmental delay, seizure disorder, cerebral palsy, genetic condition, congenital heart disease, chronic obstructive or restrictive lung disease, oncological condition, or diabetes. Hepatic dysfunction was defined by using the pediatric logistic organ dysfunction score (PELOD) criteria, including aspartate aminotransferase >950 and international normalized ratio >1.4. Malnutrition was assessed by using the Gomez approach or weight for age ratio. Classification of noncardiac surgical categories is shown in Supplemental Table 6.

The prevalence of vitamin D deficiency and insufficiency were calculated with 95% confidence intervals (CI). Descriptive statistics were presented with results for continuous variables provided as either means with standard deviations or medians with IQRs and...
percentages with 95% CI for categorical variables. Associations between vita-
mion D, patient characteristics and out-
come variables were sought by using \( \chi^2 \)
and Fisher’s tests for categorical vari-
ables, and \( t \) tests, Wilcoxon rank sum, Mann-Whitney, or Kruskal-Wallis tests
for continuous variables, where appro-
riate. Multivariate logistic regression
was used to investigate the relationship
between vitamin D deficiency and
patient characteristics. To determine
whether vitamin D was independently
associated with PICU length of stay,
characteristics with a \( P \) value <.25 in
univariate analysis were considered
through multivariate linear regression.
A \( P \) value <.05 was considered statisti-
cally significance. SAS software (ver-
sion 9.2, SAS Institute, Cary, NC) was
used for the analysis.

RESULTS

Demographics

Three hundred eighty-nine critically ill
children were enrolled in the AIP study.
For the substudy, 25(OH)D measure-
ments were performed on 326 study
participants because permission was
declined from 1 of the original centers
(\( n = 52 \)), and biological sample was
unavailable for 11 participants. Baseline
characteristics of the participants
are presented in Table 1. The overall
cohort had a median age of 3.7 years
(IQR: 0.6–13), 51% were boys, and me-
dian admission PRISM score was 6
(IQR: 3–10). Two hundred and thirty-five
patients (72%) were mechanically
ventilated, eighty-eight (27%) received
catecholamines, and the median PICU
admission length was 4 days (IQR 3–7).
A comparison of patient character-
istics between vitamin D substudy
participants and the 63 excluded AIP
participants did not demonstrate sta-
tistically significant differences in age,
gender, weight, weight for age ratio,
season, or PRISM score (Supplemental
Table 5). Excluded participants were
more likely to have a preexisting illness
and be admitted after congenital heart
disease surgery.

Risk Factors

Mean total 25(OH)D (\( D_3 + D_2 \)) was 43.2
nmol/L (SD 19.4). Mean 25(OH)D\(_2\) was
3.2 nmol/L (SD 1.6), and the mean 25
(OH)\(_3\) was 40.2 (SD 19.5). Comparison
of 25(OH)D levels for the subjects (\( n =
174 \)) with available day 1 and day 2
serum did not identify clinical or sta-
tistical differences (42.3 \( \pm \) 19.6 vs
44.1 \( \pm \) 19.6, \( P = .10 \)) in 25(OH)D concen-
trations over time. The prevalence of vita-
mion D deficiency (25(OH)D\(_2\) plus 25
(OH)\(_3\) <50 nmol/L) was 69% (95% CI:
64–74); with an additional 23% (95% CI:
19–28) having a concentration between
50 and 75 nmol/L. No baseline or ad-
mission patient characteristic was as-
associated with vitamin D deficiency in
bivariate analysis (\( P < .05 \), Table 2).
Additional evaluation using a multi-
ivariate logistic model only identified
weight ratio, trauma diagnosis, and
PRISM score as statistically associated
with vitamin D deficiency (Supplemental
Table 7). Each additional PRISM unit
increased the odds of being vitamin D
deficient by 8% (odds ratio [OR] 1.08,
95% CI: 1.02–1.14; \( P = .005 \)). Trauma di-
agnosis decreased odds of vitamin D
deficiency (OR 0.37, 95% CI: 0.14–0.93;
\( P = .034 \)), and higher weight for age
ratios (OR 1.14, 95% CI: 1.05–1.28; \( P = .013 \)) increased odds of vitamin D de-
ciency. Established risk factors (age
and season) and hepatic dysfunction
were not independently associated with
vitamin D deficiency in the multivariate
logistic model.

Illness Severity

Statistically significant differences in 25
(OH)D levels were observed between
groups with and without specific organ
dysfunction and known biochemical
markers of illness severity (Fig 1). First,
lower mean 25(OH)D levels were ob-
served in the PICU subgroups requiring
catecholamine infusion (45 \( \pm \) 19 nmol/L
vs 38.5 \( \pm \) 16 nmol/L, \( P = .006 \)) and >40
mL/kg fluid bolus on the day of ad-
mission (44.7 \( \pm \) 19.6 nmol/L vs 34.5
\( \pm \) 18.5 nmol/L, \( P = .001 \)). Mechanically
ventilated subjects had lower 25(OH)D
levels compared with the group not
requiring intubation (47.2 \( \pm \) 19.9 nmol/L
vs 41.7 \( \pm \) 19.1 nmol/L, \( P = .02 \)). Sub-
study subjects with at least 1 hypocal-
cemic episode had significantly lower
25(OH)D levels compared with those
with normal or minimally reduced
calcium levels (51.0 \( \pm \) 20.6 nmol/L
vs 36.6 \( \pm \) 15.9 nmol/L, \( P = .001 \)). Of note,
no significant relationship between 25
(OH)D levels and serum albumin could
be demonstrated (Spearman correla-
tion coefficient –0.08, \( P = .48 \)). A mod-
erate correlation between albumin and
preexisting illness was evident (0.57,
\( P < .001 \)).

Biochemical abnormalities and clini-
cally important outcome measures
were compared for study subjects with
and without vitamin D deficiency (Table 3).
A higher percentage meeting criteria
for significant hypocalcemia (78% vs
41%, \( P = .001 \)) was observed for vita-
mion D deficient subjects. Lower pH
Corrected ionized calcium levels (1.04 vs 1.09 nmol/L) were calculated for the vitamin D deficient group, with the result barely achieving statistical significance (P = .05). Vitamin D deficient participants were more likely to receive catecholamine infusion (30% vs 20%; P = .05); with a highly significant difference observed for those receiving multiple catecholamine (7% vs 0%, P = .007). Finally, a statistically significant difference in median day 1 fluid bolus administration was observed, and twice as many vitamin D deficient study participants required >40 cc/kg fluid bolus on the day of PICU admission (17% vs 8%, P = .04).

**Clinically Important Outcomes**

In multivariate regression, a 25(OH)D concentration under 50 nmol/L was independently associated with an additional 1.92 days length of stay in PICU (95% CI: 0.2–3.7, P = .03) (Table 4). When the PICU length of stay multivariate analysis was performed with 25(OH)D as a continuous variable, every 10 nmol/L decrease was associated with 0.44 additional days (P = .048). To adjust the vitamin D deficiency model for potential confounders in this relationship, relevant covariates were considered. Medical diagnosis and admission site were also independent predictors of longer PICU stay in the multivariate model. For PRISM, each additional unit was associated with an extra 0.15 days, but the finding did not achieve statistical significance (P = .06). Preexisting illness, weight for age ratio, age, and trauma diagnosis were not associated with PICU length of stay. Potential vitamin D mediators including catecholamines, mechanical ventilation, and significant fluid bolus requirements were added to the length of stay multivariate model. All three mediators were independently associated with length of stay (P < .05), discarded PRISM from the model (P > .1) and slightly attenuated the strength of association between vitamin D and length of stay (range 1.75–1.9 additional days); vitamin D deficiency remained statistically significant in all 3 models (P < .05). Given the PICU mortality rate of 1.5% (5/326), the study was not powered to evaluate for an association with vitamin D deficiency; all 5 deceased patients were vitamin D deficient.

**DISCUSSION**

Data from this multicenter prospective observational study strongly suggests that the majority of critically ill Canadian children are vitamin D deficient at PICU admission. Furthermore, lower 25(OH)D levels are associated with greater catecholamine requirements, fluid bolus administration, hypocalcemia, and longer PICU admission.

The mean serum 25(OH)D level of 40 nmol/L measured immediately after admission for 326 critically ill Canadian children demonstrates that many have concentrations well below the target suggested by the Institute of Medicine, Canadian Pediatric Society, and American Academy of Pediatrics. Utilizing 50 nmol/L as the cutoff, 69% of the study cohort was vitamin D deficient. These levels are considerably lower than those reported on healthy Canadian children, with means closer to 75 nmol/L. Serum 25(OH)D levels on critically ill children appear similar to results from adult ICU studies reporting values ranging from 32 to 61 nmol/L. Levels and deficiency rates are also comparable to those from the 1 identified pediatric study in this area, reporting an average 25(OH)D level of 49 nmol/L in 16 children with severe ALRI requiring PICU admission. This study evaluated premorbid characteristics associated with vitamin D status. Contrasting with studies on healthier children no association with age or season was observed in the PICU.
Patients with poor nutrition or chronic illness are potentially at higher risk for both greater illness severity and vitamin deficiency. For example, preexisting illness could lead to reduced vitamin D status through abnormal diets, altered metabolism, or reduced environmental ultraviolet exposure. Despite this potential, no association between vitamin D deficiency and either preexisting illness or lower weight for age was demonstrable. In fact, higher weight for age ratios were associated with lower 25(OH)D, findings consistent with existing obesity literature.30,31 Furthermore, by using albumin as a marker of poor nutrition, no relationship with 25(OH)D concentration was evident. Trauma was the only other baseline characteristic statistically linked to vitamin D, consistent with the recent publication by Cecchi and colleagues identifying higher 25(OH)D concentrations in critically ill trauma patients relative to a sepsis cohort.32

It is likely that the measured 25(OH)D concentrations do not accurately represent the preillness state because both disease and associated interventions could reduce serum levels. Acute, sometimes transient, reductions in vitamin and mineral concentrations have been previously reported after significant hemorrhage, transudative fluid loss, fluid replacement or loading, and renal replacement therapies.33–35 Serum 25(OH)D levels may be similarly reduced.

### TABLE 3 Comparison of Clinically Important Outcome Measures by Vitamin D Status

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Not Deficient (n = 101)</th>
<th>Vitamin D Deficient (n = 225)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia</td>
<td>Ionized calcium &lt;1.1 mmol/L, n (%)</td>
<td>12 (41%)</td>
<td>60 (78%)</td>
</tr>
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<td>Catecholamine use</td>
<td>Received catecholamines, n (%)</td>
<td>20 (20%)</td>
<td>68 (30%)</td>
</tr>
<tr>
<td></td>
<td>Required 2 catecholamines, n (%)</td>
<td>0 (0%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Fluid bolus</td>
<td>Fluid bolus, mL/kg/24 h, median (IQR)</td>
<td>0 (0–14)</td>
<td>9 (0–24)</td>
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<td>Fluid bolus &gt;40 mL/kg/24 h, n (%)</td>
<td>8 (8%)</td>
<td>38 (17%)</td>
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<td>Day extubated, mean (SD)</td>
<td>2.8 (4.1)</td>
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<tr>
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<td>0 (0–4)</td>
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<td>0 (0)</td>
<td>15 (2.2%)</td>
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**Note:**
- Vitamin D deficiency defined as a 25(OH)D level <50 nmol/L. Total participant number was 326 for catecholamines, fluid bolus, mechanical ventilation, and mortality analysis. Calcium data were available for 1 site (108 study participants) with 77 deficient and 29 nondeficient subjects.
- *Defined as mechanical support while endotracheally intubated.

**FIGURE 1**
Comparison of 25(OH)D levels in PICU patients with and without biochemical abnormalities and organ dysfunction. A, Hypocalcemia; B, catecholamine infusion; C, mechanical ventilation; D, fluid bolus >40 mL/kg on admission day. Total participant number was 326 for the catecholamines, fluid bolus, and mechanical ventilation analysis. Calcium data were available for 1 site (108 study participants). Graphs represent box and whisker diagrams showing sample minimum, lower quartile, median, upper quartile, and sample maximum.

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- *Defined as mechanical support while endotracheally intubated.
reduced in critically ill patients in the acute setting because of altered metabolism, transcapillary leak, and fluid administration. For example, Krishnan et al recently demonstrated that cardiopulmonary bypass fluid loading transiently reduces serum 25(OH)D by up to 40%. Furthermore, Reid et al reported an acute postoperative drop in serum 25(OH)D that only partially recovered. Regardless of etiology, the high prevalence of vitamin D deficiency in the early stages of critical illness may be relevant. In fact, acute drops in serum concentrations may be more physiologically relevant than chronic deficiency because time is required for adjustment to lower concentrations, and the extent and time to compensation would be impaired by concurrent inflammation and organ dysfunction.

It has been previously hypothesized that inadequate vitamin D status might predispose to or worsen critical illness pathophysiology. A recent large study by Braun and colleagues evaluating predmission 25(OH)D identified lower concentrations as an independent predictor of ICU survival. Numerous other small studies with adult participants have demonstrated relationships between vitamin D deficiency and both the Simplified Acute Physiology score and ICU length of stay. This study on critically ill children supports these reports, with higher admission illness severity scores (PRISM) being associated with vitamin D deficiency. Similarly, after controlling for admission illness severity and other independent predictors, a 25(OH)D level <50 nmol/L was associated with an almost 2-day-longer PICU stay.

In our cohort, lower vitamin D levels were observed in participants with hypocalcemia, significant fluid bolus requirements, and subgroups requiring cardiovascular and ventilatory support. These findings are consistent with basic science and clinical studies in non-ICU settings revealing vitamin D as a pleiotropic hormone important for proper functioning of organs central to critical illness pathophysiology. First, vitamin D plays a well-established role in calcium homeostasis. Consistent with adult studies, the current study links lower vitamin D status to critical illness hypocalcemia. Second, vitamin D has been shown to influence cardiac myocyte and endothelial function through cellular receptors, altering gene and protein expression, signal transduction, and enzymatic reactions. Clinical evidence for a role in cardiovascular health is available from both large adult studies and pediatric case series identifying vitamin D deficiency as a reversible cause of cardiovascular disease and heart failure. Third, vitamin D receptors are present on major immune blood cell types, modulating white cell proliferation, maturation, cytokine release, antimicrobial peptide, and toll-like receptor levels. Clinical research has demonstrated associations between vitamin D and severe ALRI, sepsis, and asthma exacerbations. Finally, vitamin D deficiency could impair gas exchange through mechanisms including infection, inflammation, nerve dysfunction, and muscle weakness. The multifactorial mechanism for vitamin D deficiency in critical illness may also be supported by our finding that the addition of mediators including catecholamines, mechanical ventilation, or significant fluid bolus requirements into the length of stay regression multivariate model each attenuated the strength of association (5% to 15%) with vitamin D deficiency.

This study has a number of strengths. It is the largest study, adult or pediatric, reporting 25(OH)D levels in critically ill patients. Distinct from the majority of the adult ICU studies, 25(OH)D measurements were performed by using uniform methods on blood collected within 24 hours of ICU admission. Additional aspects of the study reduced potential bias, including defined eligibility criteria, and the multicenter multyear enrollment design. A potential limitation of this study is that the original AIP was not intended to estimate the prevalence of vitamin D deficiency or designed to confer causality. Furthermore, the AIP eligibility criteria may limit generalization of study findings to all PICU admissions because only those children ill enough to require central venous or arterial lines were enrolled. However, these children
probably represent the population of interest because they are the ones in whom supplementation may be more important. Finally, blood 25(OH)D may not accurately reflect vitamin D status in ICU patients dysfunction of the parathyroid, and renal organs may limit or prevent conversion of 25(OH)D to calcitriol, active vitamin D(3).

A more involved study evaluating all components of the vitamin D axis may demonstrate a stronger relationship with clinically relevant outcomes.

In conclusion, this study provides evidence that critically ill children commonly have 25(OH)D concentrations <50 nmol/L and that lower levels are associated with hypocalcemia, catecholamine need, significant fluid bolus administration, and longer length of stay. Subsequent prospective interventional trials are required to establish whether rapid restoration of vitamin D body stores has an impact on critical illness disease course and outcome.

ACKNOWLEDGMENTS

We thank Roxanne Ward for her help with the original study design and Nathalie Earl and Christine McRoberts for assistance with sample processing and vitamin D determination.

REFERENCES

28. Jeng L, Yamschickov AV, Judd SE, et al. Alterations in vitamin D status and anti-microbial levels in patients in the
intensive care unit with sepsis. J Transl Med. 2009;7:28


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Pediatrics 2012;130;429; originally published online August 6, 2012; DOI: 10.1542/peds.2011-3059

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