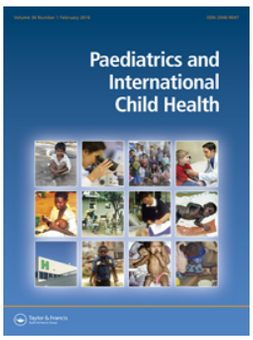

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Vitamin D deficiency in critically ill children with sepsis

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Background: Data on the prevalence of vitamin D deficiency (VDD) in critically ill children with sepsis and its association with illness severity and outcome are limited.
Aim: To investigate the prevalence of VDD in critically ill children with sepsis.
Methods: One hundred and twenty-four critically ill children with sepsis aged 1–12 years were prospectively enrolled in a paediatric intensive care unit (PICU) in North India over a 1-year period. Demographic data, clinical signs and risk factors for VDD, Paediatric Index of Mortality III (PRISM III) score, and sequential organ failure assessment (SOFA) score were recorded. Plasma 25-hydroxy vitamin D [25(OH)D] levels were measured by ELISA within 24 hours of admission. The occurrence of septic shock, multiple organ dysfunction syndrome (MODS) and healthcare-associated infection (HCAI), need for mechanical ventilation and catecholamines, length of PICU stay, and mortality were also recorded. Cases were compared with 338 apparently healthy children for baseline variables and vitamin D status.
Results: Prevalence of VDD [25(OH)D level <50 nmol/L] was higher among critically ill children with sepsis compared to healthy controls (50.8% *vs* 40.2%, $P=0.04$). VDD was not associated with any significant difference in baseline demographic variables or risk factors for VDD. Although there was a trend toward increased PRISM III score, septic shock, MODS, HCAI, need for mechanical ventilation and catecholamines, length of PICU stay, and mortality, the difference was not statistically significant.
Conclusion: A high prevalence of VDD in critically ill children with sepsis was found but it was not associated with greater severity of illness or other clinical outcomes.

Keywords: Vitamin D, Sepsis, Critically ill children, PICU, Mortality

Introduction

Vitamin D is a pleiotropic hormone that plays an important role in calcium homeostasis, bone health, cardiovascular system, and immunity.[1–3] Vitamin D and vitamin D receptor (VDR) expression and activity are associated with immunity against various infections and autoimmune diseases.[3–5] Levels of 25-hydroxy vitamin D [25(OH)D] are most often used to assess adequacy of vitamin D stores. While there is no consensus definition of vitamin D status, 25(OH)D level >75 nmol/L has traditionally been defined as sufficient, <50 nmol/L as deficient, and between 50-75 nmol/L as insufficient.[1,6–8] Various studies across the world including India have estimated the prevalence of VDD in healthy children to be in the range of 10–90%.[9–16] This high prevalence of VDD is owing to inadequate sunlight exposure because of an indoor lifestyle, use of sun screens, high levels of skin pigmentation, and inadequate dietary sources of vitamin D.[17,18]

Studies involving critically ill adults reported high prevalence of VDD and its association with higher illness severity scores, bacteraemia/sepsis, longer intensive care unit (ICU) stay, and increased short- and long-term all-cause mortality.[19–25] Recent studies involving critically ill children demonstrated that VDD is common and a few of them also identified that VDD is associated with greater severity of illness and a longer stay in the paediatric intensive care unit (PICU),[26–32] which suggests that VDD has an indirect impact on hospital burden in terms of increased duration and cost of hospital stay. So there are grounds for vitamin D supplementation in critically ill children with VDD which could be a potential novel strategy to modulate paediatric critical illness occurrence, severity and duration of illness, and length of PICU stay.

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Data on the prevalence of VDD in critically ill children are few. Moreover, none of these studies assessed vitamin D status in critically ill children with sepsis as a homogenous population. The aim of the study was to investigate the prevalence of VDD in critically ill children with sepsis admitted to the PICU, and to investigate any association between VDD and important clinical outcomes including illness severity, requirement for ventilation and catecholamines, length of PICU stay and mortality.

Methods

Subjects and protocols

This prospective observational study was undertaken in the PICU of a tertiary care teaching hospital in North India during a 1-year period from January to December 2012. Children (aged 1–12 years) admitted with a diagnosis of sepsis were eligible for inclusion. Children with underlying chronic disease (hepatic, renal, cardiac, neurological, pulmonary and gastrointestinal), who received vitamin D or calcium supplements in the past 3 months those on corticosteroids and those with haematological malignancies and immunodeficiency were excluded.

Baseline demographic data such as age, gender, weight, signs of severe acute malnutrition (SAM) (as defined by WHO),[33] season of admission to PICU, detailed physical examination, and clinical signs suggestive of VDD (craniotabes, rachitic rosary, frontal bossing, Harrison's sulcus, wrist widening, wide anterior fontanelle, double malleolus and bowing of legs) were recorded. Risk factors for VDD (family size, birth order, adequate sun exposure, and dark skin colour) were also recorded. Parents were asked about sunlight exposure, and daily sunlight exposure for >30 min exposing a minimum of 30% of the body surface area was labelled adequate.[14] Severity of illness was measured using the Paediatric Risk of Mortality III (PRISM III) score in the first 24 hours of admission to the PICU and the daily sequential organ failure assessment (SOFA) score.[34,35] Patients were followed up until discharge when the following parameters were recorded: the occurrence of septic shock, multiple organ dysfunction syndrome (MODS), healthcare-associated infection (HCAI), blood culture positivity and hypocalcaemia, the need for mechanical ventilation and catecholamines, the length of PICU stay and mortality. Standard definitions for sepsis, septic shock and MODS were used.[36]

The controls were taken from a previous prospective study that included apparently healthy children of upper socioeconomic status (USES) who attended the out-patient department (OPD) for immunization or with minor ailments over a 6-month over a 6-month period (March to August 2013) (n5338).[37] Controls were compared with cases for demographic variables, clinical signs of rickets, risk factors for VDD and vitamin D status.

Vitamin D measurement

Venous blood samples (2.0 ml) were collected in heparin vacutainers from all cases (within 24 hours of admission to the PICU) and controls for analysis of 25(OH)D. Plasma was extracted after centrifugation and stored at -20°C until analysis. Total plasma 25(OH)D was measured by ELISA (DLD Diagnostika GmbH, Germany) using calibrators and controls from the same manufacturer. The lower limit of detection was 4 nmol/L. The intra- and inter-assay co-efficients of variation were 3.2–6.9% and 7.0–8.6%, respectively. Vitamin D deficiency, insufficiency and sufficiency were defined as plasma 25(OH)D levels <50 nmol/L, 50–75 nmol/L and >75 nmol/L, respectively.[1,6–8]

Outcome

The primary outcome measure was the prevalence of VDD in critically ill children with sepsis. Secondary outcomes were to compare vitamin D-deficient and non-deficient cases for severity of illness (PRISM III and SOFA scores), shock, MODS, HCAI, need for mechanical ventilation and catecholamines, and mortality.

Statistical analysis

Data entry and statistical analyses were performed using Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) and SPSS software version 20 (SPSS Inc., Chicago, IL, USA). Demographic variables were recorded as percentages, means, standard deviations (SD), medians and interquartile ranges (IQR), as applicable. Dichotomous outcomes were compared by the χ^2 test. Continuous variables were compared by Student's *t*-test. The association between VDD and various patient characteristics was measured by the χ^2 test for categorical variables, and *t*-tests, Wilcoxon rank sum, Mann–Whitney or Kruskal–Wallis tests for continuous variables. For length of PICU stay, Kaplan–Meier curve was applied to assess the difference between vitamin D deficient and non-deficient patients. Normality of data was checked by Kolmogorov Smirnov tests. All tests were two-tailed and a $P<0.05$ was taken as significant.

Ethics

The institution's ethics committee approved the study. Informed written consent was obtained from the parents before enrollment.

Results

The study flow chart and recruitment are shown in Figure 1. Of 613 patients admitted to PICU during the study period, 495 (80.7%) were admitted with sepsis. Of those, 124 cases with sepsis were enrolled

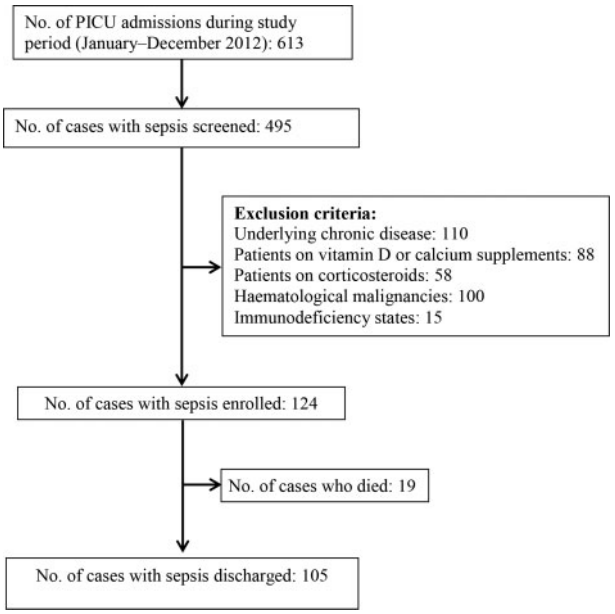

Figure 1 Study flow diagram for critically ill children with sepsis (cases)

(Fig. 1). The cases' and controls' baseline characteristics are shown in Table 1. Cases and controls were similar as far as age, gender, weight, and clinical signs and risk factors for VDD were concerned. Among cases, 17.7% (22/124) had SAM. The controls were enrolled over 6 month period (March-August 2013), so it was not possible to compare season of admission to PICU among cases with that of controls. Adequate sun exposure was reported in 40.2% (136/338) of controls and 33.9% (42/124) cases ($P=0.23$). Clinical signs of rickets were present in 12.1% cases and 8.58% controls ($P=0.28$). Table I also depicts other clinical parameters such as PRISM III score, SOFA score, need of mechanical ventilation and catecholamines, shock, MODS, HCAI, hypocalcaemia, length of PICU stay, and mortality at hospital discharge among cases with sepsis.

Cases with sepsis had significantly lower 25(OH)D levels compared with healthy controls (49.25 nmol/L *vs* 68.7 nmol/L, $P=0.03$). VDD was detected in 50.8% (63/124) cases and 40.2% (136/338) controls ($P=0.04$) (Table 2).

Vitamin D levels were significantly lower in vitamin D-deficient cases than in non-deficient cases ($P=0.02$) (Table 3). There was no difference in age, weight, gender or season between vitamin D-deficient and non-deficient cases. More cases with VDD had SAM

Table 1 Clinical characteristics of critically ill children with sepsis and healthy controls

Characteristics	Cases $n = 124$	Controls $n = 338$	*P*-value
Age, yrs, mean (SD)	4.2 (2.9)	3.3 (3.2)	0.22
Weight, kg, mean (SD)	13.8 (8.8)	12.9 (6.7)	0.13
Male, *n* (%)	80 (64.5)	188 (55.6)	0.08
Severe acute malnutrition, *n* (%)	22 (17.7)	None	0.0001
Season:*			
Winter, *n* (%)	21 (16.9)		
Summer, *n* (%)	21 (16.9)		
Monsoon, *n* (%)	54 (43.5)		
Autumn, *n* (%)	28 (22.6)		
Clinical signs of rickets	15 (12.1)	29 (8.6)	0.28
Risk factors for vitamin D deficiency:			
Family size, mean (SD)	4.2 (1.8)	3.9 (1.5)	0.27
Birth order, mean (SD)	2.3 (1.6)	1.91 (1.1)	0.12
Adequate sun exposure, *n* (%)	42 (33.9)	136 (40.2)	0.23
Dark skin colour, *n* (%)	18 (14.5)	30 (8.8)	0.08
PRISM III score, median (IQR)	16 (13–22)		
SOFA score, median (IQR)	4 (2.0–6.5)		
Mechanical ventilation:			
Mechanically ventilated, *n* (%)	61 (49.2)		
Duration of mechanical ventilation, hrs, median (IQR)	108 (58–160)		
Septic shock, *n* (%)	62 (50)		
Catecholamine use:			
Required catecholamines, *n* (%)	58 (46.8)		
≥2 catecholamines, *n* (%)	25 (20.2)		
Duration of catecholamine use, hrs, median (IQR)	68 (28–144)		
Multiple organ dysfunction syndrome, *n* (%)	45 (36.3)		
Health-care associated infection, *n* (%)†	29 (23.4)		
Bacterial culture positivity, n (%)	36 (29)		
Hypocalcaemia (calcium <2 mmol/L), *n* (%)	28 (22.6)		
Length of PICU stay in hours, median (IQR)	90 (44–168)		
Mortality at hospital discharge, *n* (%)	19 (15.3)		

* Controls were enrolled over a period of 6 months (i.e. March–August 2013) so comparison between the two groups is not possible;
† healthcare-associated infection is defined as a localised or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s), and there must be no evidence that the infection was present or incubating at the time of admission to the acute-care setting

Table 2 Distribution of critically ill children with sepsis and healthy controls according to 25(OH)D levels

25(OH)D levels, nmol/L	Cases $n = 124$	Controls $n = 338$	*P*-value
25(OH)D levels, nmol/L, mean (SD)	49.25 (33.0)	68.7 (39.7)	0.03
<50, deficient, *n* (%)	63 (50.8)	136 (40.2)	0.04
50–75, insufficient, *n* (%)	31 (25.0)	86 (25.4)	1
<75, insufficient + deficient, *n* (%)	94 (75.8)	222 (65.7)	0.04
>75, sufficient, *n* (%)	30 (24.2)	116 (34.3)	0.04

Table 3 Comparison by vitamin D status of clinical characteristics in critically ill children with sepsis

Characteristics	Deficient $n = 63$	Non-deficient $n = 61$	*P*-value
25(OH)D levels, nmol/L, mean (SD)*	36 (23.0)	60 (38.7)	0.02
Age, years, mean (SD)	4.2 (2.7)	4.2 (2.4)	0.60
Weight, kg, mean (SD)	13.1 (10.3)	14.5 (11.5)	0.67
Male, *n* (%)	38 (60.3)	42 (68.8)	0.11
Severe acute malnutrition, *n* (%)	14 (22.2)	8 (13.1)	0.24
Season:			
Winter, *n* (%)	11 (17.5)	10 (16.4)	0.29
Summer, *n* (%)	14 (22.2)	7 (11.5)	
Monsoon, *n* (%)	23 (36.5)	31 (50.8)	
Autumn, *n* (%)	15 (23.8)	13 (21.3)	
PRISM III score, median (IQR)	17 (13–22)	14 (13–22)	0.26
SOFA, median (IQR)	4 (2.0–6.8)	4 (2.0–6.3)	0.64
Mechanical ventilation:			
Mechanically ventilated, n (%)	35 (55.6)	26 (42.6)	0.15
Duration of mechanical ventilation, hrs, median (IQR)	120 (72–216)	96 (24–144)	0.52
Septic shock, *n* (%)	32 (50.8)	30 (49.2)	0.85
Catecholamine use:			
Required catecholamines, *n* (%)	31 (49.2)	27 (44.3)	0.59
≥2 catecholamines, *n* (%)	15 (23.8)	10 (16.4)	0.31
Duration of catecholamine use, hrs, median (IQR)	77 (30–154)	59 (25–92)	0.15
Multiple organ dysfunction syndrome, *n* (%)	25 (39.7)	20 (32.8)	0.83
Healthcare-associated infection, *n* (%)	15 (23.8)	14 (22.9)	0.91
Bacterial culture positivity, *n* (%)	21 (33.3)	15 (24.6)	0.32
Hypocalcaemia, calcium <2 mmol/L, *n* (%)	17 (27.0)	11 (18)	0.28
Length of PICU stay, hrs, median (IQR)	92 (43–168)	86 (12–114)	0.73
Mortality at hospital discharge, *n* (%)	10 (15.9)	9 (14.7)	0.53

* Deficient and non-deficient 25(OH)D levels are defined as <50 nmol/L and >50 nmol/L, respectively

than non-deficient cases, though the difference was not statistically significant. The severity of illness assessed by PRISM III and SOFA scores showed no significant difference between cases with VDD and those with non-deficient levels of vitamin D, though the PRISM III score was slightly higher in cases with VDD (Table 3). Also, there was a trend toward increased occurrence of septic shock and MODS, requirement for catecholamines and mechanical ventilation, development of HCAI, and occurrence of hypocalcaemia in cases with VDD, though the difference was not statistically significant (Table 3). Similarly, the length of PICU stay analysed by Kaplan–Meier did not show a significant difference between vitamin D-deficient and non-deficient cases (P=0.73). Of 124 patients, 19 (15.3%) died. Of these, ten had deficient [eight with 25(OH)D levels <25 nmol/L], seven insufficient, and two sufficient 25(OH)D levels.

Discussion

This prospective study demonstrated that the prevalence of VDD among critically ill children with sepsis was 50.8%, which was significantly higher than in healthy controls (40.2%). Only one-quarter of cases and one-third of controls had sufficient levels of vitamin D and the remainder were either deficient or insufficient (Table 2).

The improved understanding of vitamin D as an immuno-modulator hormone holds great attraction both as a potential target for treatment and for prevention of disease states. VDD is highly prevalent throughout the world even in countries with abundant sunshine.[38,39] The prevalence of VDD among healthy paediatric populations is demonstrated to be high in high-income countries (9–24%)[9–13] as well as in developing middle- and low-income countries in the Indian subcontinent (36–90%).[14–16] However, a variable proportion of children with VDD in developed countries may be from ethnic minorities and have pigmented skin. The prevalence of VDD in adult ICU patients is reported to be 17–79%, with a mean 25(OH)D level in the range of 32–73.5 nmol/L.[19–25] A few studies of critically ill children with various admission diagnoses reported

Table 4 Prevalence of vitamin D deficiency (VDD) in various studies involving critically ill children

	Author, year, ref. no.	Total no. of patients	Prevalence of VDD (%)*
1	Current study	124	50.8
2	Madden *et al.*, 2012[26]	511	40.1
3	McNally *et al.*, 2012[27]	326	69
4	Rippel *et al.*, 2012[28]	316	34.5
5	Rey *et al.*, 2014[29]	156	29.5
6	Ayulo *et al.*, 2014[30]	216	28
7	Hebbar *et al.*, 2014[31†]	61	16.4
8	Dayal *et al.*, 2014[32‡]	92	25

*VDD was defined as 25(OH)D levels <50 nmol/L in most of the studies, including the current one; †VDD was defined as 25(OH)D levels <25 nmol/L; in this study, 60.7% of children in the PICU had 25(OH)D levels <50 nmol/L; ‡included children hospitalised in a general paediatric unit of a tertiary-care centre in North India

a prevalence of VDD in the range of 16.4–69% (Table 4).[26–32] McNally *et al.*[27] reported the highest (69%) and Hebbar *et al.*[31] the lowest (16.4%) prevalence of VDD in critically ill children on admission to the PICU. In a recent study in our institution, the prevalence of VDD in 92 hospitalised children was 25% on admission and had increased to 51.1% at the time of discharge.[32] The fall in 25(OH)D levels during hospitalisation might relate to factors which operate in a hospitalised child including poor oral intake, poor intestinal absorption owing to illness, no exposure to sunlight and a lack of vitamin D supplementation during hospitalisation.[32] Similar to other studies of critically ill children, no association between VDD and the season of admission to the PICU was found in the current study.[27,28]

The wide differences in the prevalence of VDD in different studies may be owing to differences in the populations studied, sunlight exposure, weather, dietary intake, vitamin D supplementation, genotype variation in the proteins involved in vitamin D transportation, functioning and metabolism, different methods of measuring 25(OH)D and different cut-off values.[8,40] The low concentration of 25(OH)D in critically ill patients may be because of altered metabolism, transcapillary leak, fluid administration, after significant haemorrhage, renal replacement therapies or intra-operative decline after cardiopulmonary bypass.[27,41–44]

There was no relationship between vitamin D status and severity of illness (assessed by PRISM III and SOFA scores) (Table 3). The cases in this study had a higher PRISM III score (median 16, IQR 13–22) than in other studies using PRISM III as an index of severity of illness.[26,27,29,31] A few studies found an inverse correlation between VDD and various indices of illness severity[26,27] while others found no such association.[28–31]

This study found that patients with VDD had an increased incidence of shock, MODS and HCAI and an increased requirement for ventilation and catecholamines, although the difference was not statistically significant. Madden *et al.*[26] observed that fluid bolus administration before admission to the PICU had a weak inverse correlation with 25(OH)D levels (r 2.12, $P=0.01$). Also, patients who received vasopressors had lower levels of 25(OH)D than those who did not (median 19.8 *vs* 24.3 ng/ml, $P<0.0001$) and an increased use of vasopressors was correlated with decreasing 25(OH)D levels (r 2.19, $P<0.0001$). Duration of mechanical ventilation was not significantly associated with 25(OH)D levels. Similarly, McNally *et al.*[27] reported that lower mean (SD) 25(OH)D levels were detected in patients who required catecholamine infusion [45 (19) nmol/L *vs* 38.5 (16) nmol/L, $P=0.006$] and >40 ml/kg fluid bolus on the day of admission [44.7 (19.6) nmol/L *vs* 34.5 (18.5) nmol/L, $P=0.001$]. Also, patients who required mechanical ventilation had lower 25(OH)D levels than those who did not [47.2 (19.9) nmol/L *vs* 41.7 (19.1) nmol/L, $P=0.02$]. Other studies found no association between VDD with requirement of inotropes and ventilation.[28,29]

VDD had no significant effect on length of PICU stay and mortality which was 15.3% (19/124), slightly higher than that reported globally (10–13.5%).[45] Possible reasons might include increased severity of illness, increased prevalence of infectious diseases and malnutrition, gaps in healthcare delivery and late referral. McNally *et al.*[27] found that, on multivariate regression, a 25(OH)D concentration <50 nmol/L was independently associated with an additional 1.92 days in the PICU (95% CI 0.2–3.7, $P=0.03$). There was also a PICU mortality rate of 1.5% (5/326) and all five deceased patients had VDD. Similarly, Ayulo *et al.*[30] reported that five of six deaths were in patients with VDD. Other studies found no association between VDD and length of PICU stay or mortality.[28,29] A previous study from our institution[32] demonstrated that in children with VDD there was a trend to require longer hospitalisation, to require ventilation and catecholamines, to develop HCAI and to die compared with non-deficient cases, although the difference was not statistically significant.

Vitamin D has important roles in calcium homeostasis; in innate immune function by modulating white cell proliferation, maturation, cytokine release, antimicrobial peptide and toll-like receptor levels; and the

functioning of cardiac myocyte and endothelial cells through cellular receptors, altering gene and protein expression, signal transduction and enzymatic reactions. VDD might impair gas exchange through various mechanisms including infection, inflammation, nerve dysfunction and muscle weakness.[26,27,46] These multiple, critical functions of vitamin D could explain the trend in this study population towards increased PRISM III score, MODS, HCAI, hypocalcaemia, increased requirement of mechanical ventilation and catecholamines, length of PICU stay and mortality in cases with VDD.

The major strengths of this study are that the prevalence of VDD was studied in a homogeneous subgroup of critically ill children (i.e. with sepsis). Other studies in the paediatric age group evaluated the prevalence of VDD in critically ill children in general. Cases were compared with healthy controls, which was essential to demonstrate an increased prevalence of VDD in critically ill children with sepsis. Only a few studies have compared critically ill children and controls for vitamin D status.[29,31] Also, a higher prevalence of VDD in healthy controls (40.2%) was noted. This baseline high prevalence of VDD in the community could explain the high prevalence of VDD in cases (50.8%). As far as we are aware, this is the first study to assess VDD in critically ill children with sepsis.

The limitations of the study are as follows. Although cases were enrolled over a 1-year period, controls were enrolled over only 6 months, i.e. March–August (summer season).[37] As VDD is season-dependent with lower 25(OH)D levels in winter,[47,48] the controls might not represent vitamin D status throughout the year and the data might underestimate the actual prevalence of VDD in controls. The different socio-economic status in cases and controls could have influenced the difference in prevalence of VDD. Similarly, the significant difference in SAM among cases and controls might have contributed to a higher prevalence of VDD in the cases. In addition, the following factors which could have given more insight into VDD were not investigated: the administration of fluid boluses, serum phosphorus, alkaline phosphatase, parathyroid hormone, 1,25(OH)D levels and radiographs for evidence of VDD. In addition, 25(OH)D status was not assessed longitudinally during the PICU stay, nor was the effect of vitamin D supplementation, and these would be important areas for future investigation.

A higher prevalence of VDD was detected in critically ill children with sepsis in a PICU in North India, although there was no significant association between VDD and severity of illness on admission to the PICU, requirement for mechanical ventilation, catecholamine use, length of PICU stay or mortality. Further large-scale studies are needed to determine the exact prevalence of VDD in critically ill children with sepsis and the association between VDD and important clinical outcomes, and to assess the safety, feasibility and effectiveness of vitamin D supplementation in children with sepsis in the early stages of a critical illness.

Disclaimer statements

Contributors

Satheesh Ponnarmeni: Planned the study, and data collection and analysis. Suresh Kumar Angurana: Helped in data analysis, literature review, and writing manuscript. Sunit Singhi: Supervised study and critically reviewed the manuscript. Arun Bansal: Supervised patient management and data collection. Devi Dayal: Helped in literature review. Rajdeep Kaur: Helped in collection and processing of samples, and interpretation of results. Ajay Patial: Helped in collection and processing of samples, and interpretation of results. Savita Verma Attri: Planned the study, supervised data collection and analysis, literature review, critically reviewed manuscript, and approval of final version of the manuscript.

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Conflict of interest

No conflicts of interest.

Ethics approval

No ethical issues.

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