Trials

STUDY PROTOCOL

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Rapid normalization of vitamin D deficiency in PICU (VITdALIZE-KIDS): study protocol for a phase III, multicenter randomized controlled trial

Katie O'Hearn[1], Kusum Menon[1,2], Lisa Albrecht[1], Karin Amrein[3], Philip Britz-McKibbin[4], Florence Cayouette[5], Karen Choong[6], Jennifer Ruth Foster[7,8], Dean A. Fergusson[9,10,11], Alejandro Floh[12,13], Patricia Fontela[14,15], Pavel Geier[1,2], Elaine Gilfoyle[12,16], Gonzalo Garcia Guerra[17,18,19], Anna Gunz[20], Erick Helmeczi[4], Ali Khamessan[21], Ari R. Joffe[19,22], Laurie Lee[23,24], Lauralyn McIntyre[10,25], Srinivas Murthy[26], Simon J. Parsons[17], Tim Ramsay[9,10], Lindsay Ryerson[19,22], Marisa Tucci[27] and Dayre McNally[1,2*] on behalf of the Canadian Critical Care Trials Group

Abstract

Background The rate of vitamin D deficiency (VDD) in critically ill children worldwide has been estimated at 50%. These children are at risk of multiple organ dysfunction, chronic morbidity, and decreased health related quality of life (HRQL). Pediatric and adult ICU clinical trials suggest that VDD is associated with worse clinical outcomes, although data from supplementation trials are limited and inconclusive. Our group's phase II multicenter dose evaluation pilot study established the efficacy and safety of an enteral weight-based cholecalciferol loading dose to rapidly restore vitamin D levels in critically ill children.

Methods Our aim is to evaluate the impact of this dosing regimen on clinical outcomes. VITdALIZE-KIDS is a pragmatic, phase III, multicenter, double-blind RCT aiming to randomize 766 critically ill children from Canadian PICUs. Participants are randomized using a 1:1 scheme to receive a single dose at enrollment of enteral cholecalciferol (10,000 IU/kg, max 400,000 IU) or placebo. Eligibility criteria include critically ill children aged newborn (> 37 weeks corrected gestational age) to < 18 years who have blood total 25-hydroxyvitamin D < 50 nmol/L. The primary objective is to determine if rapid normalization of vitamin D status improves HRQL at 28 days following enrollment. The secondary objective is to evaluate the impact of rapid normalization of vitamin D status on multiple organ dysfunction. The study includes additional tertiary outcomes including functional status, HRQL and mortality at hospital discharge and 90 days, PICU and hospital length of stay, and adverse events related to vitamin D toxicity. Additionally, we are performing comprehensive vitamin D speciation and non-targeted metabolite profiling as part of a sub-study for the first 100 participants from whom an enrollment and at least one post-intervention blood and urine sample were obtained.

*Correspondence:
Dayre McNally
dmcnally@cheo.on.ca
Full list of author information is available at the end of the article

Discussion The VITdALIZE-KIDS trial is the first phase III, multicenter trial to evaluate whether rapid normalization of vitamin D status could represent a simple, inexpensive, and safe means of improving outcomes following pediatric critical illness. Recruitment was initiated in June 2019 and is expected to continue to March 2026.

Trial registration Clinicaltrials.gov, NCT03742505. Study first submitted on November 12, 2018 https://clinicaltrials.gov/study/NCT03742505

Keywords Vitamin D, Pediatrics, Critical care, Randomized controlled trial, Vitamin D deficiency, Health-related quality of life

Background

Approximately 12,000 critically ill children are admitted to Canadian pediatric intensive care units (PICUs) annually, where they face the risk of prolonged rehabilitation, new morbidity or chronic disease, and death [1]. Research has shown that a significant number of PICU survivors experience a long-term decline in functional status and/or health-related quality of life (HRQL) [2–4]. Novel means of decreasing mortality and reducing long-term morbidity would be of great value to these children, their families, and the healthcare system.

Given vitamin D's established pleiotropic role in the health of organs central to critical illness pathophysiology and support of immune function, it has been hypothesized that vitamin D deficiency (VDD) could represent a modifiable risk factor for improving clinical outcome following critical illness [5, 6]. Specifically, there are multiple mechanisms through which VDD could contribute to organ dysfunction, including (i) exacerbation of critical illness-related hypocalcemia (particularly in the presence of liver, parathyroid, or renal dysfunction) [7]; (ii) cardiovascular dysfunction indirectly through low body calcium stores and directly through vitamin D receptors (VDR) present on myocytes and endothelial cells; (iii) immune dysregulation through functional VDR present on all major immune cell types [8]; (iv) through the role of vitamin D signaling in innate immunity [9]; and (v) muscle weakness, a well-recognized consequence of critical illness [10] that can be further exacerbated by the impact of VDD on muscle pathology and clinically relevant weakness [11].

Multiple observational studies in the PICU have reported both high deficiency rates and associations between VDD and organ dysfunction, health resource utilization, and mortality [12–16]. The prevalence and impact of VDD in critically ill children is well established, with meta-analysis of observational studies showing a worldwide PICU VDD rate of 50% [16]. Our research group also published the first large Canadian PICU study ($n=326$) documenting high deficiency rates (60–70%) [12, 17] and association between lower vitamin D levels and worse clinical course in the PICU setting [12]. Although concerning, the high VDD rate in critically ill Canadian children is viewed by our research group and others [18–20] as an opportunity to potentially improve clinical outcomes, with far-reaching implications for children, their families, and the healthcare system. The gap in knowledge at present is whether early rapid normalization of VDD in critically ill children will causally improve outcomes.

Similar to pediatric critical illness, there is a significant body of observational evidence demonstrating VDD to be risk factor in the adult ICU setting [21–25]. In contrast to pediatrics, there have been ~ 10 RCTs evaluating the biochemical and clinical response to high dose vitamin D in critically ill adults. Meta-analyses of trial findings are inconclusive as to whether there is benefit [23, 24, 26, 27]. The definitive adult ICU trial (VITdALIZE), a multi-national RCT seeking to enroll 2400 critically ill VDD adults to determine whether rapid normalization with a 540,000 IU load improves 28-day mortality, is ongoing [28].

Current vitamin D supplementation guidelines

Vitamin D supplementation to achieve recommended daily allowances of intake thought essential to good health has been recommended in guidelines from multiple agencies. For example, the National Academy of Medicine (NAM, formerly the Institute of Medicine) provides a recommended daily allowance or adequate intake (400–600 IU/day) for children [29] that has been supported by Health Canada. As there are no ICU guidelines recommending alternative loading dose supplementation strategies, most critically ill children receive either no supplementation or the same daily dose suggested for healthy children. It is important to recognize these doses (i) are derived from studies on healthy children, (ii) are focused on preventing bone disease, and (iii) may require months to rebuild body stores [30]. Emphasizing this last point, evaluation of hospitalized patients in observational studies and clinical trials has shown that vitamin D levels often fail to rise or even fall with usual care [13, 22, 31].

In addition to standard dosing, the NAM also provides alternative dosing recommendations, referred to as the tolerable upper intake level (UL) for healthy children, ranging from 1000 to 4000 IU/day (age dependent)

[29]. We recently investigated this daily dosing regimen for potential application in the PICU setting in a systematic review [32], demonstrating that the majority of VDD patients require over a month to attain normal levels at the UL dose. This time frame was confirmed in a recent pilot study of pediatric burn patients, with only 50% of patients achieving normal levels despite 30 days of daily dosing above the UL (~ 800 IU + 100 IU/kg) [33]. The use of a supplementation approach that requires a month (or more) to correct VDD may not optimize benefit during the PICU admission and immediate recovery period, placing critically ill children at risk for new pathology and worse functional outcome during these times [33]. While this dosing regimen is of value for certain patient populations in the context of early treatment or prophylactic applications, it offers minimal value for acutely critically ill children.

Pediatric investigations to date

A novel supplementation approach that rapidly normalizes vitamin D levels is essential to realize the potential health benefits of sufficient vitamin D status. To determine the loading dose most appropriate for a randomized controlled trial evaluating rapid correction of VDD in critically ill children, we analyzed vitamin D response in 98 pediatric clinical trials (88 full-text publications, 10 conference abstracts) [32]. This systematic review demonstrated that administration of a single or repeated enteral loading dose rapidly achieved peak vitamin D (measured as blood total 25OHD) levels within 3 days of dosing [32]. Further analysis showed increased hypercalcemia risk with loading doses > 400,000 IU, but only in studies enrolling infants and young children. Based on this review, a single load of 10,000 IU/kg (maximum 400,000 IU) was determined as the regimen most likely to rapidly and safely correct VDD [32].

We subsequently evaluated the safety and efficacy of a 10,000 IU/kg (maximum 400,000 IU) loading dose in our international phase II dose evaluation pilot study VITdAL-PICU. Results from this trial confirmed this dose raised group 25OHD levels to above the 75 nmol/L threshold in > 75% of participants, with no biochemical or clinical evidence of toxicity [34]. Similarly, in a trial of VDD children undergoing CHD cardiac surgery, a loading dose of 10,000 IU/kg cholecalciferol (maximum 400,000 IU) approximately 2 weeks prior to surgery produced significantly higher concentrations in the treatment arm relative to control (83.5 nmol/L vs 27.4 nmol/L) in blood collected immediately before the surgery, without statistically significant differences in parameters pertaining to vitamin D toxicity during the perioperative period [35]. Recent RCTs in critically ill pediatric populations also support findings of negative impact of VDD on clinical outcomes for sepsis and pneumonia and suggest a positive effect of loading dose supplementation in these populations [36–38].

Trial outline

VITdALIZE-KIDS will investigate the hypothesis that loading dose vitamin D could represent a simple, inexpensive, safe, and feasible means of improving outcomes following pediatric critical illness. This trial asks the question: in critically ill VDD children, what is the effect of rapid normalization of vitamin D status compared with placebo, on health-related quality of life (HRQL) at 28 days following intervention? The secondary objective is to determine the impact of rapid normalization of vitamin D status on new and progressive multiple organ dysfunction. Tertiary objectives are to evaluate the impact of rapid normalization of vitamin D status on (1) functional status at hospital discharge and 28 and 90 days following loading dose administration; (2) PICU and hospital length of stay; (3) serious adverse events and vitamin D-related toxicities; (4) survival alone at 28 and 90 days; and (5) HRQL at hospital discharge and 90 days following loading dose administration. Further, VITdALIZE-KIDS includes a sub-study of 100 participants with pre- and post-loading dose blood and urine, where we will assess pre- and post-intervention vitamin D status, perform non-targeted metabolite profiling to better understand the pleiotropic effects of rapid correction of VDD on human metabolism beyond calcium homeostasis and active hormone levels, and identify adjunct biomarkers that when combined with 25OHD may better predict inadequate vitamin D status and response to treatment.

Methods/design

In collaboration with the Canadian Critical Care Trials Group (CCCTG), we designed VITdALIZE-KIDS as a pragmatic, phase III, multicenter, individual patient 1:1 randomized double-blind superiority RCT. Our protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (see Additional file 1). A summary of the protocol is provided in Table 1.

Trial setting

The VITdALIZE-KIDS trial will recruit up to 766 patients from PICUs at the following 11 academic centers in Canada: Children's Hospital of Eastern Ontario (CHEO), Ottawa; London Health Sciences Centre, London; Montreal Children's Hospital, Montreal; Centre hospitalier universitaire Sainte-Justine, Montreal; McMaster Children's Hospital, Hamilton; Alberta Children's Hospital, Calgary; BC Children's Hospital, Vancouver; The Hospital for Sick Children, Toronto; Stollery Children's

Table 1 World Health Organization trial registration data set—structured summary

Data category	Information
Primary registry, trial identifying number	Clinicaltrials.gov identifier-NCT03742505
Date of registration in primary registry	November 15, 2018
Secondary identifying numbers	Health Canada control number and protocol title: 223,325, VITdALIZE-KIDS; Clinical Trials Ontario REB number: 1761
Sources of monetary support	Canadian Institutes of Health Research (CIHR) Project Grant, Physician Services Incorporated (PSI) New Investigator Grant; COVID-19 emergency funding: Canada Emergency Wage Subsidy, Canada Research Continuity Emergency Fund
Sponsor	Children's Hospital of Eastern Ontario Research Institute 401 Smyth Road Ottawa, Ontario K1H 8L1 Principal Investigator Phone: 613–737-7600 ext. 3553 Principal Investigator Email: dmcnally@cheo.on.ca
Contact for public queries	JDM, Pediatric Critical Care, Children's Hospital of Eastern Ontario, Canada
Contact for scientific queries	JDM, Pediatric Critical Care, Children's Hospital of Eastern Ontario, Canada
Public title	Rapid normalization of vitamin D deficiency in PICU (VITdALIZE-KIDS)
Scientific title	Rapid correction of vitamin D deficiency in pediatric critical illness: A phase III multicentre randomized controlled trial (VITdALIZE-KIDS)
Country of recruitment	Canada
Health problem under investigation	Vitamin D deficiency in critically ill children
Inclusion and exclusion criteria[1]	*Inclusion criteria:* Admitted to PICU Corrected gestational age 37 weeks to age 18 years Vitamin D deficiency, as defined by blood total 25OHD < 50 nmol/L at the time of screening *Exclusion criteria:* Patient will be discharged from PICU before they can be enrolled (i.e., trial drug administered) into the VITdALIZE-KIDS trial and/or patient expected to be in hospital for < 3 days following enrollment Treating physician refuses enteral drug administration due to gastrointestinal disorder and expects to do so for the full duration of the patient's PICU admission Persistent hypercalcemia (ionized calcium > 1.40 mmol/L (age > 2 months), > 1.45 (age < 2 months) excluding transient abnormalities and those related to parenteral calcium administration for hypocalcemia Confirmed or suspected William's syndrome Known nephrolithiasis or nephrocalcinosis Imminent plan for withdrawal of treatment or transfer to another ICU not participating in the VITdALIZE-KIDS trial Physician refusal Previous enrollment in this trial Granulomatous disease (tuberculosis or sarcoidosis) Severe liver failure Hypersensitivity or allergy to vitamin D or any of the non-medicinal ingredients of the formulation Patient on thiazide diuretics also receiving regular ongoing calcium supplementation above the daily recommended intake (excluding patients receiving calcium supplementation for the treatment or prevention of hypocalcemia) Adolescent female of child-bearing age with a positive pregnancy serum test Patient on digoxin-therapy Treating physician intends to administer vitamin D doses above 1000 IU (e.g. patient presents with isolated clinical symptoms of severe VDD, severe burns)
Study type	Pragmatic, phase III, multicentre, double-blind randomized controlled trial
Date of first enrollment	June 20, 2019
Target sample size	766
Recruitment status	Recruitment initiated on June 17, 2019; recruitment ongoing
Primary outcome	Health-related quality of life (HRQL) at 28 ± 7 days, determined using the Pediatric Quality of Life Inventory Scale (PedsQL)™ 4.0 Generic Acute Scales[90–96] (ages 2–17) and the PedsQL™ Infant Scales (1–24 months)

[1] Justification for individual criteria were outlined in our group's pilot VITdAL-PICU dose evaluation RCT [82]

Hospital, Edmonton; IWK Health Centre, Halifax; and Centre mère-enfant Soleil du CHU de Québec Université Laval, Quebec City.

Patient enrollment and consent

Eligible participants are identified in the PICUs. Patients are screened daily (Monday through Friday) by trial staff and informed consent obtained via site-approved approaches, according to Good Clinical Practice (GCP) guidelines. These approaches include obtaining consent through the care team to screen for VDD and consent for full trial enrollment simultaneously or separately, telephone consent, and deferred consent (for screening only). In participating sites where vitamin D status has or will be measured as the standard of care, or in patient sub-groups for whom vitamin D status is measured as part of standard of care, vitamin D status is determined clinically to confirm full trial eligibility. In participating sites and/or inpatient groups for whom vitamin D status is not measured as part of standard of care, vitamin D status is determined following deferred or informed consent (site-specific) using a research sample collected at time of screening—discard blood whenever possible. Vitamin D status is measured by site clinical labs, a research lab, or using an FDA- and Health Canada-approved point of care device (Qualigen® FastPack IP system). If 25OHD is less than 50 nmol/L, the patient is considered fully eligible and randomized into the trial.

Randomization

The Data Coordinating Centre (DCC) at the Ottawa Methods Centre at the Ottawa Hospital Research Institute (OHRI) has created a computer-generated randomization list. Participants are randomized 1:1 (intervention:control) using random variable block sizes to avoid major imbalances. Randomization is stratified by site to account for site-specific practice variation.

Allocation concealment and blinding

Randomization allocation is achieved using an electronic web page, where the participant is assigned an ID number and the site pharmacist receives an email with the ID number and treatment allocation. Randomization lists are only accessible to the Ottawa Methods Centre at the OHRI and research pharmacist(s). The active drug and placebo appear identical (e.g., color, consistency, volume, taste, smell, containers), in order to maintain blinding. Post-randomization, the research pharmacist dispenses the intervention (either vitamin D or placebo solution) to the nursing staff for administration. All trial personnel (the trial research coordinator, research assistants, site qualified investigators, principal investigator (PI), co-investigators, data management personnel, and statisticians), members of the health care team (treating physicians, bedside nurses, clinical pharmacists, etc.), and participants/families are blinded to the trial group assignment. The assigned intervention will not be revealed until all participants have been discharged from hospital, follow-up data collection and determination of research-related biochemical testing is complete, and the research database has been finalized. In the event of an emergency, blinding may be broken at the request of the clinical service after obtaining PI approval if unblinding would affect patient care. Blinding may also be broken at the request of the Data Safety Monitoring Board (DSMB) during interim analyses and at trial completion for the final analysis and manuscript preparation.

Intervention and controls

Participants randomized to the intervention arm receive an enteral cholecalciferol load (vitamin D3 (cholecalciferol) Oral Solution 50,000 IU/mL, Euro-Pharm Canada Inc.) at a dose of 10,000 IU/kg (maximum 400,000 IU).

Participants randomized to the control arm receive a placebo solution equivalent in volume to the appropriate dose of cholecalciferol at enrollment. The placebo is also provided by Europharm Canada International Inc.® All participants may also receive standard vitamin D dosing at the discretion of the care team ($\leq$1000 IU/day), which is documented on the electronic case report form (eCRF). Baseline HRQL and Functional Status Scale (FSS) are obtained from parental interview within 72 h of trial enrollment. The hospital discharge (for participants with a hospital stay > 14 days, if not discharged within the 28 ± 7-day window), 28- and 90-day HRQL, and FSS measurements are obtained primarily in person, if participants remain hospitalized, or by telephone, email, or mail if participants have been discharged. Demographics, hospital course, adverse events, and health resource utilization are collected and documented on the eCRF.

Blood and urine sampling

Enrollment and up to two post-intervention (>48 h, range: Days 2–7) urine and blood samples (through arterial or central venous lines or at the time of clinically indicated bloodwork) were collected from consecutively enrolled participants until July 2022. With consent from participating families, residual biosamples are maintained in the principal investigator's laboratory at CHEO as part of the VITdALIZE-KIDS Trial Biobank. All policies and procedures surrounding this are consistent with the Organization for the Economic Co-Operation and Development (OECD) Guidelines on Human Biobanks and Genetics Research. The SPIRIT trial timeline is seen in Fig. 1.

		STUDY PERIOD			
	Pre-enrolment	Randomization	Post-randomization		
TIMEPOINT	$-t_1$		t_1 (0 + 72h)	t_2 (28 +/- 7 days)	t_3 (90 +/- 14 days)
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Study drug/placebo administration		X			
Study questionnaires			X	X and/or hospital discharge prior to day 28	X
ASSESSMENTS:					
Blood sampling (all patients)	X (Screening)				
Blood and urine sampling (subset of patients)		X	X Day 2-7		
New and/or progressive multiple organ dysfunction			Day 0, 3, 7; weekly until Day 28 or PICU discharge		
Functional status			X	X and/or hospital discharge prior to day 28	X
Serious adverse events and vitamin D toxicity			⟷		
HRQL			X	X and/or hospital discharge prior to day 28	X

Fig. 1 VITdALIZE-KIDS timeline of enrolment, interventions, and assessments

Outcomes

Our primary outcome is HRQL at 28 ± 7 days after intervention. This was identified in our survey of PICU families and caregivers as the most important outcome to them after survival [39] and is consistent with studies acknowledging HRQL as a preferred primary outcome for pediatric critical care trials [40]. HRQL is determined using the Pediatric Quality of Life Inventory Scale (PedsQL)™ 4.0 Generic Acute Scales [41] (ages 2–17) and the PedsQL™ Infant Scales (1–24 months). The PedsQL™ is one of the most widely used instruments for evaluating HRQL in pediatrics and has demonstrated reliability, sensitivity, validity, and responsiveness by self-reporting and/or proxy reporting in multiple pediatric populations including the PICU [42]. It has been used in numerous PICU studies [3, 43, 44] and was identified as one of the best HRQL tools for pediatric critical care research [2]. For infants under 1 month of age at enrollment, the baseline PedsQL™ questionnaires are not completed as no questionnaires are available or validated for that age. Proxy reporting is used for the primary outcome for consistency, but self-reporting is also completed when not prevented by age, ongoing critical illness, morbidity, or developmental status. Of note, as PICU patients often have comorbidities and impaired HRQL prior to PICU admission, pre-illness HRQL (prior to acute illness) is obtained from in person parental interview within 72 h of trial enrollment using the PedsQL™ (when baseline HRQL measurement is not feasible, bias in HRQL estimation is minimized when measurements are obtained at the earliest opportunity) [45]. Survival status is determined by review of the hospital chart and via follow-up calls; participants who cannot be contacted and have no in-hospital death recorded in their chart are considered lost to follow-up and survival is recorded as "unknown". Participants who are deceased at follow-up are assigned a HRQL score of 0. Secondary and tertiary outcome measures are summarized in Table 2.

Metabolomics sub-study

As short- and long-term clinical benefits are not mediated by cholecalciferol or 25OHD, but downstream changes in cell signaling and functioning of tissues/organs, we will perform essential translational research in a subset of 100 participants for whom enrollment and at least one set of post-intervention blood and urine samples have been collected > 48 h (range: Days 2–7, obtained as of July 2022). We will perform non-targeted metabolite profiling to better understand the effects of rapid VDD correction on human metabolism beyond calcium homeostasis, including stress response, antioxidant production, immunomodulation, and mitochondrial function [46]. Additionally, targeted metabolomics will be employed to better characterize changes following the single high-dose bolus by measuring vitamin D species beyond 25OHD [47] while also identifying new biomarkers that may predict inadequate vitamin D status or suboptimal responses to treatment [48].

Safety procedures

Participants are monitored for adverse events (AEs) from the time of intervention on a weekly basis during hospital admission (censored at 90 days) and through parent reporting at 28- and 90-day follow-ups. As the VITdALIZE-KIDS population is expected to experience AEs related to critical illness or its complications, a trial-specific definition of AEs is being used, as published by the CCCTG [49]. Specifically, in this trial, an AE is defined as any untoward medical occurrence that (1) is specified a priori as a safety endpoint (see below) or (2) is different from what is expected in the clinical course of the participant given their critical illness, co-morbidities, and related complications, AND may be related to the VITdALIZE-KIDS trial procedures (vitamin D administration and/or research procedures). Specified safety endpoints consist of the following AEs plausibly associated with vitamin D administration: (1) gastrointestinal bleeding (requiring transfusion) and/or perforation (requiring surgery) within 48 h of drug administration, (2) hypercalcemia persisting for more than and not occurring within 24 h of any parenteral bolus calcium administration AND one or more of renal failure requiring dialysis, nephrocalcinosis, hemodynamically significant arrhythmia, cardiorespiratory arrest, or death; and (3) nephrolithiasis with gross hematuria and/or nephrocalcinosis with renal failure. Should a trial participant develop significant symptoms related to vitamin D toxicity (potential drug-related adverse event), they are evaluated and followed by endocrinology and/or nephrology.

We follow Health Canada's guidelines for reporting AEs, which entails reporting AEs if they are serious, related to the intervention, and unexpected given the participants' critical illness, co-morbidities, related complications, and the known side effects of vitamin D toxicity. Similarly, we report AEs to local ethics boards according to local guidelines for reporting.

Sample size

The proposed sample size is 766 participants. Using the traditional *t*-test approach, 650 participants would provide 80% power ($\alpha = 0.05$) to detect a 4.4 point difference in the PedsQL™ 4.0 [41] (SD = 20) between study arms at day 28, corresponding to the minimal clinically important difference (MCID). MCID is defined as the smallest difference in a score that patients perceive to be beneficial and that would ideally mandate a change

Table 2 Secondary and tertiary outcomes for the VITdALIZE-KIDS trial

Secondary outcome	Time frame[1]	Outcome measure
New and/or progressive multiple organ dysfunction	Baseline; Days 0, 3, 7; Weekly until Day 28 or PICU discharge	The proportion of participants who develop new or progressive multiple organ dysfunction (NPMODS) is determined using the updated Pediatric Logistic Organ Dysfunction Score (PELOD-2). Organ dysfunction is defined as a PELOD-2 score > 0 for a given organ. For participants with no organ dysfunction at randomization, new MODS are defined as the development of ≥ 2 simultaneous organ dysfunctions during the 28 days following randomization. For participants with at least one pre-existing organ dysfunction at enrollment, it is defined as ≥ 1 new simultaneous organ dysfunction. Progressive MODS is defined as development of ≥ 1 additional simultaneous organ dysfunction in a participant with MODS at enrollment. All deaths are considered Progressive MODS
Tertiary (exploratory) outcome	Time frame[1]	Outcome measure
Functional status	Baseline, hospital discharge, Days 28, 90	Measured using the FSS, which was developed specifically for PICU research and has been validated against the pediatric cerebral and overall performance category (PCPC/POPC) scales. The FSS includes six functional domains (mental status, sensory function, communication, motor function, feeding, and respiratory status), and uses a 5-point scale to rate function from 1 (normal) to 5 (very severe dysfunction)
PICU and hospital length of stay (LOS)	N/A	LOS in PICU and hospital is determined from the time of PICU and hospital admission and from the time of trial drug administration
Serious adverse events and vitamin D toxicity	Enrollment to Day 90	We report on the frequency of (i) expected (i.e., safety endpoints specified in the study protocol) and unexpected serious adverse events plausibly associated with vitamin D administration and (ii) biochemical and clinical events potentially related to vitamin D (hypercalcemia, nephrocalcinosis/renal stones (symptomatic), gastric perforation/bleeding). This is monitored weekly during hospitalization (to a maximum of 90 days) and at Day 28 and Day 90
Mortality (alone)	Days 28, 90	Consistent with most critical care studies, we evaluate mortality alone at 28 and 90 days
HRQL at hospital discharge and 90 days	Discharge, Day 90	Measured using PedsQL™ tool, as in the primary outcome

[1] Time frames measured with reference to "Day 0" (day of trial drug administration). Baseline measurements are administered within 72 h of enrollment and inquire about the participant prior to admission. 28-day measurements are administered within a 28 ± 7-day window following enrollment. Hospital discharge measurements are administered for participants with hospital length of stay between 14 and 28 days (if administered within the 28-day window, no additional 28-day measurement is made). 90-day measurements are administered within a 90 ± 14-day window following enrollment

in patient management; it was calculated in previous work (based on the standard error of measurement, SEM [50]) to be 4.5 points by parent proxy report and 4.4 points by child report [41]. Based on our pilot RCT data and related PICU literature [42, 44], we anticipate mean baseline (pre-illness) and 28-day PedsQL™ Total Scale Scores in this study population of approximately 75 and 50, respectively. Consequently, the proposed effect size of 4.4 points difference in 28-day (absolute) total score between intervention and control arms translates to a 20% improvement in HRQL. After discussion with our executive committee, we believed this effect size to be realistic given the strong associations documented between VDD and clinical outcomes in observational studies combined with eligibility criteria (validated during our VITdAL-PICU pilot study) and ensures recruitment of a sick PICU cohort that could benefit from vitamin D optimization.

Based on our pilot VITdAL-PICU study [34] and related PICU studies [43], we anticipated no more than a 15% loss to follow-up at 28 days resulting in ~ 650 evaluable trial participants from the 766. Note that while anticipated mortality is 5–10% (7/67 in the VITdAL-PICU pilot trial), participants for whom this death has been recorded in their hospital chart and/or is communicated at follow-up will not be considered lost to follow-up but will instead be assigned a HRQL score of 0.

Recruitment, compliance, and follow-up

We did not anticipate problems with participant compliance with the trial protocol. Participants are hospitalized and followed by the research staff, and the intervention is administered by nursing staff and documented in the participant's medical record. Although we have planned for a liberal loss-to-follow up rate (15%) in our sample size calculation as participants are followed for 90 days after intervention, extensive efforts are put into participant retention (e.g., $25 gift cards for follow-up completions, collection of multiple points of contact for guardians and reminders sent via the preferred method). As ≤ 1000 IU/day vitamin D administration at care team discretion is allowable within our protocol (and an exclusion criterion is the intent of treating physician to administer doses above this for known clinical indications), we did not anticipate problems with physician compliance.

Data collection and management

Data collection is performed by research staff at each site, with 28- and 90-day follow-up assessments performed by the coordinating center staff for discharged participants. Data from questionnaires and medical records are entered into the web-based eCRF managed by The Ottawa Methods Centre—Electronic Data Capture System (OMC-EDCS) Platform, a validated EDCS platform used by over 100 studies in 15 countries for both regulated and non-regulated trials.

The following information is collected: demographic information and admission data, illness severity, relevant laboratory results and infection data, progression and resolution of organ dysfunction, fluid and inotrope administration, renal function and instances of calcium imbalance, occurrence of adverse events, length of mechanical ventilation, length of PICU and hospital stay, survival status, quality of life scores, and protocol deviations. All participant-related information (eCRFs, laboratory specimens, etc.) are kept strictly confidential. All records are kept in a secure, locked location and only research staff access the records. Participants are identified only by means of a coded number specific to each participant. The OMC-EDCS trial database is securely protected and encrypted. All computerized databases identify participants by numeric codes only.

Statistical analysis

Analyses will be performed using SAS® software (Cary, NC, USA) and will follow the intention-to-treat principle. A two-tailed p-value < 0.05 will be considered statistically significant. Study arms will be described and compared using (i) means with standard deviations or medians with inter-quartile range values for continuous variables or (ii) frequencies with percentages for categorical variables.

Primary outcome

The primary analytical plan will use the rank-based Mann–Whitney U test to compare 28-day PedsQL™ scores between the two arms. A non-parametric test is necessary as we do not expect PedQL™ data to be normally distributed, largely due to non-survivors being assigned a score of 0. Pre-specified secondary analysis of the primary outcome will also be done incorporating the PedsQL™ scores at baseline, 28 and 90 days. Participants who are lost to follow-up and do not complete the PedsQL™ at 28 days will be treated as missing in the analysis. Analysis will be done using a generalized linear repeated measures model accounting for repeated measurements on the same participant (a participant may die or be lost to follow-up). In this analysis, we will evaluate the relationship between the primary outcome measure and covariates such as baseline HRQL, 25OHD status, PedsQL™ age brackets, sex, kidney dysfunction according to RIFLE criteria [51], and illness severity measured using the pediatric risk of mortality (PRISM IV) score at enrollment. If potential relationships are observed, we will adjust for them in the analysis.

Secondary and tertiary outcomes

Other analyses will be evaluated between groups based on data type. Continuous outcome measures will be evaluated using the t-test or Mann–Whitney (where appropriate). Binary secondary outcome measures will be compared between the two treatment groups using Fisher's exact or Chi-square test. For the analysis of outcomes measures that represent time to event (PICU or hospital discharge), we will apply the log rank test and generate Kaplan–Meier curves. The analysis may be expanded to multivariate regression models (e.g., if uneven distribution of important variables is identified). Participants who are lost to follow-up and do not complete the PedsQL™ at 90 days will be treated as missing in the analysis of this tertiary outcome.

Metabolomics analysis

Non-targeted metabolomics analysis will be performed on blood and urine using an extensively validated multiplexed separation method for high throughput metabolic phenotyping based on multisegment injection-capillary electrophoresis-mass spectrometry (MSI-CE-MS) [52, 53]. This method is applicable to the analysis of a wide array of ionic/polar metabolites in volume-limited biological samples with stringent quality control protocol [52], including matching serum and urine specimens. These will be analyzed for speciation of multiple vitamin D metabolites using LC–MS/MS with parallel reaction monitoring, including the major catabolites of 25OHD3 such as the 3-epimer of 25OHD3 and 24,25$(OH)_2$D3 [54].

This technique will also allow measurement of less bioactive vitamin D catabolites that are not typically resolved by conventional immunoassays [55] but which may be more impacted by high-dose bolus intervention, when compared with low-dose daily restoration regimens [56]. Furthermore, comprehensive lipidomic analyses of serum extracts will be performed using reversed-phase liquid chromatography-mass spectrometry (LC–MS) since increases in 25OHD have been shown to generate favorable changes in several distinct lipid classes coinciding with lower 28-day mortality, including sphingomyelins, plasmalogens, lysoplasmalogens, and lysophospholipids [57]. Additional previously unexplored metabolites of potential clinical significance will be identified by acquiring high resolution MS/MS with confirmation by comparison with authentic standards, thus allowing for their biochemical interpretation [58]. Complementary multivariate and univariate statistical methods will then be used to reduce data dimensionality while ranking metabolites significantly associated with changes in serum 25OHD concentrations and HRQL after adjustment for multi-hypothesis testing (false discovery rate; $q < 0.05$) and confounders. We will also report on and compare (by interventional group) the enrollment and post-intervention levels of calcium:creatinine.

Subgroup analyses

As with the primary outcome, we will perform additional exploratory subgroup analysis based on the following baseline subgroup characteristics: 25OHD status (grouped by screening levels 0–29 nmol/L and 30–49 nmol/L), age, sex, kidney dysfunction (according to RIFLE criteria), and illness severity (PRISM IV score).

Interim analyses and DSMB

Interim analyses are scheduled to occur after primary outcome data becomes available for 100 participants (completed), and 383 participants (50% of sample size) are enrolled and have completed all study procedures, with CRFs locked (not yet completed). The second interim analysis will also include a planned futility analysis. As per the Data Safety Monitoring Board (DSMB) Charter, the trial will be stopped for futility if the conditional power of the observed difference at the interim analysis is < 20%.

The DSMB is comprised of two clinical experts (pediatric intensivist and nephrologist) and a biostatistician (DSMB chair). Terms of Reference were created and approved by all DSMB members and the PI before recruitment commenced. The DSMB functions independently and at arm's length from the trial investigators and the Steering Committee. The DSMB reviews trial deaths and adverse events potentially related to the trial intervention, makes recommendations to the Steering Committee based on these reviews regarding the continuation, modification, or termination of the trial, and comments on the relevance of new external published data from other trials that may impact on participant safety or efficacy of the trial treatments.

Monitoring

Sites are monitored once the first participant has been enrolled and primary outcome data obtained, then every 6 months (or more frequently as needed). Monitors ensure site adherence to protocol, GCP, and regulatory requirements.

Ethics and regulatory requirements

Approval from Health Canada and research ethics boards at all participating sites was obtained before the initiation of recruitment. Protocol amendments are communicated as necessary to those involved in the trial. Trial protocol was approved by Clinical Trials Ontario (CTO) (1761) and regulatory approval was obtained from Health Canada (control number 223325). The trial was first posted on Clinicaltrials.gov on November 15, 2018 (NCT03742505).

Close out

At trial close out, all research records will be retained for a minimum of 15 years. The trial drug will be returned to the coordinating center where it will be reconciled and destroyed according to site-specific pharmacy procedures and regulatory requirements. Trial data will only be accessible to the PI, research coordinator(s), or delegate.

Dissemination and access to data

The PI will submit the results of this trial for publication in a peer-reviewed journal. Metabolomics sub-study findings will be reported separately. Interim and final results will be presented at national and international scientific meetings, including at CCCTG meetings.

Data analysis will occur at the CHEO Research Institute (RI)/Ottawa Hospital Research Institute (OHRI).

Discussion

The prevalence and impact of VDD in critical illness is well established, both in Canada and around the world. Our group's international phase II dose evaluation trial, VITdAL-PICU [34], confirmed that a single loading dose of 10,000 IU/kg of cholecalciferol (maximum 400,000 IU) can rapidly restore blood 25OHD levels in deficient patients to physiological levels, with no evidence of toxicity or related AEs. The VITdALIZE-KIDS trial is the first phase III, multicenter RCT investigating the hypothesis that rapid normalization of vitamin

D status could represent a simple, inexpensive, and safe means of improving outcomes following pediatric critical illness. This trial is regulated by Health Canada and was confirmed to be compliant during a routine inspection by Health Canada (consisting of a sponsor inspection in May 2023 and two site inspections in June and September 2023).

To date, the DSMB has reviewed the first 100 participants enrolled with primary outcome data and did not have any concerns about safety, nor did they recommend any changes to the trial. However, during the recruitment phase of this trial, challenges to enrollment were encountered as outlined below. In light of these challenges, the Steering Committee and DSMB recommended that the trial continue at least until the interim analysis at 383 participants (50% enrollment target).

We had initially planned for 3 years of recruitment based on an expected 2–2.5 participants recruited per month per center (consistent with our experience across a wide variety of pediatric and adult RCTs) and assuming a VDD rate of 60–70%. However, we observed a lower-than-expected VDD rate of 41% (180 VDD out of 438 25OHD measured at the 100-participant interim analysis), resulting in an expected recruitment of an average of 1–2 participants per month per center, based on the current observed VDD rate. Additionally, due to the impact of COVID-19 related restrictions on family presence at the bedside and study staff presence and recruitment practice, it was necessary to make several modifications which have been documented by applying the CONSERVE protocol [59] and CONSERVE-SPIRIT checklist (Additional file 2). In light of these challenges, the recruitment duration has been amended to 6 years with a funding end date of March 2026.

Since initiating recruitment, we have also implemented several modifications to the protocol unrelated to COVID-19 that were aimed at removing barriers to enrollment and improving retention: (1) we have updated the length of stay (LOS) inclusion criterion from "expected PICU LOS > 48 h at trial enrollment" to the inclusion criterion of "PICU admission" and exclusion criterion of "expected PICU discharge prior to trial drug administration and/or expected hospital LOS < 3 days after enrollment." This 3-day cutoff was determined after 2.5 years of recruitment (January 2022), at which point 4595 patients had been excluded for this criterion, but on review of hospital LOS of enrolled participants to that point, fewer than 5% of patients were actually discharged prior to 48–72 h. This amendment ensured that only critically ill patients would be enrolled, but the number of eligible patients could be maximized. (2) The inclusion criterion of post-intervention bloodwork at > 48 h (range: Days 2–7) was initially included to ensure sample collection for the metabolomics sub-study and interim DSMB analysis, but this was removed when sufficient patients had been enrolled to complete these (July 2022). Similarly, all post-intervention blood and urine collection also concluded at this point, to lessen the burden for families and trial sites. Additionally, more minor changes to the protocol are presented in Additional file 3.

Conclusion

High VDD rates in Canadian PICUs are associated with worse clinical outcome for patients and higher healthcare costs. Recognized interactions between vitamin D status and the health of multiple organ systems suggest this could represent an inexpensive, safe means of improving outcomes both in terms of patient health and PICU resource use. However, the effect of rapid normalization of vitamin D status on clinical outcomes following pediatric critical illness has never been evaluated in a clinical trial, prior to this RCT. Trial findings will be used to inform guidelines for vitamin D supplementation.

Trial status

Recruitment for the VITdALIZE-KIDS trial is expected to continue until March 2026 and was started at sites on the following dates: Children's Hospital of Eastern Ontario (June 17, 2019), London Health Sciences Centre (September 26, 2019), Montreal Children's Hospital (September 9, 2020), Centre hospitalier universitaire Sainte-Justine (November 18, 2020), McMaster Children's Hospital (January 13, 2021), Alberta Children's Hospital (February 10, 2021), BC Children's Hospital (April 5, 2021), The Hospital for Sick Kids (December 13, 2021), Stollery Children's Hospital (January 30, 2023), and IWK Health Centre (May 8, 2023). At the time of this manuscript development, recruitment has not yet started at Centre mère-enfant Soleil du CHU de Québec Université Laval. As of April 20, 2024, approximately 55% ($n = 419$) of the target sample size has been enrolled with approximately 98% ($n = 411$) of those having completed all study procedures, and the interim analysis has been scheduled. Protocol v25-Oct-2023 is currently in use.

Abbreviations

VDD	Vitamin D deficiency
HRQL	Health-related quality of life
PICU	Pediatric intensive care unit
NAM	National Academy of Medicine
UL	Tolerable upper intake level
CHD	Congenital heart disease
25OHD	25-Hydroxyvitamin D
CCCTG	Canadian Critical Care Trials Group
SPIRIT	Standard protocol items: recommendations for interventional trials
GCP	Good clinical practice
DCC	Data coordinating center
OHRI	Ottawa Hospital Research Institute
eCRF	Electronic case report form

NPMODS	New or progressive multiorgan dysfunctions
PELOD-2	Pediatric logistic organ dysfunction score
FSS	Functional status scale
MSI-CE-MS	Multisegment injection-capillary electrophoresis-mass spectrometry
LC-MS	Liquid chromatography-mass spectrometry
AE	Adverse events
MCID	Minimal clinically important difference
OMC-EDCS	Ottawa Methods Centre-Electronic Data Capture System
DSMB	Data safety monitoring board

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08461-7.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions
DM is the principal investigator for the trial and took the lead in conceptualizing the study design with the help of KO, LM, TR, PG, GG, and the trial Steering Committee (KA, KM, DAF). KC, FC, JRF, AF, PF, EG, AG, ARJ, LL, SM, SJP, LR, and MT are qualified investigators at participating sites and oversee recruitment and acquisition of study data. PB-M and EH provided input into the protocol regarding biological sample collection and analysis and will perform the biochemical analysis. AK designed the intervention and is responsible for the acquisition and analysis of data related to regulatory compliance. KO, LA, and DM drafted the manuscript. All authors reviewed the manuscript critically for important intellectual content and have read and approved the final manuscript.

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Availability of data and materials
Participant level trial data will not be sent to other sites or researchers. Co-investigators and non-co-investigators may submit sub-study proposals for review by the principal investigator and Steering Committee for input (co-investigator proposals will have priority). Data analysis will take place at CHEO RI/OHRI and aggregate data corresponding to what is standard for a manuscript will be provided to co-authors. If participant level data is required, a data sharing agreement will be obtained between institutions.

Declarations

Ethics approval and consent to participate
This trial was conducted in accordance with the Declaration of Helsinki and approved by the Children's Hospital of Eastern Ontario (coordinating center) Research Ethics Board (Clinical Trials Ontario REB number: 1761, provincial approval granted April 10, 2019; institutional approval granted April 29, 2019). REB approval was also received from all other academic centers prior to trial commencement at those sites. Written, informed consent to participate was obtained from all participants and/or their parent or legal guardian.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]CHEO Research Institute, Children's Hospital of Eastern Ontario, Ottawa, ON, Canada. [2]Department of Pediatrics, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada. [3]Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Graz, Austria. [4]Department of Chemistry and Chemical Biology, McMaster University, Hamilton, ON, Canada. [5]Department of Pediatrics, Critical Care Division, Centre Mère-Enfant Soleil du CHU de Québec, Université Laval, Quebec City, QC, Canada. [6]Departments of Pediatrics and Critical Care, McMaster Children's Hospital, McMaster University, Hamilton, ON, Canada. [7]Department of Pediatric Critical Care, IWK Health, Halifax, NS, Canada. [8]Department of Critical Care, Dalhousie University, Halifax, NS, Canada. [9]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada. [10]Ottawa Hospital Research Institute, Ottawa, ON, Canada. [11]Department of Medicine, University of Ottawa, Ottawa, ON, Canada. [12]Department of Critical Care Medicine, The Hospital for Sick Children, Toronto, ON, Canada. [13]Labatt Family Heart Centre, Division of Cardiac Surgery, Department of Pediatrics, Hospital for Sick Children, Toronto, ON, Canada. [14]Division of Pediatric Critical Care, Department of Pediatrics, McGill University, Montreal, QC, Canada. [15]Department of Epidemiology, Biostatistics and Occupational Health, Department of Pediatrics, McGill University, McGill University, MontrealMontreal, QC, Canada. [16]Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada. [17]Pediatric Critical Care, Department of Pediatrics, University of Calgary, Alberta Children's Hospital, Calgary, Canada. [18]Department of Pediatrics, University of Alberta, Edmonton, AB T6G 1C9, Canada. [19]Stollery Children's Hospital, Edmonton, AB, Canada. [20]Department of Paediatrics, Schulich School of Medicine & Dentistry, Western University, Children's Health Research Institute, LondonLondon, ONON, Canada. [21]Euro-Pharm International Canada Inc, Montreal, Canada. [22]Department of Pediatrics, University of Alberta, Edmonton, AB, Canada. [23]Department of Pediatrics, Cummings School of Medicine, University of Calgary, Calgary, AB, Canada. [24]Faculty of Nursing, University of Calgary, Calgary, AB, Canada. [25]Division of Critical Care, Department of Medicine, University of Ottawa, Ottawa, Canada. [26]Division of Critical Care, Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada. [27]Division of Pediatric Critical Care Medicine, Department of Pediatrics, Sainte Justine and Montreal Heart Institute, University of Montreal, Montreal, QC, Canada.

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References

1. Pollack MM, Holubkov R, Funai T, et al. Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: a new paradigm for outcomes assessment. Crit Care Med. 2015;43(8):1699.
2. Aspesberro F, Mangione-Smith R, Zimmerman JJ. Health-related quality of life following pediatric critical illness. Intensive Care Med. 2015;41(7):1235–46.
3. Conlon NP, Breatnach C, O'Hare BP, et al. Health-related quality of life after prolonged pediatric intensive care unit stay. Pediatr Crit Care Med. 2009;10(1):41–4.
4. Pinto NP, Rhinesmith EW, Kim TY, et al. Long-term function after pediatric critical illness: results from the survivor outcomes study. Pediatr Crit Care Med. 2017;18(3):e122–30.
5. Lee P, Nair P, Eisman JA, et al. Vitamin D deficiency in the intensive care unit: an invisible accomplice to morbidity and mortality? Intensive Care Med. 2009;35(12):2028–32.
6. Amrein K, Venkatesh B. Vitamin D and the critically ill patient. Curr Opin Clin Nutr Metab Care. 2012;15(2):188–93.
7. Gauthier B, Trachtman H, Di Carmine F, et al. Hypocalcemia and hypercalcitoninemia in critically ill children. Crit Care Med. 1990;18(11):1215–9.
8. Baeke F, Gysemans C, Korf H, et al. Vitamin D insufficiency: implications for the immune system. Pediatr Nephrol. 2010;25:1597–606.
9. Jeng L, Yamshchikov AV, Judd SE, et al. Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. J Transl Med. 2009;7:1–9.
10. Banwell B, Mildner R, Hassall A, et al. Muscle weakness in critically ill children. Neurology. 2003;61(12):1779–82.

11. Al-Said YA, Al-Rached HS, Al-Qahtani HA, et al. Severe proximal myopathy with remarkable recovery after vitamin D treatment. Can J Neurol Sci. 2009;36(3):336–9.
12. McNally JD, Menon K, Chakraborty P, et al. The association of vitamin D status with pediatric critical illness. Pediatrics. 2012;130(3):429–36.
13. Rippel C, South M, Butt WW, et al. Vitamin D status in critically ill children. Intensive Care Med. 2012;38(12):2055–62.
14. Cariolou M, Cupp MA, Evangelou E, et al. Importance of vitamin D in acute and critically ill children with subgroup analyses of sepsis and respiratory tract infections: a systematic review and meta-analysis. BMJ Open. 2019;9(5): e027666.
15. He M, Cao T, Wang J, et al. Vitamin D deficiency relation to sepsis, paediatric risk of mortality III score, need for ventilation support, length of hospital stay, and duration of mechanical ventilation in critically ill children: a meta-analysis. Int J Clin Pract. 2021;75(4): e13908.
16. McNally JD, Nama N, O'Hearn K, et al. Vitamin D deficiency in critically ill children: a systematic review and meta-analysis. Crit Care. 2017;21(1):1–13.
17. McNally JD, Doherty DR, Lawson ML, et al. The relationship between vitamin D status and adrenal insufficiency in critically ill children. J Clin Endocrinol Metab. 2013;98(5):E877–81.
18. Abou-Zahr R, Kandil SB. A pediatric critical care perspective on vitamin D. Pediatr Res. 2015;77(1):164–7.
19. Suzuki AS, Berbel BT. Pediatric multiple organ dysfunction syndrome promising therapies: what about vitamin D supplementation? Pediatr Crit Care Med. 2017;18(7):731.
20. McNally JD. Vitamin D as a modifiable risk factor in critical illness: questions and answers provided by observational studies. Journal de Pediatria (Rio J). 2014;90(2):99–101.
21. Lee P. Vitamin D metabolism and deficiency in critical illness. Best Pract Res Clin Endocrinol Metab. 2011;25(5):769–81.
22. Higgins DM, Wischmeyer PE, Queensland KM, et al. Relationship of vitamin D deficiency to clinical outcomes in critically ill patients. J Parenter Enter Nutr. 2012;36(6):713–20.
23. Menger J, Lee Z-Y, Notz Q, et al. Administration of vitamin D and its metabolites in critically ill adult patients: an updated systematic review with meta-analysis of randomized controlled trials. Crit Care. 2022;26(1):268.
24. Hill A, Starchl C, Dresen E, et al. An update of the effects of vitamins D and C in critical illness. Front Med. 2023;9: 1083760.
25. Zajic P, Amrein K. Vitamin D deficiency in the ICU: a systematic review. Minerva Endocrinology. 2014;39(4):275–87.
26. Kaur M, Soni KD, Trikha A. Does vitamin D improve all-cause mortality in critically ill adults? An updated systematic review and meta-analysis of randomized controlled trials. Indian Journal of Critical Care Medicine: Peer-Reviewed, Official Publication of Indian Society of Critical Care Medicine. 2022;26(7):853.
27. Langlois PL, Szwec C, D'Aragon F, et al. Vitamin D supplementation in the critically ill: a systematic review and meta-analysis. Clin Nutr. 2018;37(4):1238–46.
28. Amrein K, Parekh D, Westphal S, et al. Effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients with severe vitamin D deficiency: a study protocol of a multicentre, placebo-controlled double-blind phase III RCT (the VITDALIZE study). BMJ Open. 2019;9(11): e031083.
29. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53–8.
30. Lewis RD, Laing E, Hill Gallant K, et al. A randomized trial of vitamin D3 supplementation in children: dose-response effects on vitamin D metabolites and calcium absorption. J Clin Endocrinol Metab. 2013;98(12):4816–25.
31. Amrein K, Schnedl C, Holl A, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA. 2014;312(15):1520–30.
32. McNally JD, Iliriani K, Pojsupap S, et al. Rapid normalization of vitamin D levels: a meta-analysis. Pediatrics. 2015;135(1):e152–66.
33. Gottschlich MM, Mayes T, Khoury J, et al. Clinical trial of vitamin D2 vs D3 supplementation in critically ill pediatric burn patients. J Parenter Enter Nutr. 2017;41(3):412–21.
34. O'Hearn K, Menon K, Weiler HA, et al. A phase II dose evaluation pilot feasibility randomized controlled trial of cholecalciferol in critically ill children with vitamin D deficiency (VITdAL-PICU study). BMC Pediatr. 2023;23(1):397.
35. Sahu MK, Bipin C, Niraghatam HV, et al. Vitamin D deficiency and its response to supplementation as "stoss therapy" in children with cyanotic congenital heart disease undergoing open heart surgery. Journal of Cardiac Critical Care TSS. 2019;3(01):17–23.
36. Labib JR, Ibrahem SK, Ismail MM, et al. Vitamin D supplementation and improvement of pneumonic children at a tertiary pediatric hospital in Egypt: a randomized controlled trial. Medicine. 2021;100(13):e25011.
37. Wang Y, Yang Z, Gao L, et al. Effects of a single dose of vitamin D in septic children: a randomized, double-blinded, controlled trial. J Int Med Res. 2020;48(6):0300060520926890.
38. El-Gendy FM, Khattab AA, Naser RG, et al. Association between vitamin D deficiency and sepsis in pediatric ICU. Menoufia Medical Journal. 2021;34(1):210.
39. Merritt C, Menon K, Agus MS, et al. Beyond survival: pediatric critical care interventional trial outcome measure preferences of families and healthcare professionals. Pediatr Crit Care Med. 2018;19(2):e105–11.
40. Gaudry S, Messika J, Ricard J-D, et al. Patient-important outcomes in randomized controlled trials in critically ill patients: a systematic review. Ann Intensive Care. 2017;7(1):1–11.
41. Varni JW, Burwinkle TM, Seid M, et al. The PedsQL™* 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambulatory Pediatrics. 2003;3(6):329–41.
42. Aspesberro F, Fesinmeyer MD, Zhou C, et al. Construct validity and responsiveness of the pediatric quality of life inventory 4.0 generic core scales and infant scales in the PICU. Pediatr Crit Care Med. 2016;17(6):e272–9.
43. Colville GA, Pierce CM. Children's self-reported quality of life after intensive care treatment. Pediatr Crit Care Med. 2013;14(2):e85–92.
44. Ebrahim S, Singh S, Hutchison JS, et al. Adaptive behavior, functional outcomes, and quality of life outcomes of children requiring urgent ICU admission. Pediatr Crit Care Med. 2013;14(1):10–8.
45. Dritsaki M, Achana F, Mason J, et al. Methodological issues surrounding the use of baseline health-related quality of life data to inform trial-based economic evaluations of interventions within emergency and critical care settings: a systematic literature review. Pharmacoeconomics. 2017;35(5):501–15.
46. Christopher KB. Nutritional metabolomics in critical illness. Curr Opin Clin Nutr Metab Care. 2018;21(2):121.
47. Jenkinson C. The vitamin D metabolome: an update on analysis and function. Cell Biochem Funct. 2019;37(6):408–23.
48. Lasky-Su J, Dahlin A, Litonjua AA, et al. Metabolome alterations in severe critical illness and vitamin D status. Crit Care. 2017;21:1–10.
49. Cook D, Lauzier F, Rocha MG, et al. Serious adverse events in academic critical care research. CMAJ. 2008;178(9):1181–4.
50. Wyrwich KW, Tierney WM, Wolinsky FD. Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. J Clin Epidemiol. 1999;52(9):861–73.
51. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:1–9.
52. Shanmuganathan M, Kroezen Z, Gill B, et al. The maternal serum metabolome by multisegment injection-capillary electrophoresis-mass spectrometry: a high-throughput platform and standardized data workflow for large-scale epidemiological studies. Nat Protoc. 2021;16(4):1966–94.
53. Kuehnbaum NL, Kormendi A, Britz-McKibbin P. Multisegment injection-capillary electrophoresis-mass spectrometry: a high-throughput platform for metabolomics with high data fidelity. Anal Chem. 2013;85(22):10664–9.
54. Ketha H, Thacher TD, Oberhelman SS, et al. Comparison of the effect of daily versus bolus dose maternal vitamin D3 supplementation on the 24, 25-dihydroxyvitamin D3 to 25-hydroxyvitamin D3 ratio. Bone. 2018;110:321–5.
55. Helmeczi E, Fries E, Perry L, et al. A high-throughput platform for the rapid screening of vitamin D status by direct infusion-MS/MS. J Lipid Res. 2022;63(5):100204.
56. Griffin G, Hewison M, Hopkin J, et al. Perspective: vitamin D supplementation prevents rickets and acute respiratory infections when given as daily maintenance but not as intermittent bolus: Implications for COVID-19. Clin Med. 2021;21(2): e144.

57. Amrein K, Lasky-Su JA, Dobnig H, et al. Metabolomic basis for response to high dose vitamin D in critical illness. Clin Nutr. 2021;40(4):2053–60.
58. Yamamoto M, Pinto-Sanchez MI, Bercik P, et al. Metabolomics reveals elevated urinary excretion of collagen degradation and epithelial cell turnover products in irritable bowel syndrome patients. Metabolomics. 2019;15:1–18.
59. Orkin AM, Gill PJ, Ghersi D, et al. Guidelines for reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances: the CONSERVE 2021 statement. JAMA. 2021;326(3):257–65.

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