Title: Randomized Clinical Trial of Hypovitaminosis D Treatment in the Neurocritical Care Unit
IRB#: IRB_00091541
IND#: 131398
Date: 8/30/17

Randomized Clinical Trial of Hypovitaminosis D Treatment in the Neurocritical Care Unit

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1. Abstract

Vitamin D has been shown as an important marker of prognosis in a variety of clinical settings, including overall mortality, acute respiratory distress syndrome (ARDS), infection/sepsis, asthma, cardiovascular disease, diabetes, and pediatric/medical/surgical intensive care unit outcomes. Vitamin D not only plays a role in bone maintenance, but also a variety of extra-axial functions including immune-dysregulation and systemic inflammation. In addition, a number of randomized clinical trials support the supplementation of vitamin D as improving outcome in critical care patients. While the evaluation of vitamin D levels remains a standard-of-care at our institution, the widespread use of vitamin D monitoring and impact on neurocritical care patients remains limited. Our recent prospective observational study of vitamin D levels in neurocritical patients showed that deficiency (<20ng/ml) was highly associated with prolonged hospital stay and increased in-hospital mortality for emergent patients. Moreover, a number of limitations arise from this study due to its observational nature. **This study proposes a randomized, double-blinded, placebo-controlled, single center evaluation of vitamin D supplementation in the neurocritical care patient population (Table 1). Patients admitted to the neurocritical care unit for emergent cases and with vitamin D deficiency (<20ng/ml) will undergo vitamin D serum draw on admission and be randomized to receive cholecalciferol/vitamin D3 supplementation (540,000 IU once orally) or placebo with the primary measured outcome being hospital length-of-stay.** Secondary outcomes will include length of hospital course, length of ICU course, complications, adverse events, discharge Glasgow Outcome Score, in-hospital and 30-day mortality, as well as quality-of-life. Power analysis estimates 198 patients will be needed for each subgroup to determine a 2 day difference in length-of-stay, and we plan to recruit 218 patients per treatment arm to account for dropout, which will take approximately 6-9 months to recruit. Interim analysis and safety monitoring will be performed. We hypothesize that vitamin D supplementation may make a significant impact on reducing morbidity and mortality in the neurocritical care population. The possibility of reducing hospital length of stay and mortality from a simple and cheap intervention such as vitamin D supplementation may be a useful adjuvant treatment in the neurocritical care population.

2. Background/Rationale

Hypovitaminosis D has a high prevalence among the general population, with some studies showing over half of the elderly population being affected (Chapuy 1997). Among critically ill patients, various studies have shown associations between hypovitaminosis D and multiple negative outcomes including mortality (De Haan 2014,

Rech 2014), ARDS (Dancer 2015), and infection (Flynn 2012). Vitamin D deficiency has also been shown to have impacts on various neurological diseases such as stroke (Yalbuzdag 2015, Chung 2015), and dementia (Littlejohns 2014). While the mechanism between vitamin D deficiency and these diseases is not entirely known, evidence suggest that vitamin D can affect vascular reactivity, inflammation, and the immune system (Carthy 1989, Vargas-Vasserot 2011) (Table S1, Figure S1-2).

Vitamin D has been shown to impact prognosis in a variety of retrospective and randomized clinical trials within an intensive care unit (ICU) environment (Amrein 2011). **Despite these findings, there have been no studies examining the impact of hypovitaminosis D in specialized neurocritical care units (NCCU).** Given the often significant differences in the management of patients in NCCU and more generalized intensive care units (Kurtz 2011) there is a need for further inquiries into the impact of low vitamin D levels in this specific environment. **This study proposes a randomized, double-blinded, placebo-controlled, single center evaluation of vitamin D supplementation in the emergent NCCU patient population (Table 1)**. We have previously conducted a prospective, observational analysis of 823 NCCU patients and shown a significant reduction in hospital length-of-stay for all patients (7.14 vs. 5.97 days, p=0.0018) and for emergent cases (8.21 vs. 6.36 days, p=0.038), as well as reduced in-hospital mortality for emergent patients with non-deficient vitamin D levels (26/203 vs. 22/321, p=0.021). Nevertheless, these results remain limited in being observational studies without randomization or controls.

3. Study purposes and objectives

1. Evaluate the impact of vitamin D supplementation on the length-of-stay of emergent neurocritical care patients (primary outcome)
2. Evaluate the impact of vitamin D supplementation on in-hospital mortality, ICU length-of-stay, Glasgow Outcome Score on discharge, complications, and quality-of-life metrics (secondary outcome)
3. Evaluate the impact of vitamin D supplementation on Glasgow Outcome score and quality-of-life metrics at 3 and 6 months post-discharge (secondary outcome)

4. Methods

4.1. Inclusion criteria

- Patients >18 years of age
- Patients admitted to the neurosurgery or neurology services
- Patients admitted to a critical care unit
- Informed consent
- Expected to stay in the ICU for 48 hours or more
- Vitamin D deficiency (<20ng/ml)

4.2. Exclusion criteria

- Patients where a vitamin D level was not drawn within 48 hours of admission
- Patients not randomized within 48 hours of admission
- Readmitted patients to the critical care unit
- Lack of informed consent

- Prior supplementation with vitamin D
- Severely impaired gastrointestinal function
- Other trial participation
- Pregnant or lactating women
- Hypercalcemia (total calcium of >10.6 mg/dL or ionized serum calcium of >5.4 mg/dL
- Tuberculosis history or clinical exam
- Sarcoidosis history or clinical exam
- Nephrolithiasis within the prior year
- Patients not deemed suitable for study participation (ie, psychiatric disease, living remotely from the clinic, or prisoner status)
- Pregnant or nursing women

4.3. General protocol

1. Patients will be identified through primary treatment teams, including the Departments of Neurosurgery and Neurology, and through screening of the electronic medical record for patients admitted to the NCCU at the University of Utah Health Sciences Center. Patients admitted for non-elective indications as outlined in the inclusion criteria will be enrolled. The full inclusion and exclusion criteria are listed in Table 1. We expect most patients to be admitted to the neurosurgery service and NCCU.
2. A Vitamin D level will be drawn on all non-electively admitted NCCU patients as part of our standard admission protocol.
3. Patients with a Vitamin D level <20ng/ml, defined as deficient, will be consented for the trial. Patients that do not consent for the trial will be studied retrospectively as part of our standard-of-care similarly to our previous prospective trial. Women between 18-45 years of age will undergo a serum or urine pregnancy test to rule out pregnancy prior to enrollment.
4. Patients will be randomized 1:1 to receive Cholecalciferol (Vitamin D3, 540,000 IU once orally or by feeding) immediately or placebo by random number generator. Treatments will be blinded to the patient and physician care teams. Placebos will include similar tablets or liquid formulations that mimic the treatment drug but are indistinguishable.
5. A subsequent Vitamin D level will be drawn 3 days after drug administration or on date of discharge if sooner than 3 days to evaluate the adequacy of vitamin D repletion.
6. Primary outcomes will total hospital length-of-stay. Secondary outcomes will include in-hospital mortality, ICU length-of-stay, ICU complications (rates of sepsis/bacteremia, pneumonia, urinary tract infection), discharge Glasgow Outcome Score, medication adverse events, and quality-of-life metrics. Various patient demographic data will be acquired.
7. Subsequent 30-day mortality will be measured on standard clinical follow-up.

8. 1, 3 month and 6 month Glasgow Outcome Scores and quality-of-life metrics will be obtained. Physical therapy gait distance measurements as well as modified Rankin scale on discharge will be obtained.

4.4. Safety monitoring

There are minimal risks related to the patient. Vitamin D treatment is a relatively safe procedure in properly selected individuals. There may be additional discomforts including close monitored by the research team in order to monitor the study and collect data. The risk and side effects for Vitamin D administration are minimal and discussed further in the drug description. We have outlined a detailed data and safety monitoring plan.

We have previously shown Vitamin D administration in our prospective, observational study for patients with Vitamin D levels <10ng/ml to be safe and without any adverse effect at dosages of 50,000 IU Qweek of ergocalciferol/vitamin D2. The dosages used in this study are comparable to other studies evaluating Vitamin D efficacy and safety (Bacon 2009, Von Restorff 2009, Amrein 2011, Amrein 2014). There was no reported adverse event from ergocalciferol/vitamin D2 administration during our prospective, observational trial along with recent trials evaluating cholecalciferol/vitamin D3.

For patient safety, we will continue daily monitoring of CBC, BMP, Calcium, Phosphate, and neurological examinations as per standard practice in the neurocritical care unit. Should risks be identified, modification of the protocol will be proposed. And should the trial prove unsafe, we plan to notify the IRB and terminate the study. The study principal investigator and co-investigators will be responsible for oversight of patient safety. In addition, an independent safety and data review committee of licensed physicians will evaluate the study data on a quarterly basis. Quarterly safety and data monitoring reports will be discussed among the investigators and safety committee. The study will remain double-blinded except in the case of possible safety issues warranting unblinding.

Participants will be withdrawn from the study should they demonstrate >grade 3 Common Terminology Criteria for Adverse Events (CTCAE) suggesting Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated. In addition, patients will be withdrawn from the study should they show other signs/symptoms of vitamin D toxicity including, hypercalcemia, anorexia, nausea, vomiting, as well as polyuria, polydipsia, weakness, nervousness, pruritus, laboratory studies suggesting renal injury or failure (proteinuria, urinary casts, azotemia, metastatic renal calcifications). A checklist will be used to monitor patients. These findings can be uncovered by routine neurological and laboratory exams as per the ICU standard. Should adverse events be identified at higher or clustered rates than expected statistically, the trial will be modified or terminated.

4.5. Informed consent

The goals of the study, including potential benefit and minimal risk, will be discussed. Patients will be told that not participating in the study will not affect their hospital care. We will provide patients with a copy of the informed consent containing contact information for the investigators. In addition, we will inform the critical care staff,

including nursing and administration, regarding the study so patients can find the appropriate research staff should they have questions. All interim and data safety analysis when analyzed will be immediately conveyed to all study participants in the event of potential adverse events or risks.

In some cases a legally authorized representative (LAR) will be used for informed consent of the patient. Many of the emergent patients admitted to the NCCU will not have the capacity for an informed consent. LARs may include spouses or patient children, as well as authorized legal healthcare proxies, depending on policies for informed consent at the University of Utah Health Sciences Center. As with studies of Vitamin D in other critical care settings, patient consent through a proxy may be possible. We will include a LAR signature block at the end of the consent document.

Phone consents will be allowed as part of the trial to ensure timely consent. Similar, to surgical or procedural consents, phone consents will involve discussion with a LAR and informed consent will be documented by the study investigator as well as a witness, usually the patient's nurse. Phone consents will be performed when the patient is incapacitated and family is unable to reach the hospital to sign the paper consent.

4.6. Privacy protection

Information about each participant, including the results of tests, will be confidential. Each participant will be assigned a study number and we will not use the participant's name in our study records. Paper records will be kept in a locked file cabinet in a secure room. Computerized records will be kept in a locked room on password-protected computers. The participant's name will not be used in any published reports.

4.7. Facilities and staff

The principal investigator and co-investigators are all licensed physicians within the department of neurosurgery with experience in both basic and clinical science research. All investigators have had prior database research experience, including IRB submission as well as data acquisition and analysis. The faculty advisor, is a licensed physician as well as a board-certified neurosurgeon and Assistant Professor at the University of Utah, has also reviewed the protocol and will be involved in patient safety monitoring as well as quality control. He has been involved in our prior prospective, observational study on Vitamin D status of neurocritical care patients. The project will be discussed by meetings and by email as necessary to discuss results, patient safety issues, and data quality. All investigators are already trained in research methodology, have completed CITI certification, receive annual training on research bioethics through the Department of Neurosurgery, and have been trained on aspects of informed consent.

The research will be primarily performed at the University of Utah Hospital. Some data analysis may be performed on computers within the Neurosciences Center at the University. The NCCU at the University Hospital will be the predominant facility used for research activity. Other ICUs will be used if neurosurgery or neurology patients are admitted. All information related to be data will be kept in a HIPAA-compliant database or locked cabinet units only accessed by the principal investigator. The University of Utah Neurocritical Care Unit (NCCU) NCCU is a 23-bed intensive care unit which

specializes in the treatment of patients with critical neurological illness, such as stroke, intracranial hemorrhage, status epilepticus, traumatic brain injury, and meningitis. The NCCU is the region's largest and most technologically advanced critical care unit and the catchment are for the NCCU comprises 20% of the geographical area of the continental United States. Nurses specially trained in caring for neurological patients who require intensive care staff the NCCU in conjunction with 5 neurointensivists and a multidisciplinary team of neurologists and neurosurgeons. L SEP

4.8. Selection of therapeutic agent

Patients will be supplemented with cholecalciferol (vitamin D3) or placebo. Two major vitamin D compounds exist in humans, ergocalciiferol (vitamin D2) and cholecalciferol (vitamin D3) and recent guidelines suggest that either vitamin D2 or vitamin D3 can be supplemented in patients with hypovitaminosis D (Holick 2011). One study evaluating short-term supplementation with vitamin D2 in an critical care setting demonstrate that only 26% of patients receiving 50,000 IU three times per week achieved normal vitamin D levels (Dickerson 2015). Critically ill patients have been suggested to have a blunted response to vitamin D supplementation. Nonetheless, a number of randomized trials have shown the ability of high dose vitamin D3 to adequate replete critically ill patients with minimal toxicity, mostly mild hypercalcemia (Quraishi 2015, Nair 2015, Amrein 2011, Amrein 2014). Intramuscular (200,000 IU) or oral (540,000 IU) have been shown to adequately replete vitamin D levels in the majority of patients by 2-7 days after treatment. For this reason we have chosen to supplement with cholecalciferol (540,000 IU orally).

4.9. Power analysis and statistical plan

A variety of variables will be collected on patients (Table 2). We estimated various sample sizes based on our preliminary, prospective, observational trial. Using length-of-stay as a primary outcome, previously we detected a significant decrease in patients with sufficient vitamin D levels (>20ng/ml) (8.21 vs. 6.36 days, p=0.002). Using an effect size of 2, alpha of 0.05, 1:1 case/control sampling, we estimate 198 patients will be required per group for this study. We plan to recruit patients to account for a 10% dropout resulting in 218 patients per group, total 436. We also performed power calculations using various other outcomes including, in-hospital mortality, as well as evaluation of both emergent and non-emergent patients. Based on a 6-month timeframe needed to enroll 512 patients in our prospective, observational trial, we estimate the trial would take 12 months for enrollment and randomization in the proposed trial. The primary outcome (length-of-stay) will be measured by T-test as well as multivariate regression to adjust for potential confounders using SPSS (IBM, Armonk, NY). Secondary outcomes will be evaluated by a variety of statistical methods.

4.10. Funding source

Planned sources of funding for this study are from internal departmental grants without potential for conflicts-of-interest. No submission for additional funding sources is planned at this time.

5. Anticipated results and potential public health impact

The potential benefit of this study would include knowledge about the success of vitamin D supplementation on various critical care outcomes. While they may not directly apply to a patient, they can be useful to additional critical care patients admitted an ICU in the future. The societal benefit will include reduced patient morbidity and mortality, as well as shorter hospital stays and therefore reduced ICU expenditure. Vitamin D is a relatively cost-effective medication that is well-tolerated. Its potential impact to reduce hospital stays, by even 1 day would play a significant role in reducing patient cost, disease morbidity, and risk from hospitalization. Future research directions can involve a multi-center randomized clinical trial to validate the effect of vitamin D in the neurocritical care patient as well as further molecular studies evaluating the non-skeletal effects of vitamin D. Additional, studies on vitamin D as a biomarker and effects on a cellular level can also be forthcoming if a potential benefit is identified clinically. Identification of the molecular mechanisms by which vitamin D may alter disease pathology may serve as a method for the development of additional treatments.

6. Protocol amendments

6.1. 1/10/17, Addition of phone consents as well as two study co-investigators, Aatman Shah, MD and Al-Wala Awad, MD was performed. Repeat vitamin D levels at 3 days following administration of study drug or placebo was modified from prior planned repeat vitamin D at 7 days.

6.2. 8/6/17, Addition of physical therapy assessment and modified Rankin scale as secondary outcomes of the study. Change of study faculty sponsor from Dr. Min S. Park to Dr. Sarah T. Menacho as Dr. Park is leaving the University of Utah.

Table 1: Summary of Study Characteristics	
Title	**Randomized Clinical Trial of Hypovitaminosis D Treatment in the Neurocritical Care Unit**
Methodology	Randomized, double-blinded, placebo-controlled clinical trial
Study Duration	1-1.5 years (12 months recruitment, 3-6 month analysis)
Study Center(s)	University of Utah Health Sciences Center
Objectives	1. Evaluate the impact of vitamin D supplementation on the length-of-stay of emergent neurocritical care patients (primary outcome) 2. Evaluate the impact of vitamin D supplementation on in-hospital mortality, ICU length-of-stay, Glasgow Outcome Score on discharge, complications, and quality-of-life metrics (secondary outcome)
Primary Aims	Length-of-stay
Secondary Aims	ICU length-of stay, in-hospital mortality, 30-day mortality, ICU complications (sepsis, pneumonia, urinary tract infection), Glasgow Outcome Score, medication adverse events , modified Rankin Scale, physical therapy assessments
Number of Subjects	218 per treatment arm, total 436
Intervention	Vitamin D3 540,000 IU oral vs. placebo
Diagnosis and Main Inclusion Criteria	Patients >18 years of age Patients admitted to the neurosurgery or neurology services Patients admitted to a critical care unit Informed consent Expected to stay in the ICU for 48 hours or more Vitamin D deficiency (<20ng/ml)
Exclusion criteria	Patients where a vitamin D level was not drawn within 48 hours of admission Patients not randomized within 48 hours of admission Readmitted patients to the critical care unit Lack of informed consent Prior supplementation with vitamin D Severely impaired gastrointestinal function Other trial participation Pregnant or lactating women Hypercalcemia (total calcium of >10.6 mg/dL or ionized serum calcium of >5.4 mg/dL Tuberculosis history on clinical exam Sarcoidosis history on clinical exam Nephrolithiasis within the prior year Patients not deemed suitable for study participation (ie, psychiatric disease, living remotely from the clinic, or prisoner status) Pregnant or nursing women
Data and safety	Monthly review of data entry

monitoring	Quarterly independent review of data safety metrics Daily review of patient neurological exam, and laboratory values (CBC, BMP, calcium, phosphate) Interim 6-month data analysis
Statistical Methodology	T-test (parametric), Chi-square (non-parametric), univariate regression, multivariate linear regression, logistic regression, Kaplan-Meier survival, Cox proportional hazards modeling, interim analysis SPSS (IBM, Armonk, NY)

Table 2: Demographic, Clinical, and Safety Variables

Demographic Variables

- Name
- Medical record number
- Date of birth
- Gender
- Diagnosis
- Ethnicity/race

Clinical Variables

- Date of admission to NCCU
- Disease category (tumors, trauma, vascular, other)
- Disease severity: Glasgow Coma Scale, Simplified Acute Physiology Score II
- Medical comorbidities: diabetes, hypertension, heart disease, cancer history
- Any surgeries during hospitalization
- Randomization – vitamin D or placebo
- Vitamin D level on admission
- Date vitamin D level
- Vitamin D level 3 days post treatment
- Date vitamin D level 3 days post treatment
- Date ICU discharge
- Date hospital discharge
- Date deceased
- Glasgow Outcome Score on discharge
- EQ-5D on discharge
- Discharge disposition
- Hospital complications (specifically: deep vein thrombosis, bacteremia, urinary tract infection, pneumonia, readmission to NCCU)
- Glasgow Outcome Score at 3 and 6 months
- EQ-5D at 1, 3 and 6 months
- Physical therapy assessments at discharge
- Modified Rankin Scale on discharge

Safety Monitoring

- Common Terminology Criteria for Adverse Events (CTAE) V4.0
- Daily ICU laboratory studies (CBC, BMP, calcium, phosphate)
- Daily neurological exam
- Quarterly independent review of safety and data
- Monitoring of adverse events

Table S1: Clinical Studies Evaluating Vitamin D in a Critical Care Environment			
Reference	**Study type**	**Participants/ groups**	**Summary**
Van den Berghe 2003	RCT	22 200 IU vs. 500IU	Minimal change in serum markers
Ostermann 2007	Retrospective cohort	100 Normal vs. insufficient vs. deficient	Hospital-free days were significantly different between patients with deficiency and sufficiency No significant relationship between 25(OH)D concentrations and mortality
Lucidarme 2010	Retrospective cohort	100 Normal vs. insufficient vs. deficient vs. undetectable	28-day mortality was significantly different between the four groups No significant association between 25(OH)D concentrations and length of ICU stay. 79% of patients had low 25(OH)D concentrations
Mata-Granados 2010	RCT	33 Placebo vs. 60,000 IU PO, vs. 2mcg IV vit D3	97% of critically ill patients were vitamin D deficient. Group B (60,000 IU) showed a statistically significant increase in 25(OH)D concentrations.
Cecchi 2011	Retrospective cohort	170 Severe sepsis vs. non-septic trauma	28-day mortality was not statically different between the two groups with rates of 27.9% in severe septic patients and 11.1% in trauma patients
Braun 2011	Retrospective cohort	2,399 Normal vs. insufficient vs. deficient	Preadmission 25(OH)D deficiency is associated with mortality Adjusted 30-day morality odds ratio was 1.00, 1.36, and 1.69, respectively
Amrein 2011	RCT	25 Placebo vs. 540,000 IU enteral	The mean serum 25(OH)D increased in the treatment group 25 ng/mL. Deficiency was corrected in 2 days with
Venkatram 2011	Retrospective cohort	437 Normal vs. insufficient vs.	Higher hospital mortality for patients with vitamin D deficiency but not insufficiency

		deficient	
Braun 2012a	Retrospective cohort	1,325 Normal vs. insufficient vs. deficient	Adjusted 30-day mortality odds ratio was 1.00, 1.35, and 1.94 b respectively
Braun 2012b	Retrospective cohort	2,075 Normal vs. insufficient vs. deficient	Adjusted 30-day mortality odds ratio was 1.00, 1.41, and 1.61, respectively Preadmission 25(OH)D deficiency is significantly associated with acute kidney injury
Arnson 2012	Prospective cohort	130 Normal vs. insufficient	Mortality was lower for vitamin D deficient patients (15±12.4 days vs. 24.2 ± 16.5 days) Vitamin D levels correlated with WBC count
Flynn 2012	Prospective cohort	66 Normal vs. deficient	Longer length of stay, infection rates and rates of sepsis in patients with vitamin D deficiency
Higgins 2012	Prospective cohort	196 Normal vs. deficient vs. insufficient	Vitamin D levels decreased 3 days after admission and remained through 10 days Higher vitamin D levels were associated with shorter time to ICU discharge (HR 2.11) Vitamin D not associated with mortality or infection rate
Nair 2012	Prospective cohort	100 Normal vs. deficient vs. insufficient	Vitamin D deficiency associated with fewer hospital-free days. Secondary hyperparathyroidism was highly prevalent in the critically ill population
Remmelts 2012	Prospective cohort	272 Normal vs. deficient vs. insufficient	Vitamin D deficiency associated with increased risk of ICU admission and 30-day mortality in patients with community-acquired pneumonia
Nair 2013	Retrospective cohort, RCT	196 Normal vs. insufficient vs. deficient Placebo vs. low (200IU) vs. high (500IU) supplement	Mean time-to-alive at ICU discharge was 5.9 ± 5.4, 6.8 ± 6.0, and 10.6 ±8.4 respectively 25(OH)D insufficiency was not associated with mortality 25(OH)D levels were higher in the high dose group on days 2, 6, and 7. Doses studied did not

			normalize 25(OH)D serum concentrations
Aygencel 2013	Prospective cohort	201	Increased mortality in vitamin D deficient (<20ng/mL) patients (43 vs. 26%) Increase rates of severe acute disease, worsened laboratory studies on admission, morbidity and exposure to invasive therapy in deficient patients.
Su 2013	Prospective cohort	206 (105 ICU) Normal vs. ICU sepsis	Lower vitamin D seen in patients with ICU sepsis compared to normal patients No difference in mortality with vitamin D levels
Amrein 2014	RCT	475, (patients with deficiency ≤20 ng/ml) Placebo vs. 540,000 IU x1, monthly 90,000 IU for 5 month	No difference in mean hospital stay (19.3 vs. 20.1), hospital mortality (35.3% vs. 28.3%), 6-month mortality (42.9% vs. 35.0%) Severe vitamin D subgroup (n=200) showed no difference in hospital stay (19 vs 20.1 days) and 6-month mortality (50% vs. 34.7%) Severe vitamin D subgroup showed significantly lower hospital mortality (46.1% vs. 28.6%, p=0.04),
Moromizato 2014	Retrospective cohort, two-center	3,386 Normal vs. insufficiency vs. deficiency	Preadmission vitamin D deficiency was predictive for risk of sepsis including after adjustement for other variables 90-day mortality was 1.6x higher in patients with preadmission vitamin D insufficiency and deficiency (HR. 1.63)
Dickerson 2015	Retrospective cohort	65 50,000 IU qweek, Blweek, Tlweek for 4 weeks	Normal vitamin D levels achieved in 6%, 11% and 26% of patients
Brook 2015	Retrospective cohort	300 Normal vs. deficient	Vitamin D levels showed an inverse correlation with non-home discharge destination
Nair 2015	RCT	50 150,000 IU vs.	65% vs. 67% of patients normalized vitamin D levels by 7

		300,000 IU vitamin D3 IM	days 80% vs. 83% of patients normalized vitamin D levels by 14 days Secondary hyperparathyroidism manifest in 25% of patients
Alizadeh 2015	Retrospective cohort	70 Normal vs. deficient	Longer length of stay (7.8 vs. 4.05 days) with deficient patients but no difference in hospital mortality
Quraishi 2015	RCT	30 Placebo vs. 200,000 IU cholecalciferol vs. 400,000 IU cholecalciferol	Plasma levels of vitamin D peaked on day 5 of treatment CRP levels did not differ between groups
Verceles 2015	Retrospective cohort	183 Normal vs. deficient	Deficiency was common (61% patients) and not associated with days to wean from ventillation

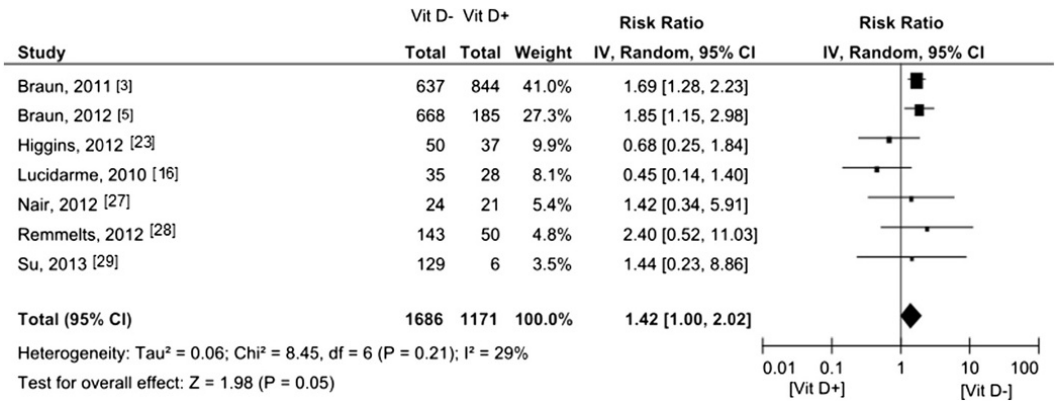

Figure S1: Forest plot of 30-day mortality in studies with univariate analysis of vitamin D sufficiency vs. deficiency. Adapted from de Haan et al. 2014.

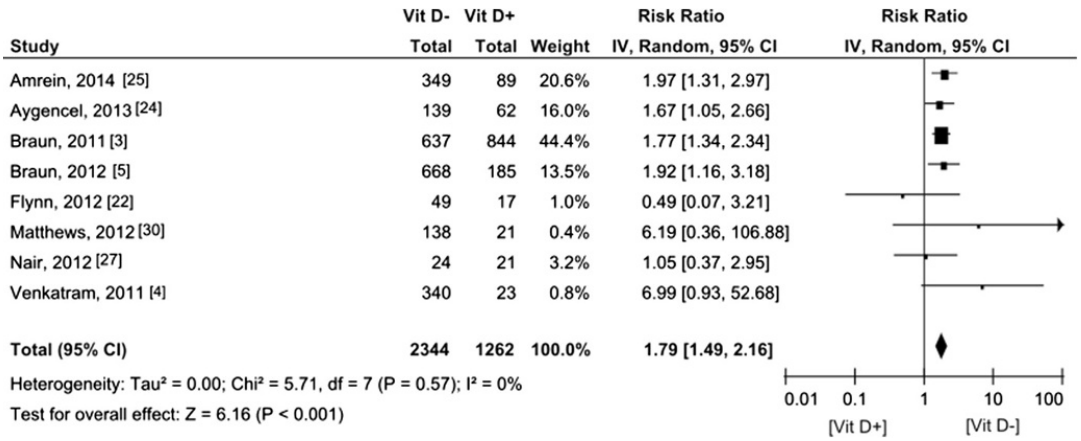

Figure S2: Forest plot of in hospital mortality in studies with univariate analysis of vitamin D sufficiency vs. deficiency. Adapted from de Haan et al. 2014.

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