12.0 Vitamin D May 2015

2015 Recommendation: *There are insufficient data to make a recommendation for the use of Vitamin D in critically ill patients*

2015 Discussion: The committee noted the addition of the awaited large trial (Amrein 2014) of vitamin D supplementation in Vit D deficient (<20 ng/ml or <50 nmol/L) critically ill patients from the same group who conducted the pilot trial already included in this section (Amrein 2011). This trial had a high internal validity and demonstrated that Vit D supplementation was associated with a trend towards a reduction in hospital mortality and a significant reduction only in the subgroup that was severely Vit D deficient (<12 ng/ml or <30 nmol/L). No effect was seen on length of stay in ICU or hospital. In the absence of statistically significant results, the committee considered that the subgroup results ought to be regarded as hypothesis generating and requires further study. Although there are several observational studies describing low levels of Vit D and its association with worse clinical outcomes in critically ill patients (Nair NEJM 2009, Braun Critical Care Medicine 2011, Am J Surgery 2012, Higgins JPEN 2012, etc), the committee agreed that based on the data from the 2 randomized trials, one of which only showed an effect in a subgroup, the data are insufficient to put forward a recommendation for the use of Vit D supplementation in the critically ill.

2013 Recommendation: *There are insufficient data to make a recommendation for the use of Vitamin D in critically ill patients.*

Discussion: Although there are several observational studies describing low levels of Vit D and its association with worse clinical outcomes in critically ill patients (Nair NEJM 2009, Braun Critical Care Medicine 2011, Am J Surgery 2012, Higgins JPEN 2012, etc), the committee noted that there was only on small pilot RCT focused on biochemical outcomes only. The committee decided to await the results of ongoing randomized trial in ICU patients before making a recommendation and decided to forgo the scoring of values.

Semi Quantitative Scoring

Values	Definition	2013 Score (0,1,2,3)	2015 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	0	1
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	0	1
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	2	3
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	n/a	3
Adequacy of control group	Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3)	2	3
Biological Plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal consistencies=2, very consistent=3)	2	2
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre=1, moderate likelihood i.e. multicentre with limited patient population or practice setting=2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings=3)	1	3
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	3	3
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	3	3
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	2	3

12.0 Vitamin D

Question: Does supplementation with Vitamin D result in better outcomes in critically ill vitamin D deficient adult patients?

Summary of evidence: There were two level 1 studies that compared the use of a single oral high dose Vitamin D3 to placebo in critically ill patients that were deficient in Vitamin D (defined as blood values of <20 ng/ml or <50 nmol/L).

Mortality: In the aggregated analyses, a trend towards a reduction in hospital mortality was seen with supplementation of vitamin D in vitamin D deficient patients (RR 0.82, 95% CI 0.64, 1.06, p=0.13, heterogeneity I^2=0%; figure 1). In a subgroup analysis of severely vitamin D deficient (<12 ng/ml or <30 nmol/L) patients in one study (Amrein 2014), supplementation with vitamin D was associated with a significant reduction in hospital mortality (p=0.01), 28 day mortality (p=0.02) and 6 month mortality (p=0.02) as well as a trend in reduction of ICU mortality (p=0.18).

Infections: Data on infectious complications were not reported.

LOS and ventilator days: No differences in ICU length of stay (WMD -1.49, 95% CI -5.16, 2.18, p=0.43, heterogeneity I^2=0%; figure 2) , hospital length of stay (WMD 0.03, 95% CI -4.30, 4.36, p=0.99, heterogeneity I^2=0%; figure 3), or duration of ventilation (WMD -1.85, 95% CI -5.10, 1.39, p=0.26, heterogeneity I^2=0%; figure 4) was found between the two groups.

Other: Serum levels of 1,25 (OH)D showed a transient significant increase in the Vitamin D group only in both studies. No adverse effects such as hypercalcemia or hypercalciuria were observed in the Amrein 2011 study. Mild hypercalcemia was seen in Amrein 2014 though no serious adverse events were recorded and hypercalcuria was no different between groups.

Conclusions:

1) Vitamin D3 supplementation in critically ill vitamin D deficient adult patients may reduce hospital mortality.
2) Vitamin D3 supplementation in critically ill severely vitamin D deficient patients is associated with reduced hospital mortality, 28-day mortality and 6 month mortality and may reduce ICU mortality.
3) Vitamin D3 supplementation in critically ill vitamin D deficient adult patients has no effect on ICU length of stay, hospital LOS or duration of ventilation.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.
Level 2 study: If any one of the above characteristics are unfulfilled.

Table 1. Randomized studies evaluating vitamin D supplementation in critically ill patients

Study	Population	Methods (score)	Intervention (both interventions started at same time)	Mortality # (%)†		Infections # (%)‡	
1) Amrein 2011	ICU patients with Vit D deficiency Expected LOS > 48 hrs N=25	C.Random: yes ITT: yes Blinding: double (11)	Single dose D3 (540 000 IU) via NG vs placebo	Vit D Hospital 6/12 (50)	Placebo Hospital 6/13 (46)	NR	NR
2) Amrein 2014	Medical and surgical ICU pts with Vit D deficiency. Expected LOS >48 hrs N=492	C.Random: yes ITT: yes Blinding: double (12)	Loading dose of 540 000 IU vitamin D3 in 45 mL of oleum arachidis (Oleovit D3 [containing 180 000 IU of vitaminD3 in 15mLof oleum arachidis per bottle], Fresenius Kabi) PO or NG vs 45 mL of oleum arachidis. Starting 28 days after loading dose, 5 monthly maintenance doses of 90 000 IU of oral vitamin D3 vs placebo.	ICU 54/237 (22.8) Hospital 67/237 (28.5) 6 month 83/237 (35)	ICU 63/238 (26.5) Hospital 84/238 (35.3) 6 month 102/238 (42.9)	NR	NR

Table 1. Randomized studies evaluating vitamin D supplementation in critically ill patients (continued)

Study	LOS days		Ventilator days		Other
1) Amrein 2011	Vit D ICU 13.4 ± 11.7 (12) Hospital 23.7 ± 24.7 (12)	Placebo ICU 14 ± 16.3 (13) Hospital 23.2 ± 21.2 (13)	Vit D 10.57 ± 7.96 (10)	Placebo 13.49 ± 14.23 (11)	Serum 1,25OH-D levels Vit D group: significant increase in 8/10 patients
2) Amrein 2014	ICU 15.7 ± 20.9 (237) Hospital 26.7 ± 25.3 (237)	ICU 17.3 ± 22.3 (238) Hospital 26.7 ± 24.3 (238)	11.58 ± 14.03 (159)	13.3 ± 17.23 (161)	Serum 1,25OH-D levels (ng/ml), Exp vs Control Baseline: 13.0 vs 13.1 Day 3: 33.5 vs 13.9 Day 7: 35.5 vs 14.5 P <0.001

C.Random: concealed randomization
ITT: intent to treat; NA: not available
† presumed hospital mortality unless otherwise specified
‡ refers to the # of patients with infections unless specified
± ( ) : mean ± Standard deviation (number)

Figure 1. Hospital Mortality

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Amrein 2011	6	12	6	13	9.6%	1.08 [0.48, 2.45]	2011
Amrein 2014	67	237	84	238	90.4%	0.80 [0.61, 1.04]	2014
Total (95% CI)		**249**		**251**	**100.0%**	**0.82 [0.64, 1.06]**	
Total events	73		90				

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)

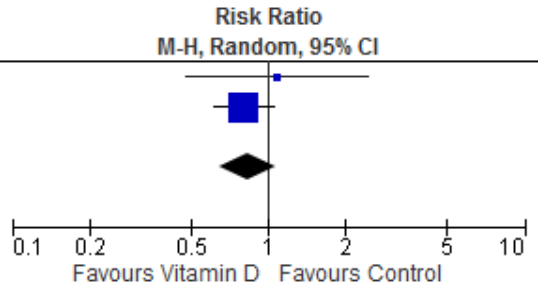

Figure 2. ICU LOS

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Amrein 2011	13.4	11.7	12	14	16.3	13	11.0%	-0.60 [-11.66, 10.46]	2011
Amrein 2014	15.7	20.9	237	17.3	22.3	238	89.0%	-1.60 [-5.49, 2.29]	2014
Total (95% CI)			**249**			**251**	**100.0%**	**-1.49 [-5.16, 2.18]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.43)

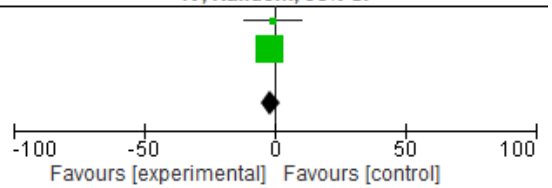

Figure 3. Hospital LOS

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Amrein 2011	23.7	24.7	12	23.2	21.2	13	5.7%	0.50 [-17.61, 18.61]	2011
Amrein 2014	26.7	25.3	237	26.7	24.3	238	94.3%	0.00 [-4.46, 4.46]	2014
Total (95% CI)			**249**			**251**	**100.0%**	**0.03 [-4.30, 4.36]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)

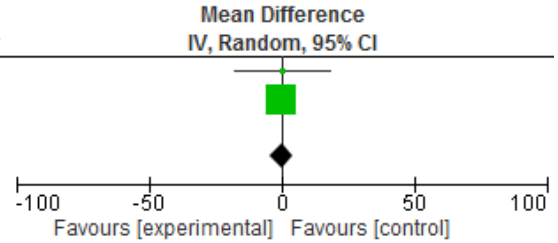

Figure 4. Mechanical Ventilation