6.5 Enteral Nutrition: Other Formulas: ß Hydroxyl Methyl Butyrate (HMB)

Question: Does the use of a formula supplemented with ß hydroxyl methyl butyrate (HMB) result in better outcomes in the critically ill adult patient?

Summary of evidence: There was one level 2 study that studied the effect of supplementation of an enteral formula with ß hydroxyl methyl butyrate (HMB), alone to standard enteral nutrition (EN) with an isonitrogenous isocaloric placebo in trauma patients (Kuhls 2007). One level 2 study compared HMB in addition to arginine and glutamine to isocaloric standard EN in a mixed ICU population, with both groups receiving early rehabilitation with electrical muscle stimulation (Nakamura 2019). The data pertaining to the second intervention from the Kuhls 2007 study comparing enteral nutrition supplemented with ß hydroxyl methyl butyrate, arginine and glutamine (Juven®) to standard enteral nutrition alone, is described in section 4.1: Diets supplemented with Arginine and select other nutrients.

Mortality: When the data from the two studies were aggregated, formula supplemented with HMB had no effect on mortality compared to standard EN (RR 0.53, 95% CI 0.17, 1.59, p=0.26, test for heterogeneity I^2 = 0%, figure 1).

Infections: Based on one study, formula supplemented with HMB had no effect on the number of infectious complications per patient (WMD 0.20, 95% CI -1.33, 1.73, p=0.80).

Length of Stay (LOS): HMB supplemented formula had no effect on ICU LOS (WMD 1.31, 95% CI -4.53, 7.16, p=0.66, test for heterogeneity I^2 = 47%, figure 2) or hospital LOS (WMD 4.63, 95% CI -11.36, 20.62, p=0.57, test for heterogeneity I^2 = 83%, figure 3), when compared to standard EN.

Ventilator days: When the data from both studies were aggregated, HMB supplemented formula compared to standard EN, had no effect on the number of ventilator days (WMD -0.26, 95% CI -2.08, 1.57, p=0.78, test for heterogeneity I^2 =6%, figure 4).

Other: In the Kuhls 2007 study, there was no effect of HMB supplementation on nitrogen intake however nitrogen balance was significantly better in the HMB group (p=0.05). HMB supplementation did not inhibit femoral muscle loss compared to standard EN (11.4±8.1% vs. 14.4±7.1% respectively ; p=0.18, Nakamura 2019).

Conclusions:

Compared to standard enteral nutrition,

1) Supplementation with ß hydroxyl methyl butyrate (HMB) has no effect on mortality or duration of mechanical ventilation.
2) Supplementation with ß hydroxyl methyl butyrate (HMB) has no effect on ICU length of stay.
3) Supplementation with ß hydroxyl methyl butyrate (HMB) has no effect on hospital length of stay.
4) Supplementation with ß hydroxyl methyl butyrate (HMB) may be associated with better nitrogen balance in trauma patients.
5) Supplementation with ß hydroxyl methyl butyrate (HMB) does not inhibit femoral muscle loss in heterogenous ICU patients.

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 other enteral formulas in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)† HMB vs. Control	Infections # (%)‡ HMB vs. Control
1) Kuhls 2007*	Trauma patients in ICU Injusry Severity Score >18 N=100	C.Random: No/not sure ITT: No** Blinding: Double (10)	Standard EN + supplement of 3 gms ß hydroxyl methyl butyrate (HMB) vs. Standard EN + isonitrogenous placebo supplement Isonitrogenous/isocaloric 25kcal/kg/day, 1.5g pro/kg/day	0/28 (0) vs. 2/22 (9)	**# infections per patient** 4.8 ± 2.65 (28) vs. 4.6 ± 2.81 (22) WMD 0.20, 95% CI -1.33, 1.73, p=0.80
2) Nakamura 2020	Mix ICU population N=88	C.Random: Yes ITT: Yes Blinding: single (12) Level: 2	Daily 3 grams HMB+14 grams arginine+14 grams of glutamine vs. standard EN. Both groups received early rehabilitation with electrical muscle stimulation from day 2. Isocaloric 20-30 Kcal/kg	**28 day** 4/45 (8.7%) vs. 6/43 (13.6%); p=0.30	NR

Table 1. Randomized studies evaluating other enteral formulas in critically ill patients (continued)

Study	LOS days HMB vs. Control	Ventilator days HMB vs. Control	Other HMB vs. Control
1)) Kuhls 2007*	**ICU** 28.9 ± 17.46 (28) vs. 22.4 ± 17.35 (22) **Hospital** 44.4 ± 23.28 (28) vs. 30.3 ± 22.98 (22)	24.2 ± 12.70 (28) vs. 20.9 ± 12.66 (22)	**# Patients with SIRS Score >3 or >4** Significantly less in HMB group on day 3 ($p<0.01$) and day 7 ($p<0.02$) **Average Nitrogen Balance** -6.50 ± 6.35 vs. -9.0 ± 6.10 **Change in Nitrogen Balance Comparing Week 1 to Week 2** Greater in HMB vs placebo ($p<0.05$)
2) Nakamura 2020	**ICU** 5.4 ±3.5 (45) vs. 5.8 ±3.8 (43); p=0.83 **Hospital** 21.9 ±8.8 (45) vs. 24.3 ±7.8 (43); p=0.18	4.8 ± 2.4 (45) vs. 5.3 ± 3.8 (43); p=0.45	**Subgroup of femoral muscle analyses (n=50)** **Total energy, kcal/d** 1015±319 vs. 1098±462; p=0.90 **Total protein, g/d** 54.5±10.8 vs. 50.1±14.1; p=0.31 **Femoral muscle loss, %** 11.4±8.1 vs. 14.4±7.1; p=0.18

* all "standard error" reported in the Kuhls 2007 study have been converted to "standard deviation"
** 100 pts randomized but only 72 reported on as 72 received at least 7 days of supplementation. Additional statistical exclusion criteria were established based on 50% treatment compliance, therefore 72 pts were used.
† presumed hospital mortality unless otherwise specified
‡ refers to the # of patients with infections unless specified

ICU: Intensive care unit
C. Random: concealed randomization
ITT: intent to treat
EN: enteral nutrition
SIRS: systemic inflammatory response syndrome
WMD: weighted mean difference; CI: Confidence interval

Data pertaining to enteral nutrition supplemented with ß hydroxyl methyl butyrate, arginine and glutamine (Juven®) to standard enteral nutrition alone not shown here. Refer to section 4.1: Diets supplemented with Arginine and select other nutrients

Figure 1. Mortality

Study or Subgroup	HMB Events	HMB Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kuhls	0	28	2	22	13.8%	0.16 [0.01, 3.14]	2007
Nakamura	4	45	6	43	86.2%	0.64 [0.19, 2.10]	2020
Total (95% CI)		**73**		**65**	**100.0%**	**0.53 [0.17, 1.59]**	
Total events	4		8				

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)

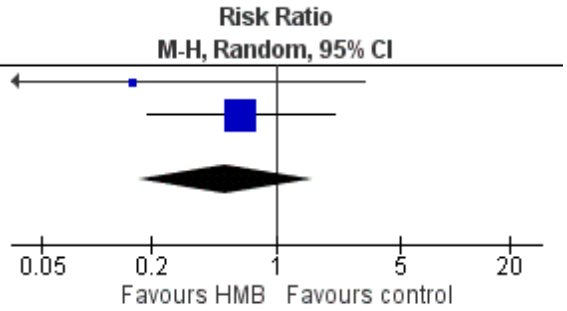


Figure 2. ICU Length of Stay

Study or Subgroup	HMB Mean	HMB SD	HMB Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kuhls	28.9	17.46	28	22.4	17.35	22	24.8%	6.50 [-3.22, 16.22]	2007
Nakamura	5.4	3.5	45	5.8	3.8	43	75.2%	-0.40 [-1.93, 1.13]	2020
Total (95% CI)			**73**			**65**	**100.0%**	**1.31 [-4.53, 7.16]**	

Heterogeneity: Tau² = 11.22; Chi² = 1.89, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 0.44 (P = 0.66)

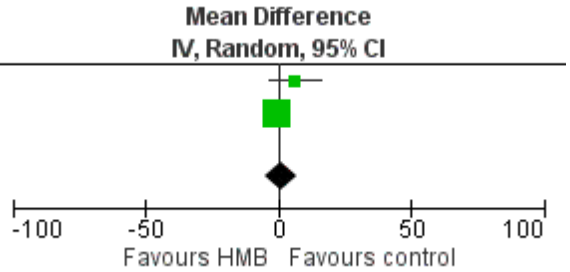


Figure 3. Hospital Length of Stay

Study or Subgroup	HMB Mean	HMB SD	HMB Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kuhls	44.4	23.28	28	30.3	22.98	22	42.6%	14.10 [1.19, 27.01]	2007
Nakamura	21.9	8.8	45	24.3	7.8	43	57.4%	-2.40 [-5.87, 1.07]	2020
Total (95% CI)			**73**			**65**	**100.0%**	**4.63 [-11.36, 20.62]**	

Heterogeneity: Tau² = 112.88; Chi² = 5.86, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 0.57 (P = 0.57)

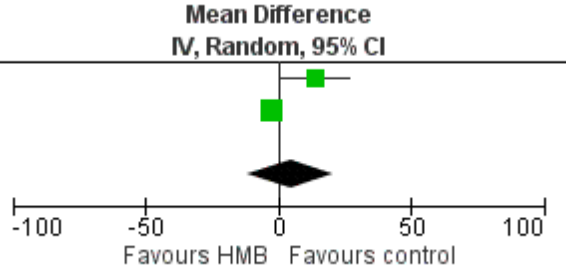
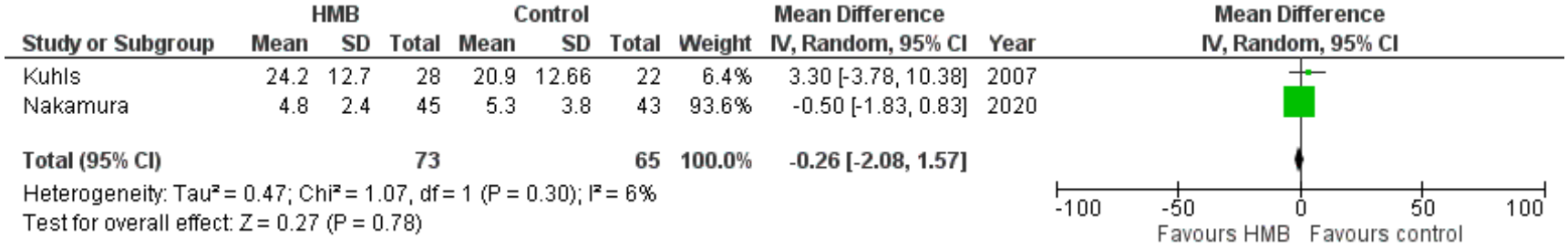


Figure 4. Ventilator Days



Included Articles

1. Kuhls DA, Rathmacher JA, Musngi MD, Frisch DA, Nielson J, Barber A, MacIntyre AD, Coates JE, Fildes JJ. Beta-hydroxy-beta-methylbutyrate supplementation in critically ill trauma patients. J Trauma. 2007 Jan;62(1):125-31; discussion 131-2. PubMed PMID: 17215743.
2. Nakamura K, Kihata A, Naraba H, Kanda N, Takahashi Y, Sonoo T, Hashimoto H, Morimura N. β-Hydroxy-β-methylbutyrate, Arginine, and Glutamine Complex on Muscle Volume Loss in Critically Ill Patients: A Randomized Control Trial. JPEN J Parenter Enteral Nutr. 2020 Feb;44(2):205-212. doi: 10.1002/jpen.1607. Epub 2019 May 27. PMID: 31134640.

Excluded Articles	Reason
Hsieh LC, Chien SL, Huang MS, Tseng HF, Chang CK. Anti-inflammatory and anticatabolic effects of short-term beta-hydroxy-beta-methylbutyrate supplementation on chronic obstructive pulmonary disease patients in intensive care unit. Asia Pac J Clin Nutr. 2006;15(4):544-550.	No clinical outcome
Bear DE, Langan A, Dimidi E, et al. β-Hydroxy-β-methylbutyrate and its impact on skeletal muscle mass and physical function in clinical practice: a systematic review and meta-analysis. Am J Clin Nutr. 2019;109(4):1119-1132. doi:10.1093/ajcn/nqy373	Systematic review