9.1 Composition of Parenteral Nutrition: Branched Chain Amino Acids (BCAA) May 2015

There were no new randomized controlled trials since the 2013 update and hence there are no changes to the following summary of evidence.

2013 Recommendation: *In patients receiving parenteral nutrition or enteral nutrition, there are insufficient data to make a recommendation regarding the use of intravenous supplementation with higher amounts of branched chain amino acids in critically ill patients.*

2013 Discussion: The committee noted that there were no changes in the effect size on mortality with the addition of one study (Ozgultekin 2008) that used supplemental IV BCAAs in patients receiving enteral nutrition. This trend towards a reduction in mortality had statistical heterogeneity and the committee therefore agreed to not make any changes in the recommendation for the supplementation with BCAAs.

2009 Recommendation: *In patients receiving parenteral nutrition, there are insufficient data to make a recommendation regarding the use of branched chain amino acids in critically ill patients.*

2009 Discussion: The committee noted the modest treatment effect for mortality with wide confidence intervals. The committee was concerned about the heterogeneity of findings in these 5 studies (test for heterogeneity p =0.16) only one study demonstrating a statistically significant reduction in mortality (Garcia De Lorenzo). Safety was not considered to be a great concern however feasibility and cost were unfavourable.

Semi Quantitative Scoring

Values	Definition	2009 Score (0,1,2,3)	2013 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	2 (mortality)	2 (mortality)
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	2	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	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	1	1
Adequacy of control group	Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3)	3	3
Biological Plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal consistencies=2, very consistent=3)	1	1
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	1
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	1	1
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	1	1
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	2

9.1 Composition of Parenteral Nutrition: Branched Chain Amino Acids (BCAA)

Question: Do BCAA in parenteral nutrition affect outcomes in the critically ill adult patient?

Summary of evidence: There were 6 level 2 studies reviewed. One of the studies supplemented IV with BCAA in patients receiving EN and had another experimental group i.e. supplementation with IV glutamine (Ozgultekin 2008) and only the data pertaining to the BCAA group are presented here. Refer to section 9.4 for data on IV glutamine supplementation vs control from Ozgultekin 2008.

Mortality: There were 5 studies that reported on mortality, 4 of these found no significant difference in mortality between the groups receiving higher amounts of BCAA and lower amounts (von Meyenfeldt 1990 ,Vanway 1995, Kuhl 1990, Ozgultekin 2008). Only one study found a significant reduction in mortality ($p<0.03$) in septic patients receiving 45% BCAA vs lower (standard) amounts (Garcia de-Lorenzo). Meta-analysis of these studies showed a trend towards a reduction in mortality in the groups receiving BCAA (RR 0.71, 95% CI 0.42, 1.18, p=0.19, heterogeneity I^2=43%; figure 1). When a sensitivity analysis that excluded the Ozgultekin study was done, BCAA was still associated with a trend towards a reduction in mortality (RR 0.58, 95% CI 0.26, 1.28, p=0.18, heterogeneity I^2=54%; figure 2).

Infections: Two studies reported on infections and found no differences in infections with the use of BCAA (Ott 1988, p=0.68; Kuhl 1990, p=NS).

Length of Stay: Two studies reported on ICU length of stay (Garcia de Lorenzo, Ozgultekin) in which there were no differences between the groups receiving higher amounts of BCAA and standard amounts. The studies could not be aggregated since one study (Garcia de Lorenzo) did not report the standard deviation of the outcome.

Ventilator days: One study reported duration of ventilation and found no differences between the groups (Ozgultekin, p = 0.811).

Other complications: Not reported.

Conclusions:

1) Supplementation with higher amounts of BCAA is associated with a trend towards a reduction in mortality, when compared to standard amounts of BCAA.
2) No differences found in infections, LOS or ventilated days between groups receiving higher and standard amounts of BCAA.

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 BCAA (PN) in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
1) Ott 1988	Brain injured patients N=20	C.Random: not sure ITT: yes Blinding: no (6)	BCAA (Aminosyn) vs standard PN (travasol)	BCAA NR	Standard NR	BCAA 4/10 (40)	Standard 4/10 (40)
2) Von Meyenfeldt 1990	Septic and traumatized patients N=101	C.Random: not sure ITT: yes Blinding: double (10)	50 % BCAA vs 16% BCAA (standard)	BCAA Hospital 17/49 (35)	Standard Hospital 16/52 (31)	BCAA NR	Standard NR
3) Van Way 1985	Mixed surgical population, severely stressed N=12	C.Random: not sure ITT: yes Blinding: no (7)	45 % BCAA vs 25% BCAA (standard)	BCAA Hospital 1/6 (17)	Standard Hospital 4/6 (67)	BCAA NR	Standard NR
4) Garcia De Lorenzo 1997	Septic patients from 7 ICUs N=69	C.Random: not sure ITT: yes Blinding: no (8)	3 groups: (A) standard BCAA + 1.5 g/kg/day AA (B) 45% BCAA + 1.5 g/kg/day AA (C) 45% BCAA + 1.1 g/kg/day AA Compared (B) + (C) to (A)	(A) 9/22 (41) ICU 10/22 (46)	(B) 2/25 (8) Hospital 2/25 (8)	(C) 5/22 (23) 6/22 (27)	NR
5) Kuhl 1990	Trauma patients requiring PN N=20	C.Random: not sure ITT: yes Blinding: no (8)	46% BCAA vs. 21% BCAA (standard)	BCAA 1/10 (10)	Standard 2/10 (20)	BCAA 9/10 (90)	Standard 9/10 (90)
6) Ozgultekin 2008	CHI & GCS patients, ventilated, sedated, mean APACHE II 18-19 N=60	C.Random: not sure ITT: no Blinding: none (4)	EN + IV BCAA x 10 days vs standard EN	BCAA 30-day 11/20 (55)	Standard 30-day 12/20 (60)	BCAA NR	Standard NR

Table 1. Randomized studies evaluating BCAA (PN) in critically ill patients (continued)

Study	LOS days		Ventilator days		Cost		Other	
1) Ott 1988	BCAA NR	Standard NR	BCAA NR	Standard NR	BCAA NR	Standard NR	BCAA NR	Standard NR
2) Von Meyenfeldt 1990	BCAA NR	Standard NR	BCAA NR	Standard NR	BCAA NR	Standard NR	BCAA NR	Standard NR
3) Van Way 1995	BCAA NR	Standard NR	BCAA NR	Standard NR	BCAA NR	Standard NR	BCAA NR	Standard NR
4) Garcia De Lorenzo 1997	(A) 18.5	(B) (C) ICU 14.4 17.8	NR		NR		NR	
5) Kuhl 1990	BCAA NR	Standard NR	BCAA NR	Standard NR	BCAA NR	Standard NR	BCAA NR	Standard NR
6) Ozgultekin 2008	BCAA ICU 13.6 ± 9.4	Standard ICU 17.3 ± 16.4	BCAA 11.8 ± 8	Standard 14.4 ± 14	BCAA NR	Standard NR	BCAA NR	Standard NR

C.Random: concealed randomization
ITT: intent to treat
BCAA: Branched chain amino acids
AA: amino acids

NR: not reported
** RR= relative risk, CI= Confidence intervals
‡ number of patients with infections unless specified

Figure 1. Mortality

Study or Subgroup	High BCAA Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kuhl	1	10	2	10	4.8%	0.50 [0.05, 4.67]	1990
Von Meyenfeldt	17	49	16	52	32.0%	1.13 [0.64, 1.97]	1990
Van Way	1	6	4	6	6.5%	0.25 [0.04, 1.63]	1995
Garcia De Lorenzo	8	47	10	22	23.6%	0.37 [0.17, 0.82]	1997
Ozgultekin	11	20	12	20	33.1%	0.92 [0.54, 1.56]	2008
Total (95% CI)		**132**		**110**	**100.0%**	**0.71 [0.42, 1.18]**	
Total events	38		44				

Heterogeneity: Tau² = 0.13; Chi² = 7.05, df = 4 (P = 0.13); I² = 43%
Test for overall effect: Z = 1.32 (P = 0.19)

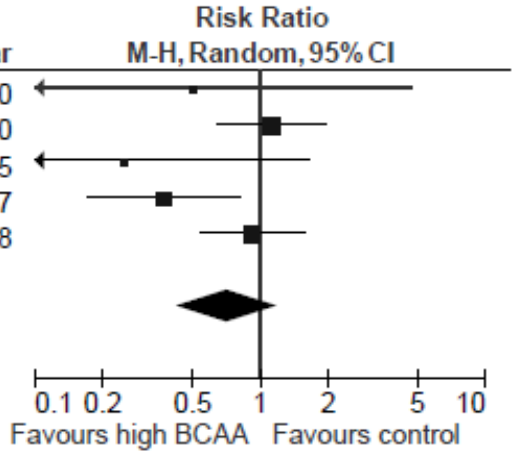

Figure 2. Mortality (excluding Ozgultekin)

Study or Subgroup	High BCAA Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Von Meyenfeldt	17	49	16	52	41.5%	1.13 [0.64, 1.97]	1990
Kuhl	1	10	2	10	10.2%	0.50 [0.05, 4.67]	1990
Van Way	1	6	4	6	13.4%	0.25 [0.04, 1.63]	1995
Garcia De Lorenzo	8	47	10	22	34.8%	0.37 [0.17, 0.82]	1997
Total (95% CI)		**112**		**90**	**100.0%**	**0.58 [0.26, 1.28]**	
Total events	27		32				

Heterogeneity: Tau² = 0.32; Chi² = 6.50, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 1.35 (P = 0.18)