4.1 (a) EN composition: Immune Enhancing: Diets supplemented with arginine and select other nutrients* January 8th 2007

Recommendation:

Based on 4 level 1 studies and 17 level 2 studies, we recommend that diets supplemented with arginine and other select nutrients not be used for critically ill patients.*

Discussion: The committee noted the lack of a treatment effect with respect to mortality and infections. These results differ from other meta-analyses [1,2] on immune enhancing diets which included elective surgery patients and did not include seven recent studies (Capparos, Conejero, Kieft, Saffle, Chuntrasakul, Tseui, Wibbenmeyer). The committee noted the results of the subgroup analysis, which shows that in higher quality studies, diets supplemented with arginine and other nutrients had no effect on mortality whereas in lower quality studies there was a trend towards a reduction in mortality. In light of the potential harm (increased mortality) associated with the use of diets supplemented with arginine and other nutrients, the reduction in length of stay and mechanical ventilation is difficult to interpret. Given the possible harm in septic patients (Bower, Ross, Bertolini) and the increased costs, the committee decided to recommend against their use in critically ill patients.

[1] Montejo JC et al Immunonutrition in the intensive care unit. A systematic review and consensus statement. Clin Nutr. 2003 Jun;22(3):221-33.

[2] Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence.JAMA 2001 Aug 22-29;286(8):944-53.

Values	definition	Score : 0, +, ++, +++
Effect size	magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	0 1+ (subgroup)
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	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+
Homogeneity	similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	1+
Safe	estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	1+
Feasible	ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2+
Cost	estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2+

The term “Immune-enhancing diets” has been used to describe products that have immune-modulating properties such as arginine, glutamine, omega-3 fatty acids, and others. There are several commercially available enteral feeding products that contain varying amounts of arginine in combination with other immune modulating nutrients. Since arginine is the common ingredient across these various formulas, we elected to descibe this section as “Diets supplemented with Arginine and other select Nutrients”.

* (refer to tables for specific nutrients)

4.1 (a) EN composition: Immune Enhancing: Diets Supplemented With Arginine And Other Select Nutrients January 8th 2007

Question: Compared to standard enteral feeds, do diets supplemented with arginine and other nutrients result in improved clinical outcomes in critically ill patients?

Summary of Evidence: There were 21 studies reviewed, 4 level 1 studies and 17 level 2 studies. The data from the Bertolini study was not included in the meta-analysis as the control feed was parenteral nutrition, not an enteral formula. The data from Tsuei trial was not included as EN was supplemented with arginine alone.

Mortality: All 21 studies reported on mortality and when the results of the 19 studies (Bertolini and Tsuei excluded) were aggregated, there was no effect on mortality (RR 1.06 95% confidence intervals 0.90, 1.24, p =0.49). A subgroup analysis of high quality studies (score $\geq$ 8) vs. low quality studies (score < 8) showed that in higher quality studies, diets supplemented with arginine and other nutrients had no effect on mortality (RR = 1.11, 95 % confidence intervals 0.93, 1.33, p=0.25), whereas in lower quality studies diets supplemented with arginine and other nutrients were associated with a trend towards a reduction in mortality (RR = 0.75, 95 % confidence intervals 0.49, 1.15, p = 0.19). The difference between these two subgroups was borderline significant. When the studies of trauma (RR 0.94, 95 % CI 0.47,1.85, p = 0.85) vs. non-trauma patients (RR 1.08, 95% CI 0.88,1.33 p =0.47) were compared, there were no differences in mortality. (See figures page 4.1(a)-7 to 4.1(a)-9).

Infections: Based on the 13 studies that reported on infectious complications, there was no difference in the rate of infectious complications (RR 0.98 95% CI, 0.83,1.15, p = 0.81). Subgroup analysis also showed no differences in infectious complications when high quality studies (RR =0.98, 95%CI 0.81,1.17, p = 0.80) were compared to lower quality studies (RR 0.97, 95% CI 0.65,1.45, p= 0.9) and when studies of trauma patients (RR 0.79 95% CI 0.41,1.50, p=0.5) were compared to studies of non-trauma patients (RR 1.00, 95%CI 0.86, 1.16, p = 0.96) (see figures pages 4.1(a)-10 to 4.1(a)-12).

LOS, Ventilated days: Diets supplemented with arginine and other nutrients were associated with a trend towards a reduction in hospital length of stay (SMD –0.33, 95% CI -0.72, 0.06, p =0.06*), a reduction on ICU length of stay (SMD –0.36, -0.73, 0.01, p=0.05)*, and a trend towards a reduction of mechanical ventilation (SMD –0.30, -0.64, 0.05, p = 0.09)*. (See pages 4.1(a) 13 and 4.1(a) 14).
* Denotes the presence of statistical heterogeneity (p< 0.05).

Conclusions:

1) Diets supplemented with arginine and other nutrients have no effect on rate of infectious complications in critically ill patients.
2) Diets supplemented with arginine and other nutrients overall have no effect on mortality.
3) Diets supplemented with arginine and other nutrients may possibly reduce hospital length of stay, ICU length of stay and mechanical ventilation.

Table 1. Randomized studies evaluating diets supplemented with arginine and other nutrients in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)‡		Infections # (%)		Length of Stay mean ± SD		Ventilator days mean ± SD	
				Experiment	Control	Experiment	control	Experiment	Control	Experiment	Control
1) Cerra 1990	Surgical ICU N=20	C.Random: yes ITT: no Blinding: Yes (8)	Impact *(see below)* vs Osmolite HN Non-isonitrogenous diets	1/11 (9)	1/9 (11)	NA	NA	hospital 36.7 ± 8.5	54.7 ± 10.5	NA	NA
2)Gottschlich 1990	Critically ill burns N=31	C.Random: not sure ITT: yes Blinding: Yes (10)	Experimental formula (arginine, histidine, cysteine, ω 3 fatty acids) vs Osmolite HN + protein Isonitrogenous diets	2/17 (12)	1/14 (7)	NA	NA	NA	NA	9 ± 4.5	10 ± 2.5
3) Brown 1994	Trauma N=37	C. Random: not sure ITT: no Blinding: No (5)	Experimental formula (arginine, β carotene, lactalbumin, α linoleic acid) vs. Osmolite HN + protein Isonitrogenous diets	0/19 (0)	0/18 (0)	3/19 (16)	10/18 (56)	NA	NA	NA	NA
4) Moore 1994	Trauma N=98	C.Random: not sure ITT: no Blinding: No (5)	Immun-Aid *(see below)* vs. Vivonex TEN Non-isonitrogenous diets	1/51 (2)	2/47 (4)	9/51 (18)	10/47 (21)	hospital 14.6 ± 1.3 ICU 5.3 ± 0.8	17.2 ± 2.8 8.6 ± 3.1	1.9 ± 0.9	5.3 ± 3.1
5) Bower 1995	Mixed ICU N=296	C.Random: yes ITT: no Blinding: Yes (9)	Impact *(see below)* vs. Osmolite Isonitrogenous diets	24/153 (16)	12/143 (8)	86/153 (56)	90/143 (63)	hospital 27.6 ± 23	30.9 ± 26	NA	NA
6) Kudsk * 1996	Trauma N=35	C.Random: yes ITT: yes Blinding: Yes (10)	Immun-Aid *(see below)* Vs. Isonitrogenous diets	1/17 (6)	1/18 (6)	5/16 (31)	11/17 (65)	hospital 18.3 ± 2.8 ICU 5.8 ± 1.8	32.6 ± 7 9.5 ± 2.3	2.4 ± 1.3	5.4 ± 2.0
7) Dent 2003	Mixed ICU N=170	C.Random: yes ITT: yes Blinding: Yes (11)	Optimental (arginine, Vit E, β carotene structured lipids, MCT) vs. Osmolite HN Isonitrogenous diets	20/87 (23)	8/83 (10)	57/87 (66)	52/83 (63)	hospital 25.4 ± 26 ICU 14.8 ± 19.6	20.9 ± 17 12 ± 10.9	14.3 ± 22.4	10.8 ± 12.8

Table 1 continued. Randomized studies evaluating diets supplemented with arginine and other nutrients in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)‡		Infections # (%)		Length of Stay mean ± SD		Ventilator days mean ± SD	
8) Engel 1997	Trauma N=36	C.Random: not sure ITT: yes Blinding: No (6)	Impact (see below) vs standard Non-isonitrogenous diets	Experiment ICU 7/18 (39)	Control ICU 5/18 (28)	Experiment 6/18 (33)	Control 5/18 (28)	Experiment hospital NA ICU 19 ± 7.4	Control NA 20.5 ± 5.3	Experiment 14.8 ± 5.6	Control 16 ± 5.6
9) Mendez 1997	Trauma N=43	C.Random: no ITT: no Blinding: Yes (6)	Experimental (arginine, selenium, carnitine, taurine) vs. Osmolite HN + protein Isonitrogenous diets	ICU 1/22 (4.5)	ICU 1/21 (5)	19/22 (86)	12/21 (57)	hospital 34 ± 21.2 ICU 18.9 ± 20.7	21.9 ± 11 11.1 ± 6.7	16.5 ± 19.4	9.3 ± 6
10) Rodrigo 1997	Mixed ICU N=30	C. Random:no ITT: yes Blinding: No (5)	Impact *(see below)* vs standard Isonitrogenous diets	ICU 2/16 (12.5)	ICU 1/14 (7)	5/16 (31)	3/14 (21)	hospital NA ICU 8 ± 7.3	NA 10 ± 2.7	NA	NA
11) Saffle 1997	Burns N=50	C. Random:no ITT: no Blinding: double (8)	Impact (see below) Vs. Replete (high protein, ω 3 fatty acids, glutamine) Isonitrogenous diets	5/25 (21)	3/24 (13)	2.36 per patient	1.71 per patient	hospital 37 ± 4	38 ± 4	22 ± 3	21 ± 2
12)Weimann 1998	Trauma N=29	C.Random: no ITT: no Blinding: Yes (9)	Impact (see below) vs standard Isonitrogenous diets	2/16 (12.5)	4/13 (31)	NA	NA	hospital 70.2 ± 53 ICU 31.4 ± 23.1	58.1 ± 30 47.4 ± 32.8	21.4 ± 10.8	27.8 ± 14.6
13) Atkinson 1998	Mixed ICU N=390	C.Random: no ITT: yes Blinding: Yes (11)	Impact (see below) vs. standard Isonitrogenous diets	95/197 (48)	85/193 (44)	NA	NA	hospital 20.6 ± 26 ICU 10.5 ± 13.1	23.2 ± 32 12.2 ± 23.2	8 ± 11.1	9.4 ± 17.7
14) Galban 2000	Critically ill septic N=176	C.Random:yes ITT: no Blinding: No (6)	Impact (see below) vs standard Isonitrogenous diets	17/89 (19)	28/87 (32)	39/89 (44)	44/87 (51)	hospital NA ICU 18.2 ± 12.6	NA 16.6 ± 12.9	12.4 ± 10.4	12.2 ± 10.3

Table 1 continued. Randomized studies evaluating diets supplemented with arginine and other nutrients in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)‡		Infections # (%)		Length of Stay mean ± SD		Ventilator days mean ± SD	
				Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control
15) Capparos 2001	Mixed ICU patients N=235	C.Random:Yes ITT: Yes Blinding: Yes (10)	Experimental formula (arginine,75gpro/L, vit A,C E, MCT & fibre) vs control 62.5 g pro/L Non isonitrogenous diets	27/130 (21)	30/105 (29)	64/130 (49)	37/105 (35)	hospital † 29 (16.8-51) ICU † 15 (9.8-25)	26 (17.8-42) 13 (8.8-20.3)	10 (5-18) †	9 (5-14) †
16) Conejero 2002	SIRS patients N = 84	C.Random:Yes ITT: No Blinding: yes (8)	Experimental formula 8.5 g/L arginine, 27 g/L glutamine,52.5 g pro/L) vs. control 66.2 g pro/L	28 day 14/43 (33)	28 day 9/33 (27)	11/43 (26)	17/33 (52)	14 (4-63) †	15(4-102) †	14 (5-25) †	14 (5-29) †
17) Bertolini 2003 **	Pts with severe Sepsis N = 39	C.Random:Yes ITT: Yes Blinding: no (10)	Perative (see below) vs. Parenteral Nutrition Non isocaloric	ICU 8/18 (44) 28 day 8/18 (44)	ICU 3/21 (14) 28 day 5/21 (24)	N/A	N/A	13.5 (9-26) †	15 (11-29) †	N/A	N/A
18) Kieft 2005	Mixed ICU pts N = 597	C.Random:Yes ITT: Yes Blinding: double (10)	Stresson (Nutricia) (see below) vs. control 50 g pro/L Isocaloric, non-isonitrogenous	Hospital 114/302 (38) ICU 84/302 (28) 28 day 93/302 (34)	Hospital 106/295 (36) ICU 78/295 (26) 28 day 82/295 (30)	130/302 (43)	123/295 (42)	hospital 20 (10-35)† ICU 7 (4-14) †	hospital 20 (10-34) † ICU 8 (5-16) †	6 (3-12) †	6 (3-12) †
19) Chuntrasakul 2003	Trauma, burns N = 36	C.Random: no ITT: Yes Blinding: single (6)	Neommune (12.5 g/L Arginine, 62.5 g pro/L) vs. Traumacal (83 g pro/L, 6.25 g/L glutamine and fish oils) non-isocaloric, non-isonitrogenous	1/18 (5)	1/18 (5)	NA	NA	hospital 44.9 ± 30.2 ICU 3.4 ± 5.8	28.8 ± 25.7 7.8 ± 13.6	2.7 ± 5.2	7.4 ± 1.3
20) Tsuei 2004***	Trauma with ISS > 20 N =25	C.Random: no ITT: yes* Blinding: single (9)	EN supplemented with 30 gms arginine vs. EN supplemented with 28 gms Casec isocaloric, isonitrogenous	1/13 (8)	0/12	8/13 (61)	6/11 (55)	hospital 22 ± 9 ICU 13 ± 6	27 ± 17 16 ± 10	10 ± 5	14 ± 10
21) Wibbenmeyer 2006	Burns with >20% TSBA N =23	C.Random: no ITT: yes Blinding: double (10)	Crucial (19 g/L arginine, 63 g pro/L, 2.9 gms fish oils) vs. control (67 g pro/L) Isonitrogenous, isocaloric	2/12 (17)	0/11	9/12 (75)	7/11 (64)	NA		Reported to be longer in experimental group. Data not shown	

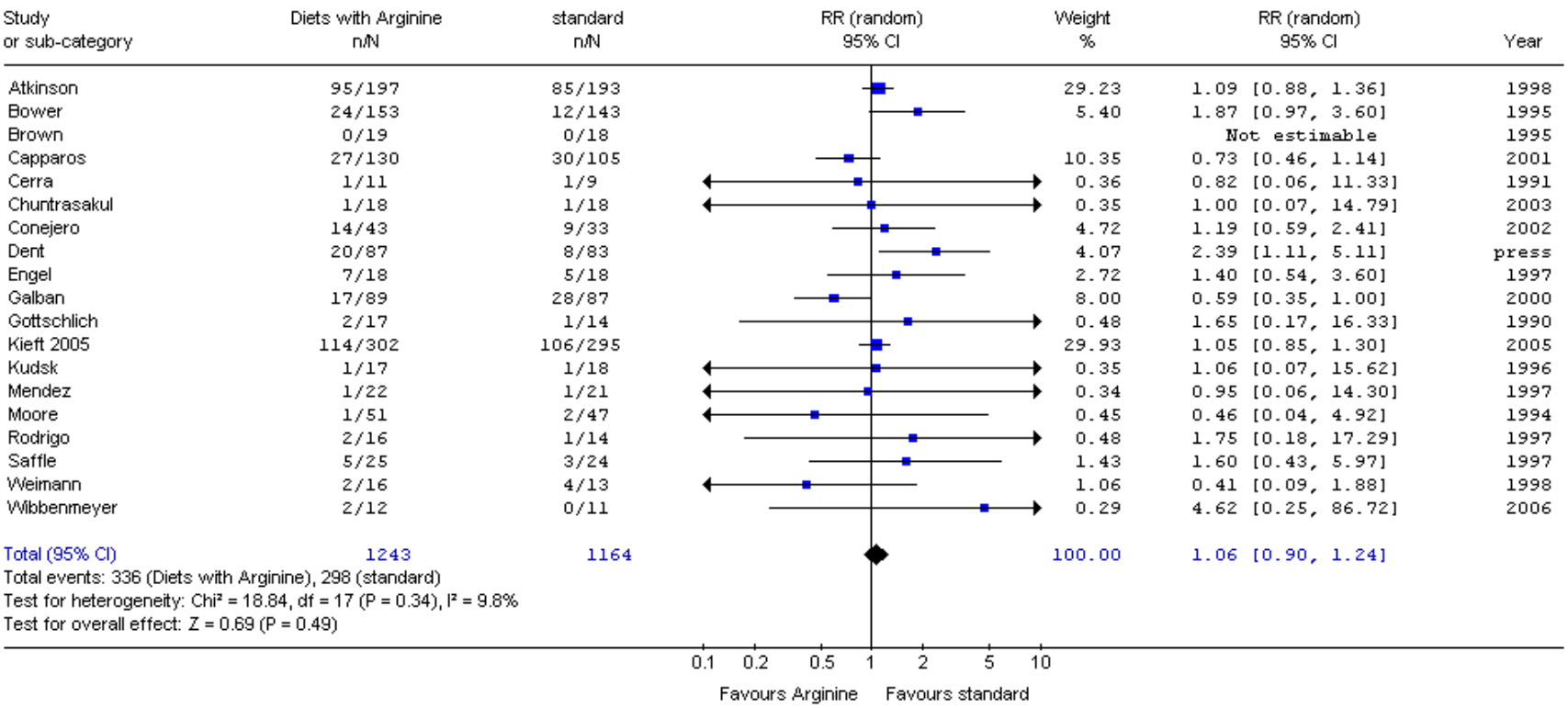
** Mortality data was ITT, data on infections was non ITT*

*** Bertolini data not included in meta-analysis as control formula was Parenteral Nutrition, not an enteral formula.*
**** Tsuei data not included as EN supplemented with arginine only.*

C.Random: concealed randomization EN: enteral nutrition; TPN Total parenteral nutrition NA: not available ITT: intent to treat
† median or interquartile ranges, not SD hence not included in m.analysis
± ( ) : mean ± SD (Standard deviation)
± ‡ hospital mortality reported or presumed unless specified

Impact: 12.5 g/L arginine, ω3 fatty acids, ribonucleic acid and 55.8 gm protein/litre
Immun-Aid: 14 g/L arginine, glutamine, BCAA, ω3 fatty acids, nucleic acids, Vit E, selenium, zinc and 80gms protein/litre
Perative: 6.8 g/L arginine, ω3 fatty acids, Vit E, beta Carotene, zinc and selenium and 66 gms protein/litre
Optimental: 5.5 g/L arginine, ω3 fatty acids, VitC, E, beta-carotene and 51 gms protein/litre
Stresson: 9g/L arginine, 13 g/L glutamine, ω3 fatty acids, Vitamin E, C, beta-carotene, 75g protein/litre
Crucial: 10 g/L arginine, ω3 fatty acids, VitC, E, 67 g protein/litre.

Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 01 Mortality

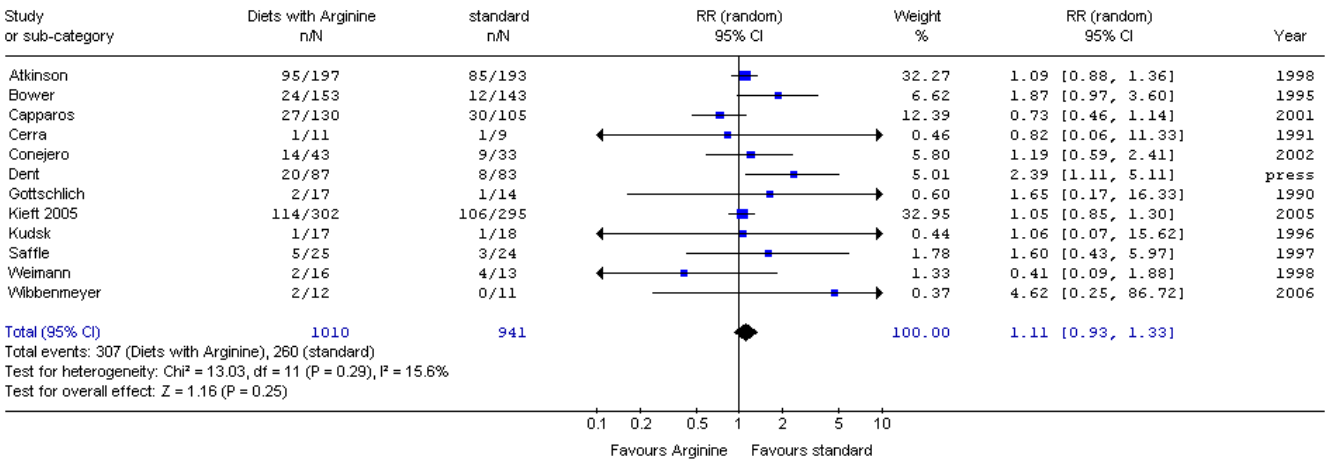


Total events: 336 (Diets with Arginine), 298 (standard)
Test for heterogeneity: Chi² = 18.84, df = 17 (P = 0.34), I² = 9.8%
Test for overall effect: Z = 0.69 (P = 0.49)

Sub group analysis

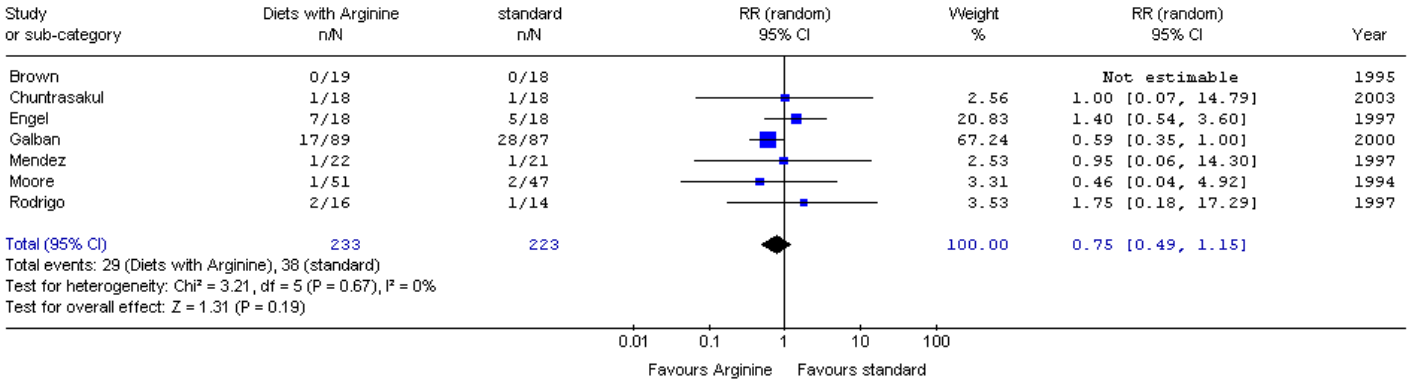
Mortality with high quality studies (≥ 8 score)

Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 01 Mortality



Mortality with low quality studies (< 8 score)

Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 01 Mortality

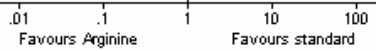


Sub group analysis

Mortality in trauma patients

Study	Diets with Arginine n/N	standard n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)	Year
x Brown	0 / 19	0 / 18		0.0	Not Estimable	1995
Engel	7 / 18	5 / 18		56.1	1.40[0.54,3.60]	1997
Kudsk	1 / 17	1 / 18		6.9	1.06[0.07,15.62]	1996
Mendez	1 / 22	1 / 21		6.8	0.95[0.06,14.30]	1997
Moore	1 / 51	2 / 47		8.9	0.46[0.04,4.92]	1994
Weimann	2 / 16	4 / 13		21.3	0.41[0.09,1.88]	1998
Total(95%CI)	12 / 143	13 / 135		100.0	0.93[0.46,1.89]	

Test for heterogeneity chi-square=2.23 df=4 p=0.69
Test for overall effect z=-0.20 p=0.8

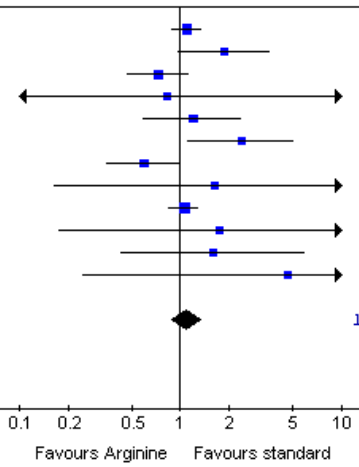


Mortality in non-trauma patients

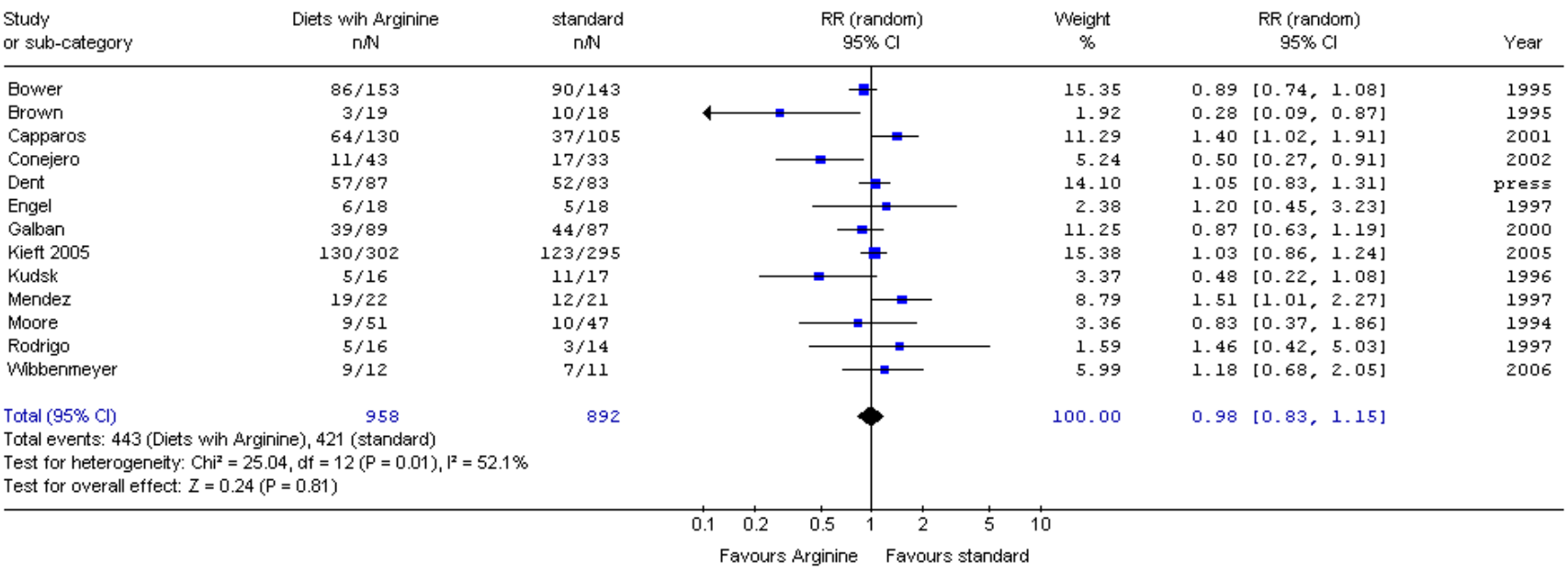
Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 01 Mortality

Study or sub-category	Diets with Arginine n/N	standard n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Atkinson	95/197	85/193		24.89	1.09 [0.88, 1.36]	1998
Bower	24/153	12/143		7.83	1.87 [0.97, 3.60]	1995
Capparos	27/130	30/105		13.10	0.73 [0.46, 1.14]	2001
Cerra	1/11	1/9		0.62	0.82 [0.06, 11.33]	1991
Conejero	14/43	9/33		6.99	1.19 [0.59, 2.41]	2002
Dent	20/87	8/83		6.14	2.39 [1.11, 5.11]	press
Galban	17/89	28/87		10.78	0.59 [0.35, 1.00]	2000
Gottschlich	2/17	1/14		0.81	1.65 [0.17, 16.33]	1990
Kieft 2005	114/302	106/295		25.19	1.05 [0.85, 1.30]	2005
Rodrigo	2/16	1/14		0.81	1.75 [0.18, 17.29]	1997
Saffle	5/25	3/24		2.34	1.60 [0.43, 5.97]	1997
Wibbenmeyer	2/12	0/11		0.50	4.62 [0.25, 86.72]	2006
Total (95% CI)	1082	1011		100.00	1.08 [0.88, 1.33]	

Total events: 323 (Diets with Arginine), 284 (standard)
Test for heterogeneity: Chi² = 16.54, df = 11 (P = 0.12), I² = 33.5%
Test for overall effect: Z = 0.73 (P = 0.47)



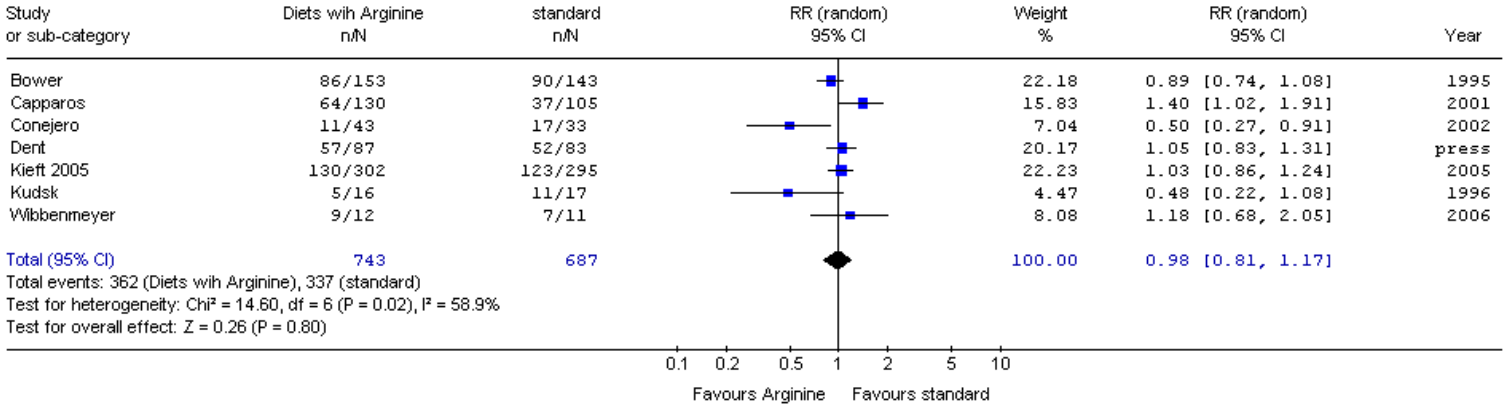
Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 02 Infectious complications



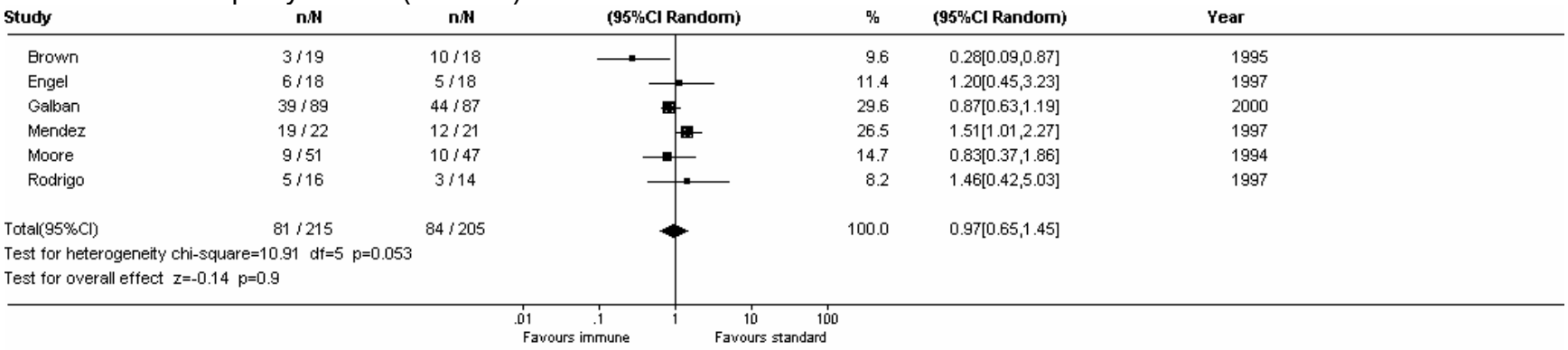
Sub group analysis

Infections with high quality studies (≥ 8 score)

Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 02 Infectious complications

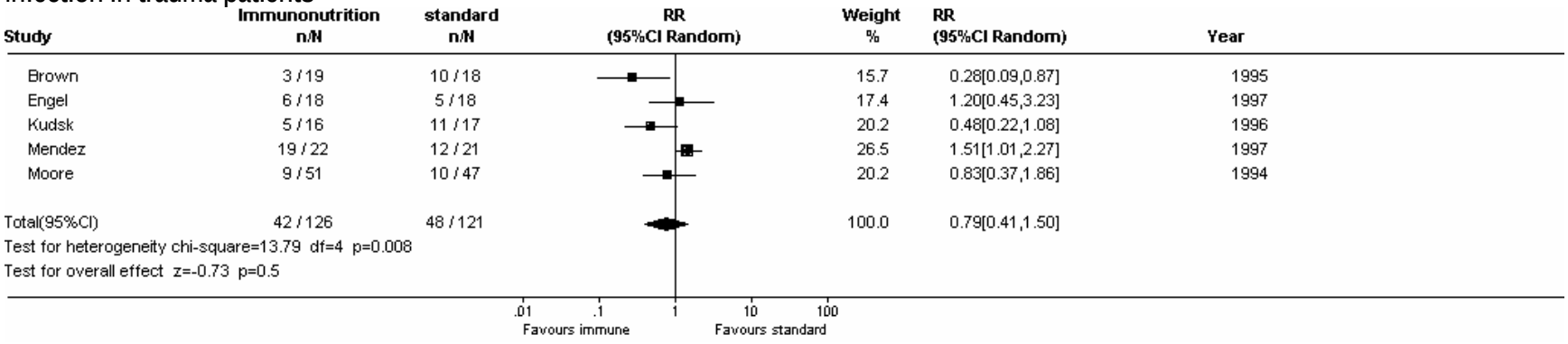


Infections with low quality studies (< 8 score)



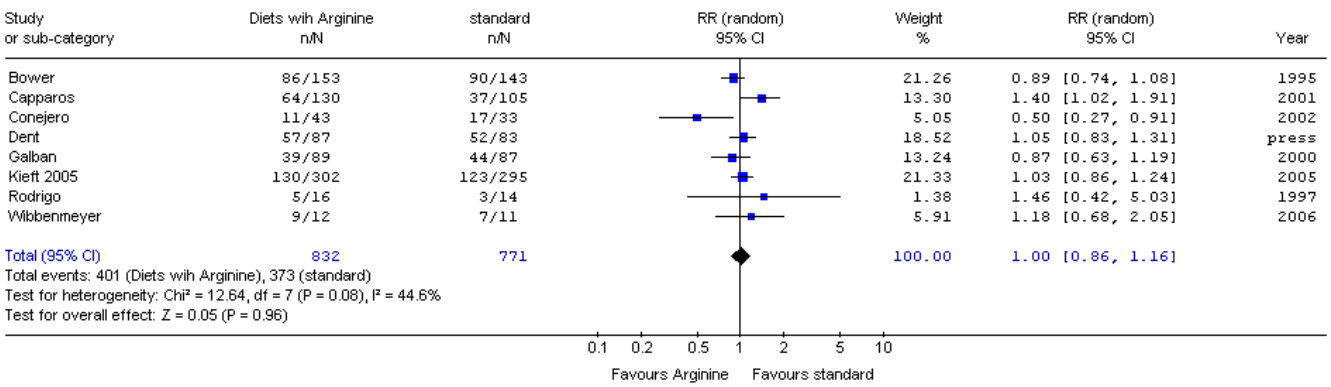
Sub group analysis

Infection in trauma patients



Infection in non-trauma patients

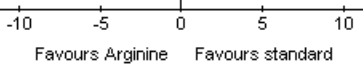
Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 02 Infectious complications



Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 03 Hospital Length of Stay

Study or sub-category	Diets with Arginine N	Diets with Arginine Mean (SD)	standard N	standard Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Year
Atkinson	197	20.60(26.00)	193	23.20(32.00)		12.53	-0.09 [-0.29, 0.11]	1998
Bower	153	27.60(23.00)	143	30.90(26.00)		12.40	-0.13 [-0.36, 0.09]	1995
Cerra	11	36.70(8.50)	9	54.70(10.50)		6.45	-1.83 [-2.91, -0.74]	1991
Chuntrasakul	18	45.00(30.00)	18	29.00(26.00)		9.37	0.56 [-0.11, 1.22]	2003
Dent	87	25.00(26.00)	83	21.00(17.00)		12.01	0.18 [-0.12, 0.48]	press
Kudsk	16	18.30(2.80)	17	32.60(7.00)		7.28	-2.59 [-3.54, -1.63]	1996
Mendez	22	34.00(21.20)	21	21.90(11.00)		9.76	0.70 [0.08, 1.32]	1997
Moore	51	14.60(1.30)	47	17.20(2.80)		11.17	-1.20 [-1.63, -0.77]	1994
Saffle	25	37.00(4.00)	24	38.00(4.00)		10.19	-0.25 [-0.81, 0.32]	1997
Weimann	16	70.20(53.00)	13	58.10(30.00)		8.85	0.27 [-0.47, 1.00]	1998
Total (95% CI)	596		568			100.00	-0.33 [-0.72, 0.06]	

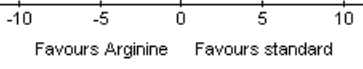
Test for heterogeneity: Chi² = 74.83, df = 9 (P < 0.00001), I² = 88.0%
Test for overall effect: Z = 1.65 (P = 0.10)



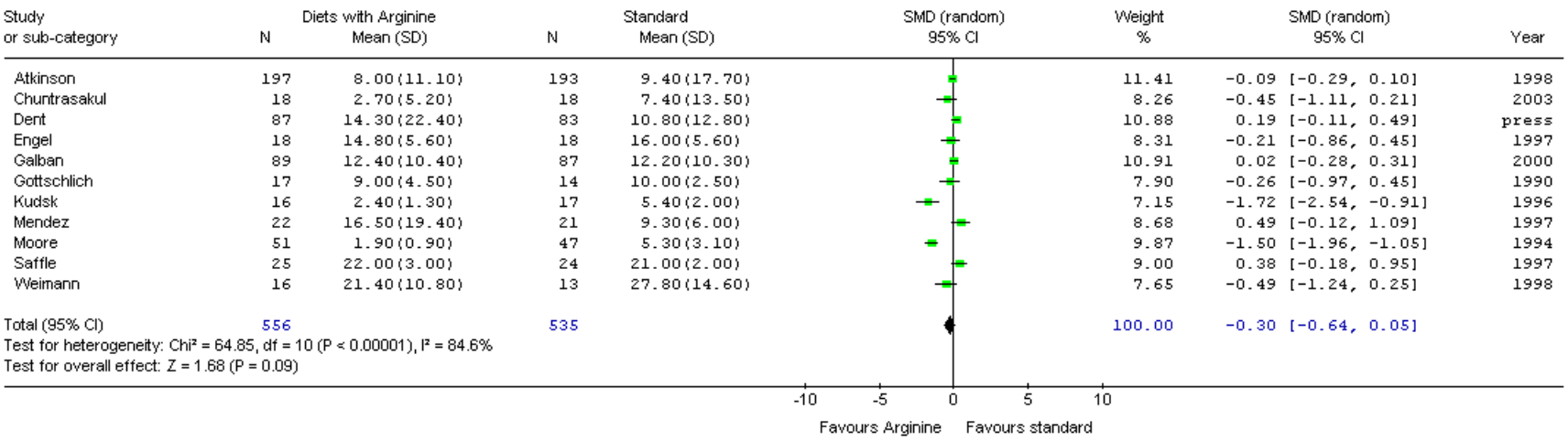
Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 04 ICU Length of Stay

Study or sub-category	Diets with Arginine N	Diets with Arginine Mean (SD)	standard N	standard Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Year
Atkinson	197	10.50(13.10)	193	12.20(23.20)		12.46	-0.09 [-0.29, 0.11]	1998
Chuntrasakul	18	3.40(5.80)	18	7.80(13.60)		9.13	-0.41 [-1.07, 0.25]	2003
Dent	87	14.80(19.60)	83	12.00(10.90)		11.90	0.17 [-0.13, 0.48]	press
Engel	18	19.00(7.40)	18	20.50(5.30)		9.17	-0.23 [-0.88, 0.43]	1997
Galban	89	18.20(12.60)	89	16.60(12.90)		11.94	0.12 [-0.17, 0.42]	2000
Kudsk	16	5.80(1.80)	17	9.50(2.30)		7.91	-1.74 [-2.56, -0.92]	1996
Mendez	22	18.90(20.70)	21	11.10(6.70)		9.56	0.49 [-0.12, 1.10]	1997
Moore	51	5.30(0.80)	47	8.60(3.10)		10.85	-1.47 [-1.92, -1.02]	1994
Rodrigo	16	8.00(7.30)	14	10.00(2.70)		8.63	-0.34 [-1.07, 0.38]	1997
Weimann	16	31.40(23.10)	13	47.40(32.80)		8.44	-0.56 [-1.31, 0.19]	1998
Total (95% CI)	530		513			100.00	-0.36 [-0.73, 0.01]	

Test for heterogeneity: Chi² = 62.50, df = 9 (P < 0.00001), I² = 85.6%
Test for overall effect: Z = 1.92 (P = 0.05)



Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 05 Ventilated days



TOPIC: 4.1 (a) Composition of EN: Immune Enhancing: Diets with arginine and other

(reviewers: Deborah Schroter-Noppe & Carmen Christman)

Article inclusion log

Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill, ventilated patients (no elective surgery patients)
Intervention: TPN and /or EN
Outcomes: mortality, LOS, QOL, functional recovery, complications, cost. Exclude studies with only biochemical, metabolic or nutritional outcomes.

	Author	Journal	I	E	why rejected
1.	Cerra	Nutrition 1990	√		
2.	Gottschlich	JPEN 1990	√		
3.	Mendez	J Trauma 1997	√		
4.	Atkinson	CC Med 1998	√		
5.	Brown	Pharmacotherapy 1994	√		
6.	Bower	CC Med 1995	√		
7.	Moore	J Trauma 1994	√		
8.	Weimann	Nutrition 1998	√		
9.	Rodrigo	Nutr Hosp 1997	√		
10.	Engel	Anaesthiol Intensiv 1997	√		
11.	Galban	CC Med 2000	√		
12.	Kudsk	Ann Surg 1996	√		
13.	Caparros	JPEN 2001	√		
14.	Heyland	JAMA 2001		√	All studies from this review were included separately
15.	Heys	Annals Surgery 1999		√	Excluded as elective surgery patients,. ICU studies included in ID # 23
16.	Beale	CCMedicine 1999		√	Excluded as elective surgery patients,. ICU studies included in ID # 23
17.	Saffle	J Trauma 1997	√		Compared Impact to Replete; not immune to non-immune
18.	Tepaske	Lancet 2001		√	Elective surgery patients
19.	Riso	Clinical Nutrition 2000		√	Elective surgery patients
20.	Heslin	Annals of surgery 1997		√	Elective surgery patients
21.	Preiser	JPEN 2001		√	No significant outcomes
22.	Suchner	Br J Nutr 2002		√	No RCT
23.	Evoy	Nutrition 1998		√	No RCT
24.	Van Bokhorst	Am J Clin Nutr 2001		√	Elective surgery patients
25.	McCowen	Am J Clin Nutr 2003		√	Not RCT, Review
26.	Bastian	Br Journal Nutr 2002		√	Not RCT, Review
27.	Kieft	Intensive Care Medicine 2005	√		
28.	Dent	CCMedicine 2003	√		
29.	Chuntrasakul	J Med Ass Thai 2003	√		
30.	Tsuei	J Surgical Research 2004	√		
31.	Wibbenmeyer	J Burn Care and Rehab 2006	√		

I = included, E = excluded

Reference List

1. Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. Guy's Hospital Intensive Care Group.Crit Care Med. 1998 Jul;26(7):1164-72.

2. Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: A systematic review of clinical outcome. Critical Care Medicine 1999;27:2799-805.

3. Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL, Van Buren CT, Rothkopf MM, Daly JM, Adelsberg BR. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. Crit Care Med. 1995 Mar;23(3):436-49

4. Brown RO, Hunt H, Mowatt-Larssen CA, Wojtysiak SL, Henningfield MF, Kudsk KA. Comparison of specialized and standard enteral formulas in trauma patients.Pharmacotherapy. 1994 May-Jun;14(3):314-20.

5. Caparros T, Lopez J, Grau T. Early enteral nutrition in critically ill patients with a high-protein diet enriched with arginine, fiber, and antioxidants compared with a standard high-protein diet. The effect on nosocomial infections and outcome. J Parenter Enteral Nutr. 2001 Nov-Dec;25(6):299-308

6. Cerra FB, Lehman S, Konstantinides N, Konstantinides F, Shronts EP, Holman R. Effect of enteral nutrient on in vitro tests of immune function in ICU patients: a preliminary report. Nutrition. 1990 Jan-Feb;6(1):84-7

7. Dent D, Heyland DK, et al. Increased mortality in patients with pneumonia receiving an immune-enhancing diet. Crit Care Med 2003 (in press).

8. Engel JM, Menges T, Neuhauser C, Schaefer B, Hempelmann G. [Effects of various feeding regimens in multiple trauma patients on septic complications and immune parameters] Anasthesiol Intensivmed Notfallmed Schmerzther. 1997 Apr;32(4):234-9. German.

9. Evoy D, Lieberman MD, Fahey TJ 3rd, Daly JM. Immunonutrition: the role of arginine. Nutrition. 1998 Jul-Aug;14(7-8):611-7.

10. Galban C, Montejo JC, Mesejo A, Marco P, Celaya S, Sanchez-Segura JM, Farre M, Bryg DJ. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. Crit Care Med. 2000 Mar;28(3):643-8.

11. Gottschlich MM, Jenkins M, Warden GD, Baumer T, Havens P, Snook JT, Alexander JW. Differential effects of three enteral dietary regimens on selected outcome variables in burn patients. J Parenter Enteral Nutr. 1990 May-Jun;14(3):225-36.

12. Heslin MJ, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW, Shike M,Brennan MF. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy.Ann Surg. 1997 Oct;226(4):567-77.

13. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically III patients? A systematic review of the evidence. Journal of the American Medical Association 2001;286:944-53.

14. Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: A meta-analysis of randomized controlled clinical trials. Annals of Surgery 1999;229:467-77.

15. Kieft H, Roos AN, Van Drunen J, Bindels A, Hofman Z. Clinical Outcomes of an immune enhancing diet in a heterogenous intensive care population. Crit Care Med 2003 (31), 12:SA82

16. Kudsk KA, Minard G, Croce MA, Brown RO, Lowrey TS, Pritchard FE, Dickerson RN, Fabian TC. A randomized trial of isonitrogenous enteral diets after severe trauma. An immune-enhancing diet reduces septic complications. Ann Surg. 1996 Oct;224(4):531-40.

17. Mendez C, Jurkovich GJ, Garcia I, Davis D, Parker A, Maier RV. Effects of an immune-enhancing diet in critically injured patients. J Trauma. 1997 May;42(5):933-40.

18. Moore FA, Moore EE, Kudsk KA, Brown RO, Bower RH, Koruda MJ, Baker CC, Barbul A. Clinical benefits of an immune-enhancing diet for early postinjury enteral feeding. J Trauma. 1994 Oct;37(4):607-15.

19. Preiser JC, Berre PJ, Van Gossum A, Cynober L, Vray B, Carpentier Y, Vincent JL. Metabolic effects of arginine addition to the enteral feeding of critically ill patients.JPEN J Parenter Enteral Nutr. 2001 Jul-Aug;25(4):182-7.

20. Riso S, Aluffi P, Brugnani M, Farinetti F, Pia F, D'Andrea F. Postoperative enteral immunonutrition in head and neck cancer patients. Clin Nutr. 2000 Dec;19(6):407-12.

21. Rodrigo Casanova MP, Garcia Pena JM. [The effect of the composition of the enteral nutrition on infection in the critical patient] Nutr Hosp. 1997 Mar-Apr;12(2):80-4. Spanish.

22. Saffle JR, Wiebke G, Jennings K et al. Randomized trial of immune-enhancing enteral nutrition in burn patients. Journal of Trauma-Injury Infection & Critical Care 1997;42:793-802.

23. Suchner U, Heyland DK, Peter K. Immune-modulatory actions of arginine in the critically ill. Br J Nutr. 2002 Jan;87 Suppl 1:S121-32. Review.

24. Tepaske R, te Velthuis H, Oudemans-van Straaten HM et al. Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomised placebo-controlled trial . Lancet 2001;358:696-701.

25. van Bokhorst-De Van Der Schueren MA, Quak JJ, von Blomberg-van der Flier BM, Kuik DJ, Langendoen SI, Snow GB, Green CJ, van Leeuwen PA. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients. Am J Clin Nutr. 2001 Feb;73(2):323-32.

26. Weimann A, Bastian L, Bischoff WE, Grotz M, Hansel M, Lotz J, Trautwein C, Tusch G, Schlitt HJ, Regel G. Influence of arginine, omega-3 fatty acids and nucleotide-supplemented enteral support on

systemic inflammatory response syndrome and multiple organ failure in patients after severe trauma. Nutrition. 1998 Feb;14(2):165-72.

27. Conejero R, Bonet A, Grau T, Esteban A, Mesejo A, Montejo JC, Lopez J, Acosta JA. Effect of a glutamine-enriched enteral diet on intestinal permeability and infectious morbidity at 28 days in critically ill patients with systemic inflammatory response syndrome: a randomized, single-blind, prospective, multicenter study. Nutrition. 2002 Sep;18(9):716-21.

28. Bertolini G, Iapichino G, Radrizzani D, Facchini R, Simini B, Bruzzone P,Zanforlin G, Tognoni G. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial.Intensive Care Med. 2003 May;29(5):834-40.

29. Kieft H, Roos A, Bindels A et al. Clinical Outcome of an Immune Enhancing Diet in a Heterogenous Intensive Care population. Intensive Care Medicine 2005, 31:524.

30. Tsuei BJ, Bernard AC, Barksdale AR, Rockich AK, Meier CF, Kearney PA. Supplemental enteral arginine is metabolized to ornithine in injured patients.J Surg Res. 2005 Jan;123(1):17-24.

31. Chuntrasakul C, Siltham S, Sarasombath S, Sittapairochana C, Leowattana W, Chockvivatanavanit S, Bunnak A. Comparison of a immunonutrition formula enriched arginine, glutamine and omega-3 fatty acid, with a currently high-enriched enteral nutrition for trauma patients.J Med Assoc Thai. 2003 Jun;86(6):552-61.

32. Wibbenmeyer LA, Mitchell MA, Newel IM, Faucher LD, Amelon MJ, Ruffin TO, Lewis RD. Effect of a fish oil and arginine-fortified diet in thermally injured patients. J Burn Care Res. 2006 Sep-Oct;27(5):694-702.