

4.1 (a) EN composition: Immune Enhancing: Diets supplemented with arginine and select other nutrients* June 28th, 2005

Recommendation:

Based on 4 level 1 studies and 16 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 six recent studies (Capparos, Conejero, Kieft, Saffle, Chuntrasakul, Tseui). 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 describe 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

June 28th 2005

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 20 studies reviewed, 4 level 1 studies and 14 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 20 studies reported on mortality and when the results of the 18 studies (Bertolini and Tsuei excluded) were aggregated, there was no effect on mortality (RR 1.05, 95 % confidence intervals 0.90, 1.25, $p = 0.53$). A subgroup analysis of high quality studies (score ≥ 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 0.92, 1.32, $p=0.27$), 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 1.07, 95% CI 0.87, 1.32 $p = 0.51$) were compared, there were no differences in mortality. (See figures page 4.1(a)-7 to 4.1(a)-9).

Infections: Based on the twelve studies that reported on infectious complications, there was no difference in the rate of infectious complications (RR 0.97 95% CI, 0.81, 1.15, $p = 0.70$). Subgroup analysis also showed no differences in infectious complications when high quality studies (RR = 0.96, 95%CI 0.78, 1.17, $p = 0.66$) 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 0.97, 95%CI 0.83, 1.14, $p = 0.71$) (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 hospital	Experiment	Control
1) Cerra 1990	Surgical ICU N=20	C.Random: yes ITT: no Blinding: Yes (8)	Impact (<i>see below</i>) vs Osmolite HN Non-isonitrogenous diets	1/11 (9)	1/9 (11)	NA	NA	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 (<i>see below</i>) vs. Vivonex TEN Non-isonitrogenous diets	1/51 (2)	2/47 (4)	9/51 (18)	10/47 (21)	14.6 ± 1.3 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 (<i>see below</i>) vs. Osmolite Isonitrogenous diets	24/153 (16)	12/143 (8)	86/153 (56)	90/143 (63)	27.6 ± 23	30.9 ± 26	NA	NA
6) Kudsk * 1996	Trauma N=35	C.Random: yes ITT: yes Blinding: Yes (10)	Immun-Aid (<i>see below</i>) Vs. Isonitrogenous diets	1/17 (6)	1/18 (6)	5/16 (31)	11/17 (65)	18.3 ± 2.8 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)	Optimential (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)	25.4 ± 26 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	
				Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control
8) Engel 1997	Trauma N=36	C.Random: not sure ITT: yes Blinding: No (6)	Impact (see below) vs standard Non-isonitrogenous diets	ICU 7/18 (39)	ICU 5/18 (28)	6/18 (33)	5/18 (28)	Experiment NA 19 ± 7.4	Control hospital NA ICU 20.5 ± 5.3	14.8 ± 5.6	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)	34 ± 21.2 18.9 ± 20.7	hospital 21.9 ± 11 ICU 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)	8 ± 7.3	hospital NA ICU 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	37 ± 4	hospital 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	70.2 ± 53 31.4 ± 23.1	hospital 58.1 ± 30 ICU 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	20.6 ± 26 10.5 ± 13.1	hospital 23.2 ± 32 ICU 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)	18.2 ± 12.6	hospital NA ICU 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)	26 (17.8-42)	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

* 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, ω 3 fatty acids, ribonucleic acid and 55.8 gm protein/litre

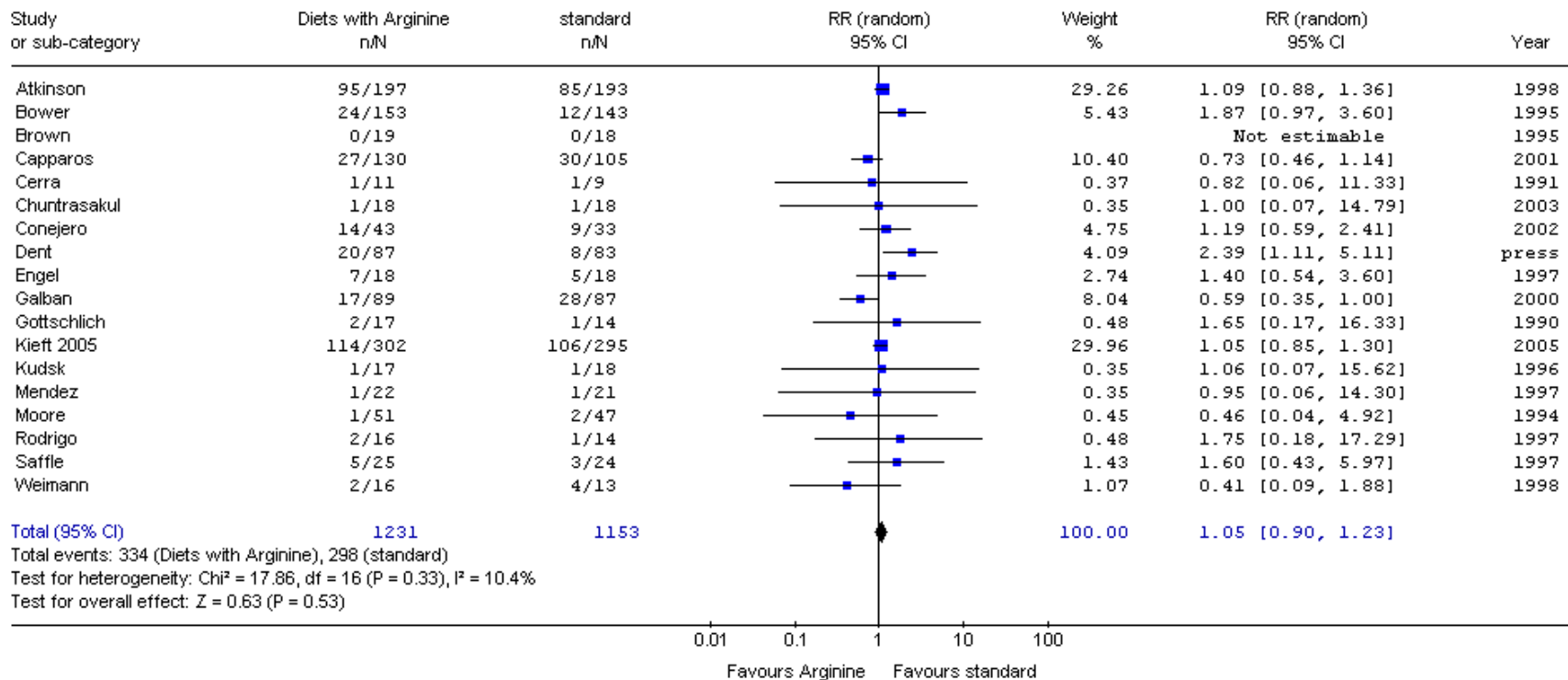
Immun-Aid: 14 g/L arginine, glutamine, BCAA, ω 3 fatty acids, nucleic acids, Vit E, selenium, zinc and 80gms protein/litre

Perative: 6.8 g/L arginine, ω 3 fatty acids, Vit E, beta Carotene, zinc and selenium and 66 gms protein/litre

Optimal: 5.5 g/L arginine, ω 3 fatty acids, VitC, E, beta-carotene and 51 gms protein/litre

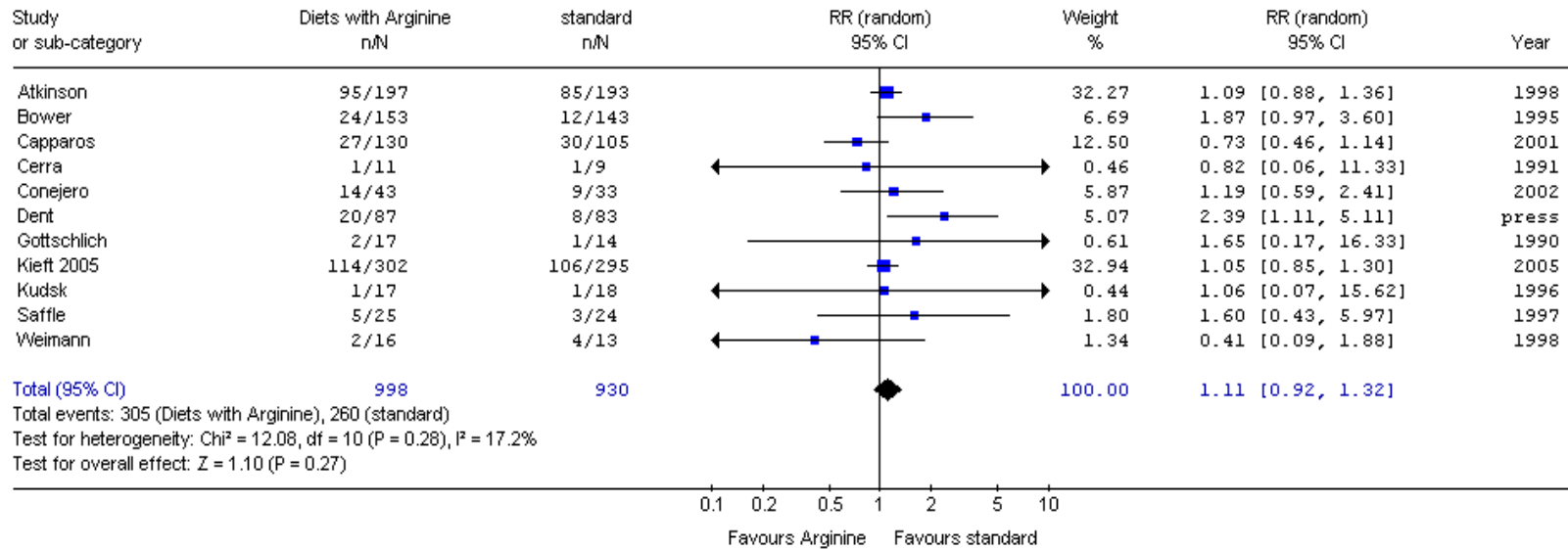
Stresson: 9g/L arginine, 13 g/L glutamine, ω 3 fatty acids, Vitamin E, C, beta-carotene, 75g protein/litre

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



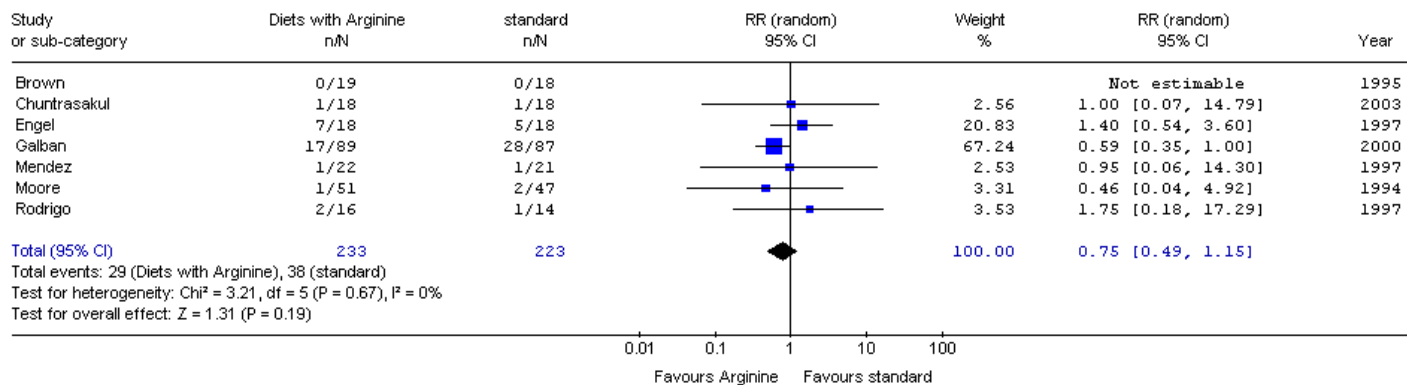
Sub group analysis

Mortality with high quality studies (≥ 8 score)

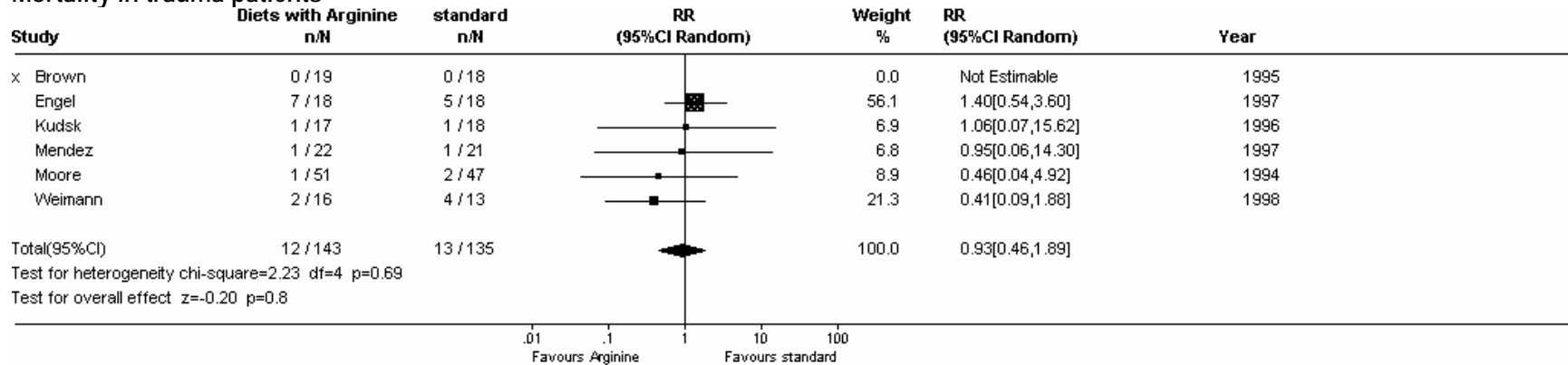


Mortality with low quality studies (< 8 score)

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

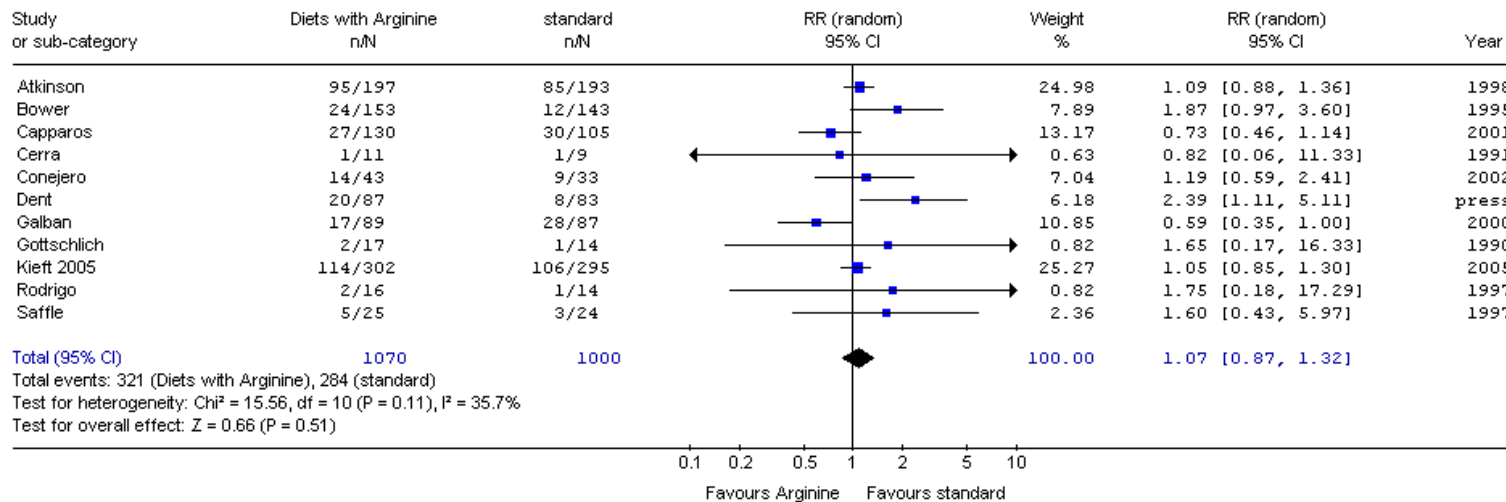


Sub group analysis Mortality in trauma patients

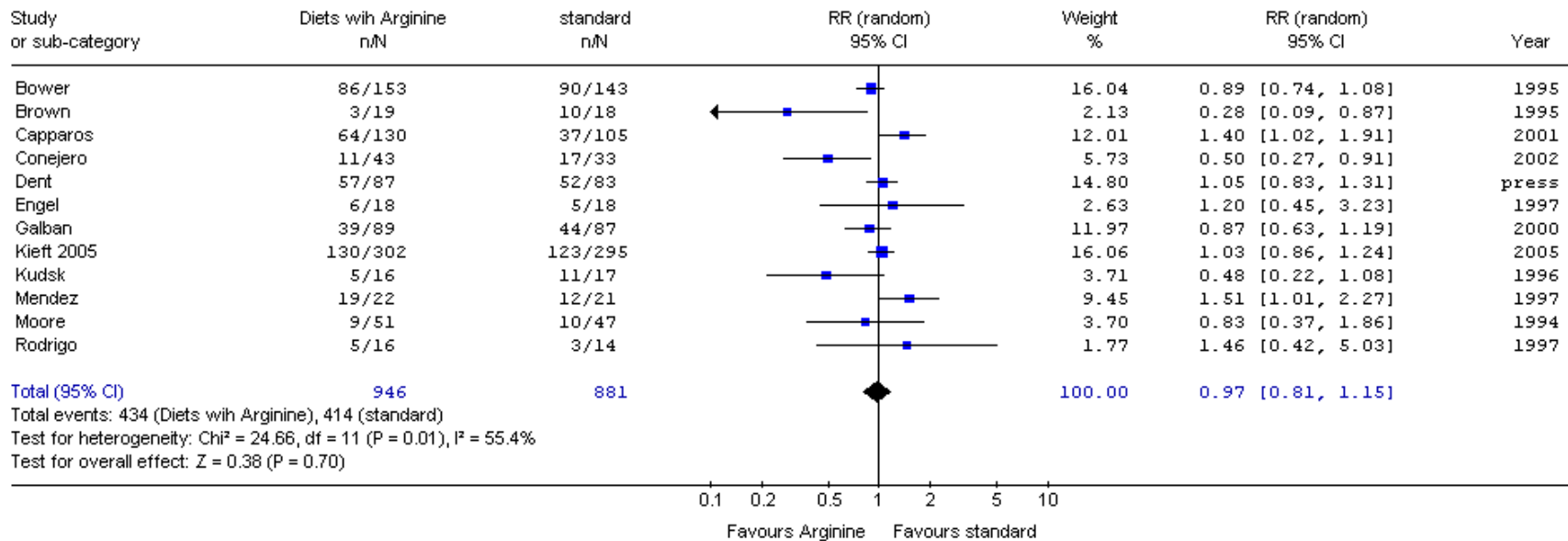


Mortality in non-trauma patients

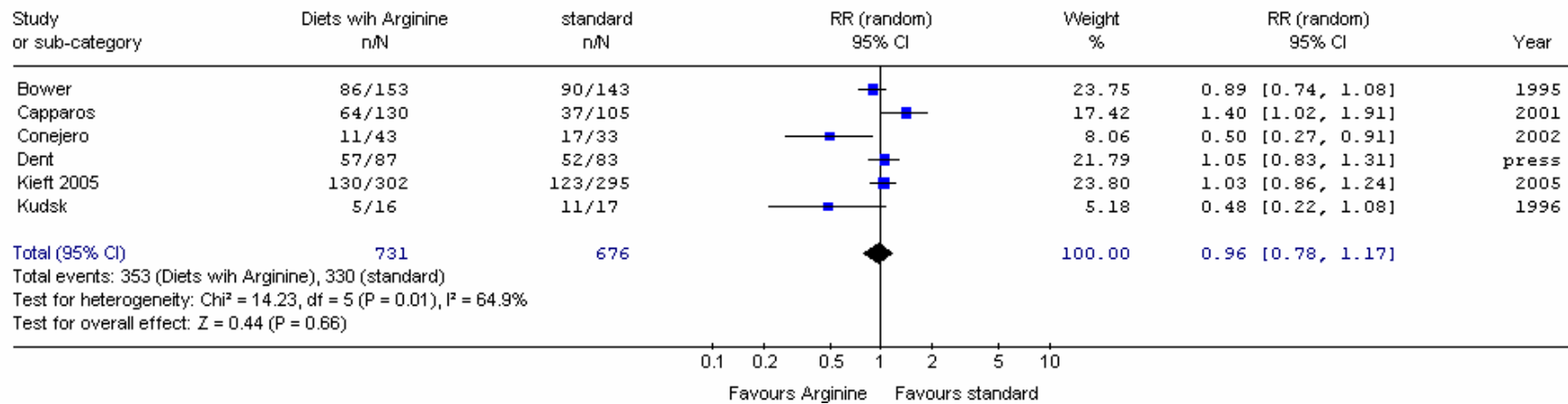
Review: Immunonutrition (combined)
Comparison: 01 Diets with arginine and other vs. standard
Outcome: 01 Mortality



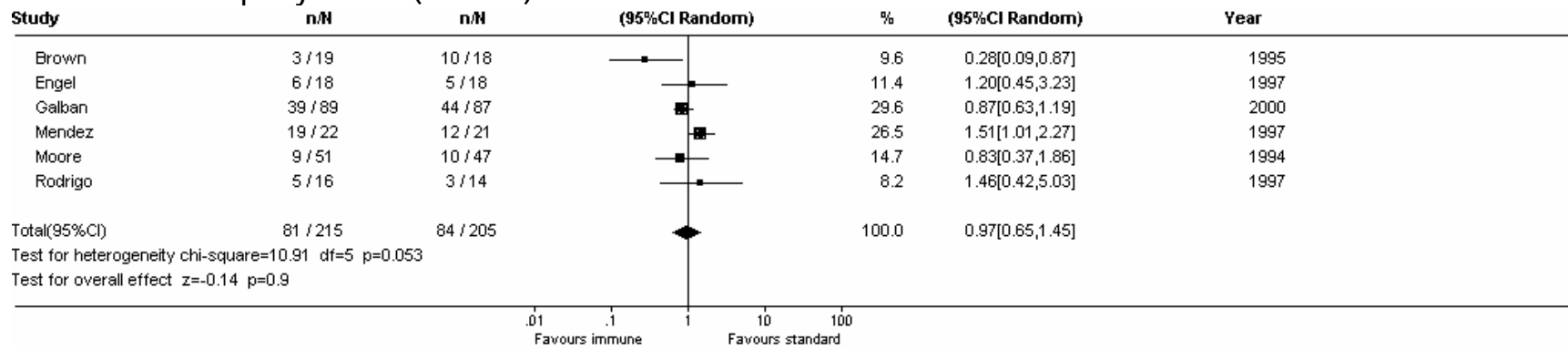
Review: Immunonutrition (combined)
 Comparison: 01 Diets with arginine and other vs. standard
 Outcome: 02 Infectious complications



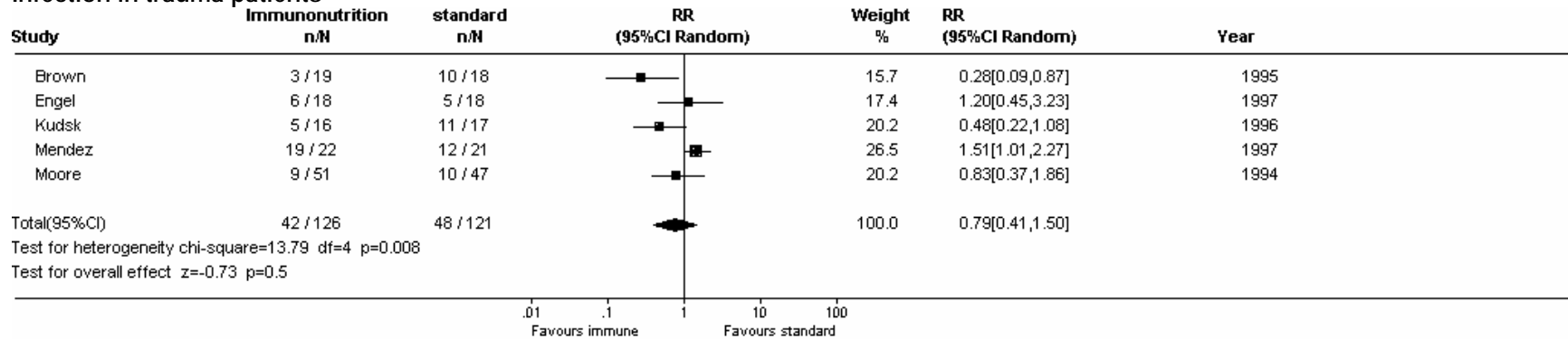
Sub group analysis Infections with high quality studies (≥ 8 score)



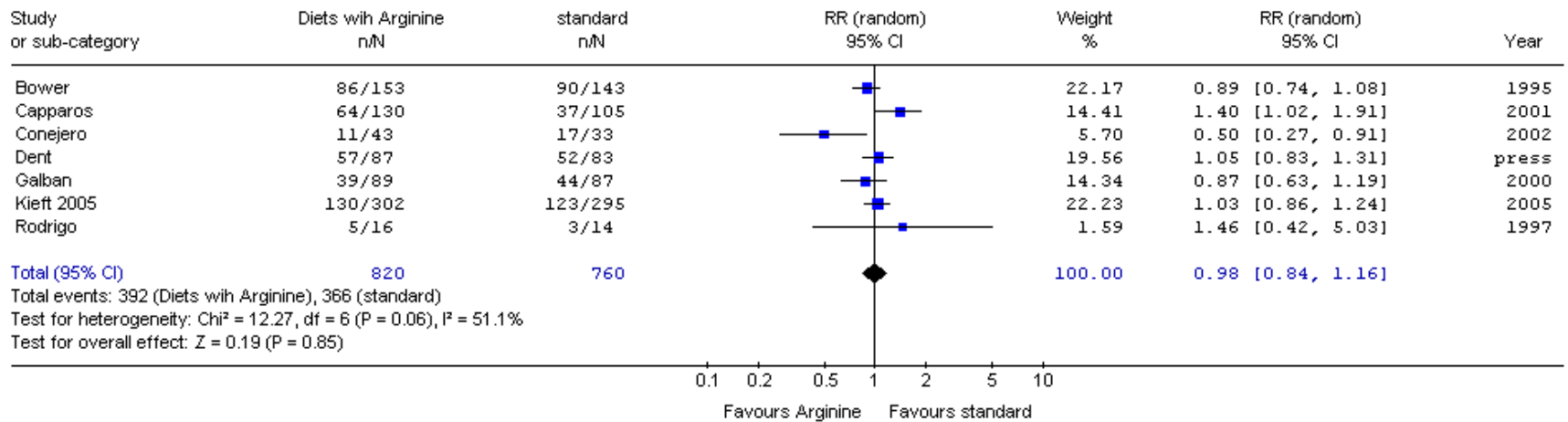
Infections with low quality studies (< 8 score)



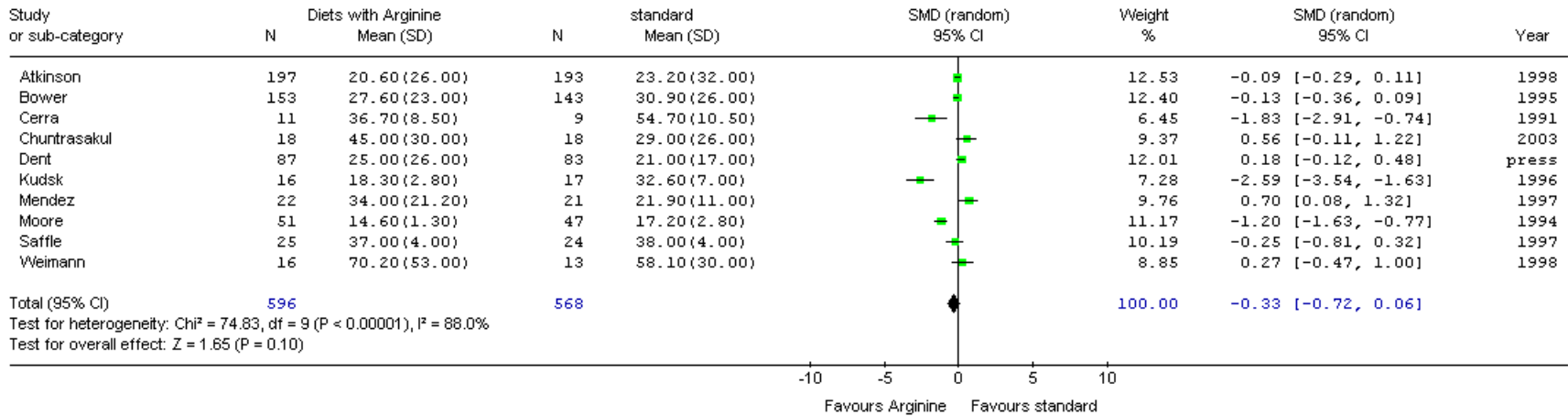
Sub group analysis Infection in trauma patients



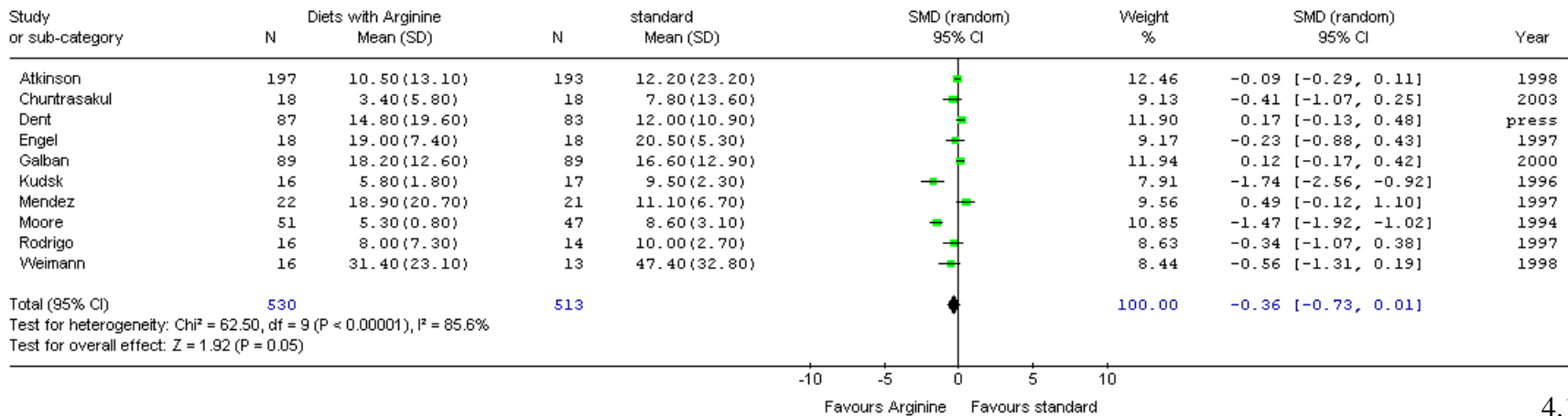
Infection in non-trauma patients



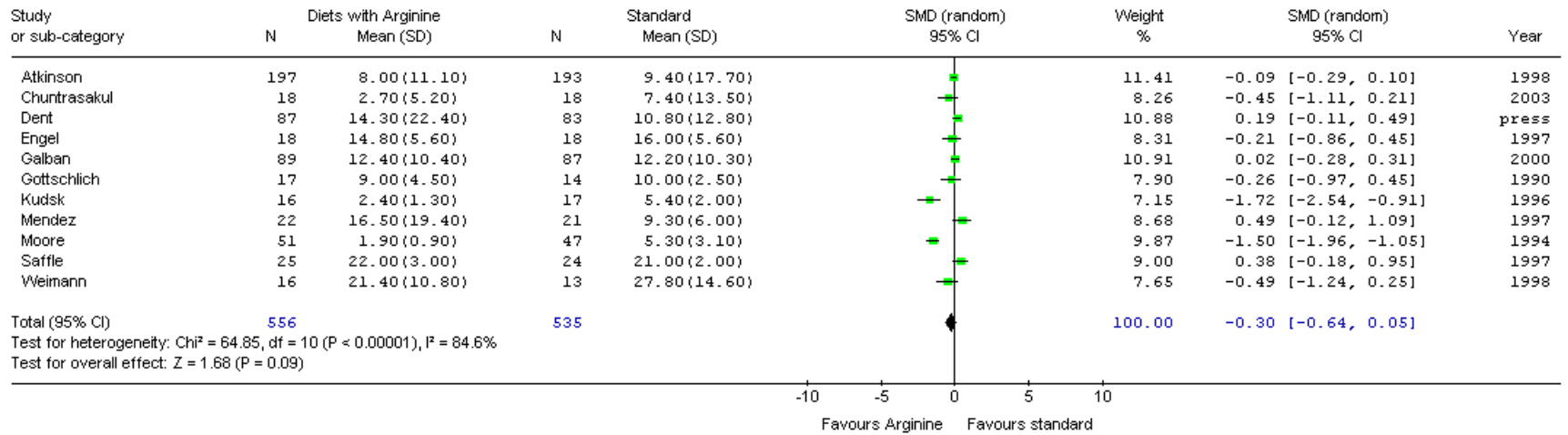
Review: Immunonutrition (combined)
 Comparison: 01 Diets with arginine and other vs. standard
 Outcome: 03 Hospital Length of Stay



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



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.

ID #	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	Anaesthesiol 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	√		

I = included, E = excluded

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