FINAL DRAFT

4.1 (a) EN composition: Diets supplemented with arginine and select other nutrients* January 31st 2009

Recommendation:
Based on 4 level 1 studies and 18 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 are similar to those in a recent meta-analysis of immunonutrition in ICU, trauma and burn patients [(1)] (Marik and Zaloga 2008).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)] Marik PE, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. Intensive Care Med. 2008 (11):1980-90.

Value	Definition	Score 0, 1, 2 or 3
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	0
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 or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	2
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	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.	2
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2
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	1

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: Diets Supplemented with Arginine and Other Select Nutrients January 31st 2009

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 22 studies reviewed, 4 level 1 studies and 18 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. In one recent study (Beale 2008), the results were confounded by having two interventions combined in the experimental group (arginine and glutamine).

Mortality: All 22 studies reported on mortality and when the results of the 21 studies (Bertolini excluded) were aggregated, there was no effect on mortality (RR 1.06 95% CI 0.93, 1.20 p= 0.40) (figure 1). 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 were associated with a trend towards a reduction in mortality (RR 1.10 95% CI 0.95, 1.26, p =0.20) (figure 2), 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 % CI 0.49, 1.15, p = 0.19) (figure 3). The difference between these two subgroups was not statistically significant (p = NS). When the studies of trauma (RR 0.98, 95 % CI 0.49, 1.96, p = 0.96) vs. non-trauma patients (RR 1.07, 95% CI 0.89, 1.30, p =0.47) were compared, there were no differences in mortality (figures 4,5).

Infections: Based on the 13 studies that reported on infectious complications, there was no difference in the rate of infectious complications (RR 0.99 95% CI, 0.85,1.15, p = 0.88) (figure 6). Subgroup analysis also showed no differences in infectious complications when high quality studies (RR =0.99, 95% CI 0.83, 1.17, p =0.87) (figure 7) were compared to lower quality studies (RR 0.97, 95% CI 0.65,1.45, p= 0.9) (figure 8) and when studies of trauma patients (RR = 0.86, 95 % CI 0.52, 1.42, p = 0.55) were compared to studies of non-trauma patients (RR 1.00, 95%CI 0.86, 1.16, p = 0.96) (figures 9,10).

LOS, Ventilated days: Diets supplemented with arginine and other nutrients were associated with a trend towards a reduction in hospital length of stay (WMD -2.40 95% CI -5.90, 1.09, p =0.18) (figure 11), a significant reduction on ICU length of stay (WMD -1.74, 95%CI -3.18, 0.30, p =0.02)* and a significant reduction in mechanical ventilation (WMD -1.41, 95%CI -2.85, 0.04, p =0.06)* (figures 12, 13).
* Denotes the presence of statistical heterogeneity (p< 0.05).

Conclusions:

1) Diets supplemented with arginine and other nutrients overall have no effect on mortality.
2) Diets supplemented with arginine and other nutrients have no effect on rate of infectious complications in critically ill patients.

3) Diets supplemented with arginine and other nutrients may possibly reduce hospital length of stay, ICU length of stay and mechanical 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 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	
1) Cerra 1990	Surgical ICU N=20	C.Random: yes ITT: no Blinding: Yes (8)	Impact *(see below)* vs Osmolite HN Non-isonitrogenous diets	Experiment 1/11 (9)	Control 1/9 (11)	Experiment NR	Control NR	Experiment Hospital 36.7 ± 8.5	Control 54.7 ± 10.5	Experiment NR	Control NR
2)Gottschlich 1990	Critically ill burn pts from 2 ICUs 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)	NR	NR	NR	NR	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)	NR	NR	NR	NR
4) Moore 1994	Trauma pts from 5 ICUs 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 from 8 ICUs 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	NR	NR
6) Kudsk * 1996	Trauma N=35	C.Random: yes ITT: yes Blinding: Yes (10)	Immun-Aid *(see below)* vs. Promote + protein supplement 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) Engel 1997	Trauma N=36	C.Random: not sure ITT: yes Blinding: No (6)	Impact (see below) vs. oligopeptide standard (Survimed OPD) Non-isonitrogenous diets	Experiment ICU 7/18 (39)	Control ICU 5/18 (28)	Experiment 6/18 (33)	Control 5/18 (28)	Experiment Hospital NR ICU 19 ± 7.4	Control NR 20.5 ± 5.3	Experiment 14.8 ± 5.6	Control 16 ± 5.6

8) 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 21.9 ± 11 ICU 18.9 ± 20.7 11.1 ± 6.7	16.5 ± 19.4	9.3 ± 6
9) Rodrigo 1997	Mixed ICU N=30	C. Random :no ITT: yes Blinding: No (5)	Impact *(see below)* Vs. standard (Precitene high protein) Isonitrogenous diets	ICU 2/16 (12.5)	ICU 1/14 (7)	5/16 (31)	3/14 (21)	Hospital NR NR ICU 8 ± 7.3 10 ± 2.7	NR	NR
10) 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
11)Weimann 1998	Trauma N=29	C.Random: no ITT: no Blinding: Yes (9)	Impact (see below) vs. standard formula (Sandoz) Isonitrogenous diets	2/16 (12.5)	4/13 (31)	NR	NR	Hospital 70.2 ± 53 58.1 ± 30 ICU 31.4 ± 23.1 47.4 ± 32.8	21.4 ± 10.8	27.8 ± 14.6
12) Atkinson 1998	Mixed ICU N=390	C.Random: no ITT: yes Blinding: Yes (11)	Impact (see below) vs. specially prepared isocaloric, isonitrogenous control	95/197 (48)	85/193 (44)	NR	NR	Hospital 20.6 ± 26 23.2 ± 32 ICU 10.5 ± 13.1 12.2 ± 23.2	8 ± 11.1	9.4 ± 17.7
13) Galban 2000	Critically ill septic pts from 6 ICUs N=176	C.Random:yes ITT: no Blinding: No (6)	Impact (see below) vs standard (Precitene high protein) Isonitrogenous diets	17/89 (19)	28/87 (32)	39/89 (44)	44/87 (51)	Hospital NR NR ICU 18.2 ± 12.6 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	
14) Capparos 2001	Mixed ICU patients from 15 ICUs N=235	C.Random:Yes ITT: Yes Blinding: Yes (10)	Experimental formula (glutamine,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) ICU † 15 (9.8-25) 13 (8.8-20.3)		10 (5-18) †	9 (5-14) †
15) Conejero 2002	SIRS patients from 11 ICUs 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) †
16) Dent 2003	Mixed from 14 ICUs 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 20.9 ± 17 ICU 14.8 ± 19.6 12 ± 10.9		14.3 ± 22.4	10.8 ± 12.8
17) Bertolini 2003 **	Pts with severe sepsis from 33 ICUs 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)	NR	NR	13.5 (9-26) †	15 (11-29) †	NR	NR
18) 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)	NR	NR	Hospital 44.9 ± 30.2 28.8 ± 25.7 ICU 3.4 ± 5.8 7.8 ± 13.6		2.7 ± 5.2	7.4 ± 1.3
19) Tsuei 2004***	Trauma with ISS > 20 N =25	C.Random: no ITT: yes* Blinding: single (9)	EN (Deliver 2.0) plus 30 gms arginine vs. EN (Deliver 2.0) plus 28 gms Casec isocaloric, isonitrogenous	1/13 (8)	0/12	8/13 (61)	6/11 (55)	Hospital 22 ± 9 27 ± 17 ICU 13 ± 6 16 ± 10		10 ± 5	14 ± 10
20) Kieft 2005	Mixed ICU pts from 2 ICUs N = 597	C.Random:Yes ITT: Yes Blinding: double (10)	Stresson (Nutricia) (see below) vs.standard 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) †

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

Study	Population	Methods (score)	Intervention	Mortality # (%)‡ Experiment	Mortality # (%)‡ Control	Infections # (%) Experiment	Infections # (%) Control	Length of Stay Mean ± SD Experiment	Length of Stay Mean ± SD Control	Ventilator days Mean ± SD Experiment	Ventilator days Mean ± SD Control
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)	NR		Reported to be longer in experimental group. Data not shown	
22) Beale 2008	SIRS patients N = 55	C.Random: no ITT: yes Blinding: double (9)	Intestamin (30 g glutamine) + Reconvan (10 g glutamine/L, 6.7 gm arginine/L), 98 g pro/L vs. Control supplement + Fresubin 38 g pro/L. Both received 20% IV glucose Nonisonitrogenous, isocaloric	ICU 6/27 (21) Hospital 7/27 (25) 28 day 5/27 (18) 6 month 10/27 (36)	ICU 4/27 (15) Hospital 7/28 (25) 28 day 3/28 (11) 6 month 8/27 (30)	NR	NR	Hospital 43.8 ± 36.6	31.3 ± 27.2 ICU 16.6 ± 14.8	NR	13.4 ± 11.5

** 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.*

C.Random: Concealed randomization EN: Enteral nutrition; TPN Total parenteral nutrition NR: Not Reported 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.

Figure 1.

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

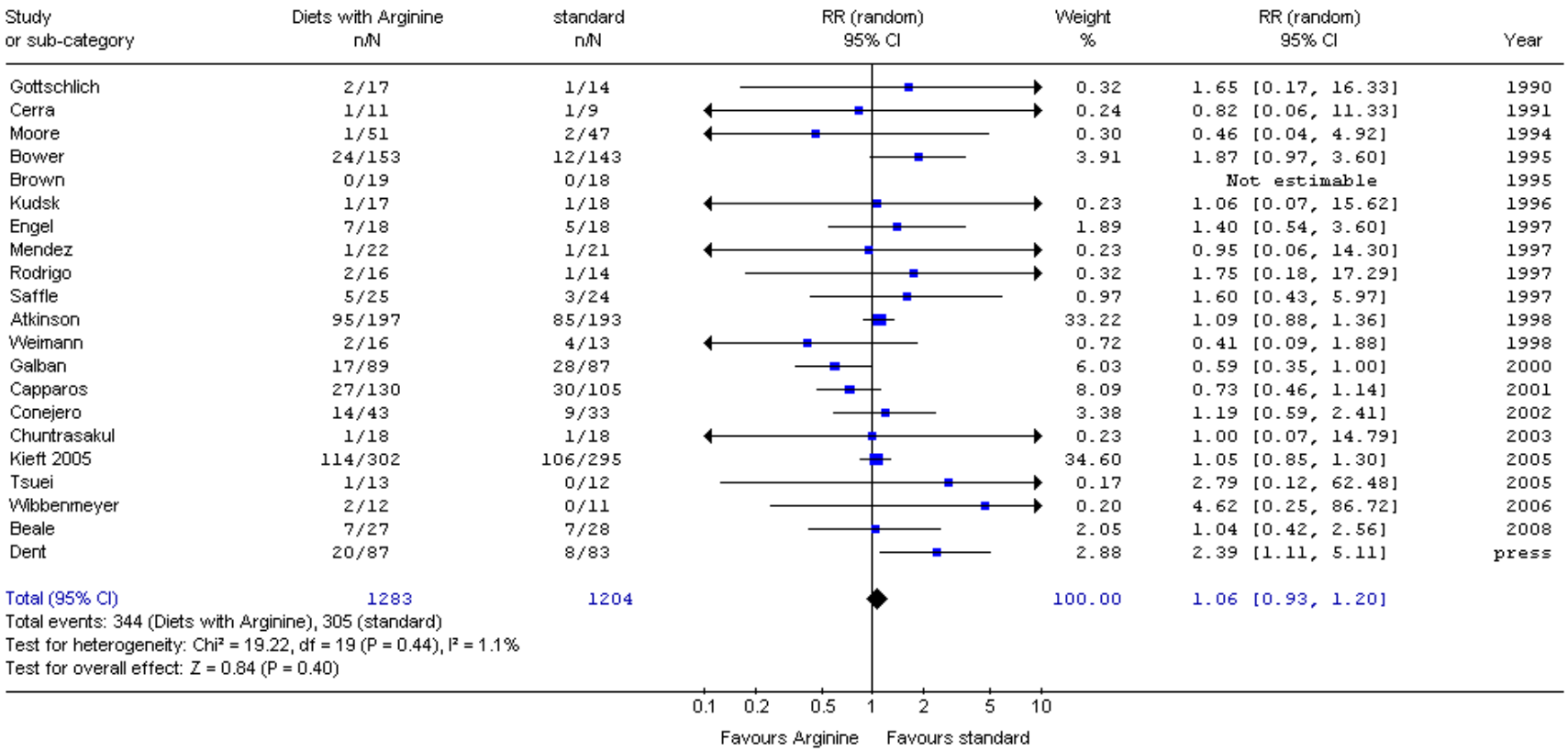


Figure 2. Sub group analysis Mortality with high quality studies (≥ 8 score)

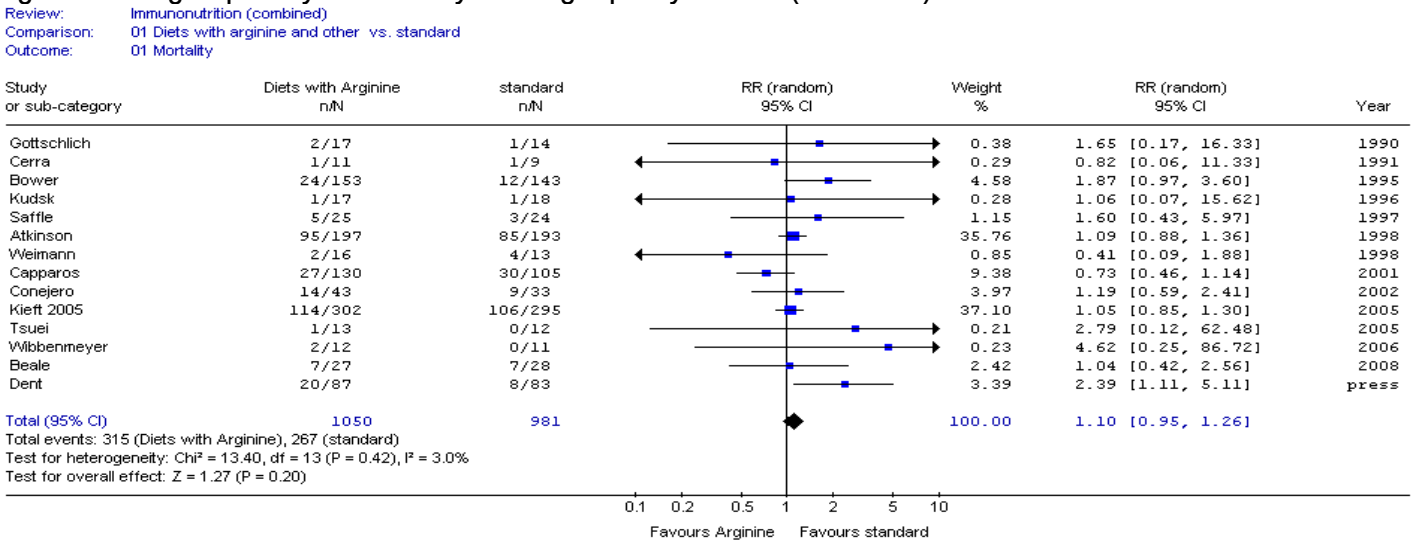


Figure 3. Mortality with low quality studies (< 8 score)

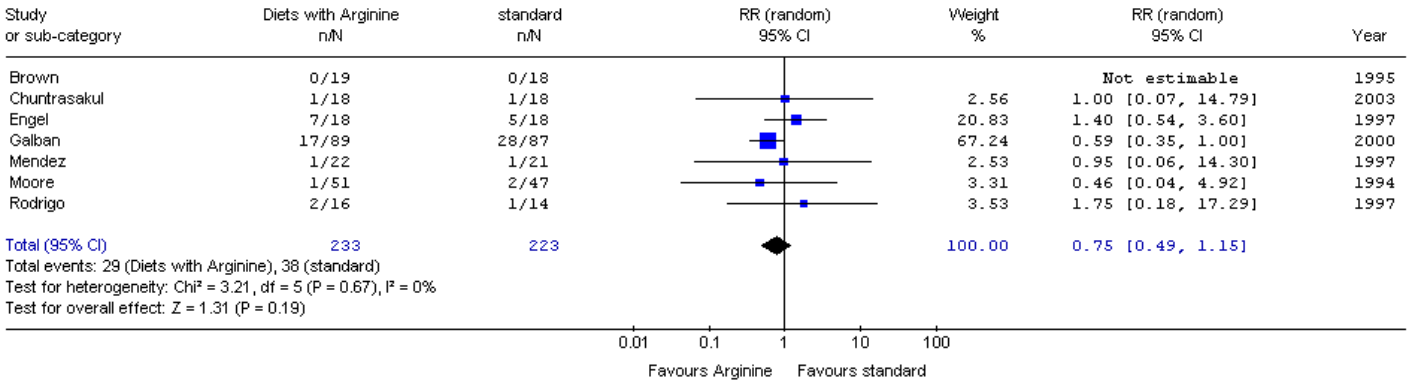


Figure 4. Sub group analysis Mortality in trauma patients

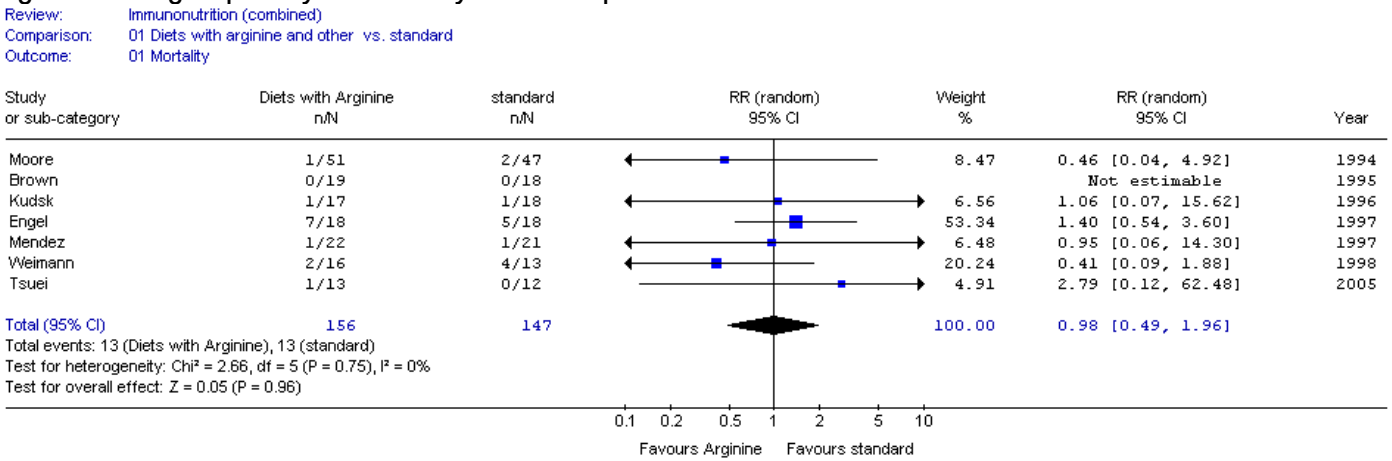


Figure 5. Mortality in non-trauma patients

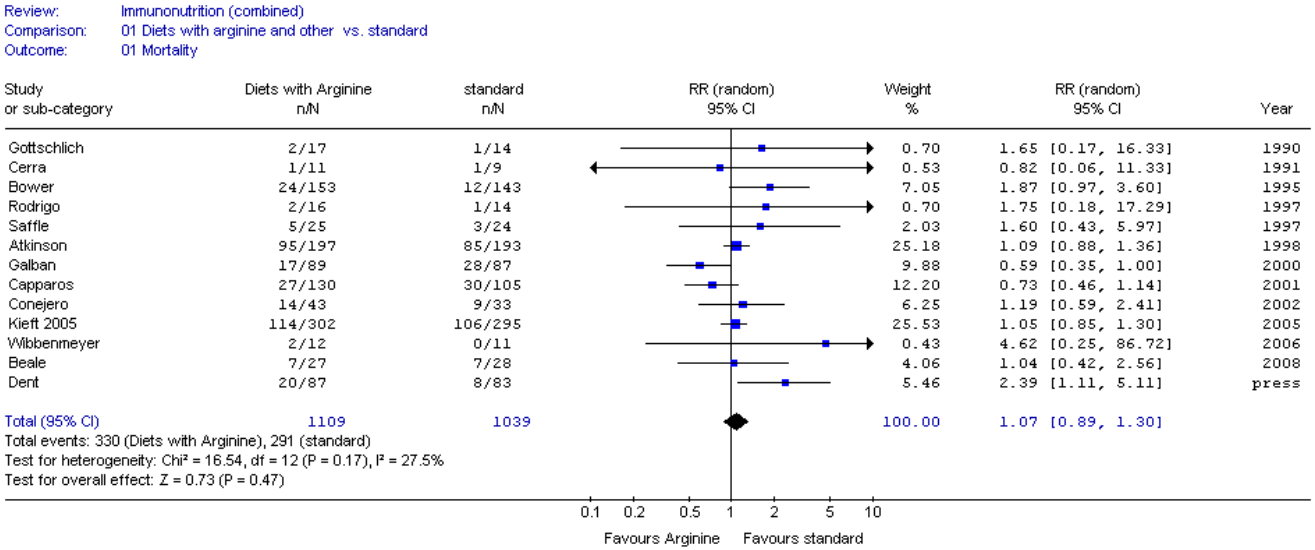


Figure 6.

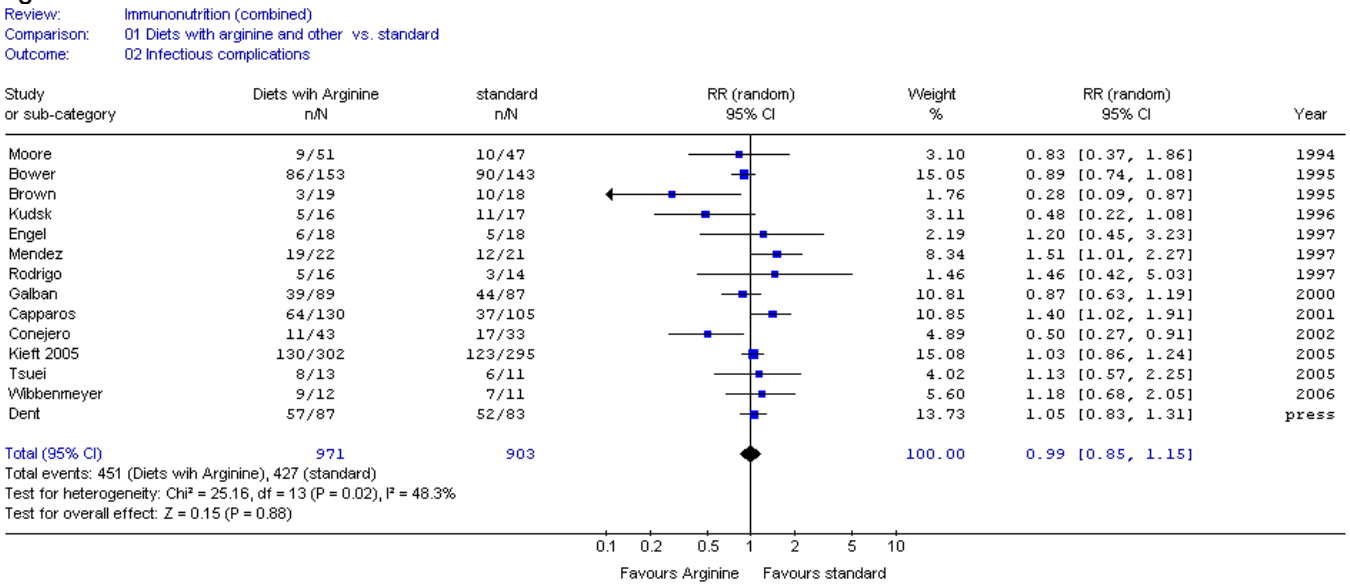


Figure 7. Sub group analysis Infections with high quality studies (≥ 8 score)

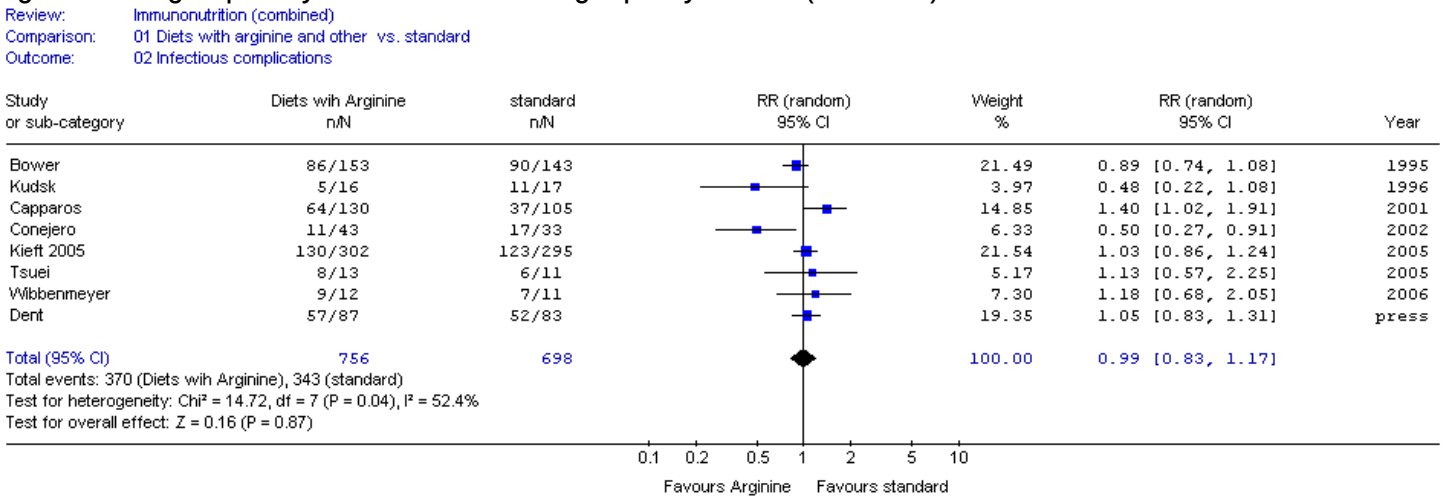


Figure 8. Infections with low quality studies (< 8 score)

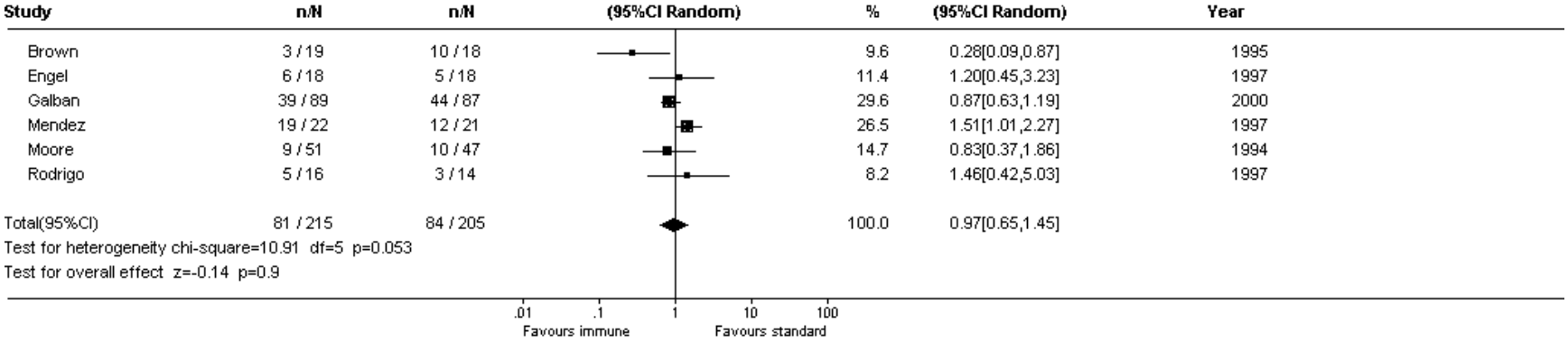


Figure 9. Sub group analysis Infection in trauma patients

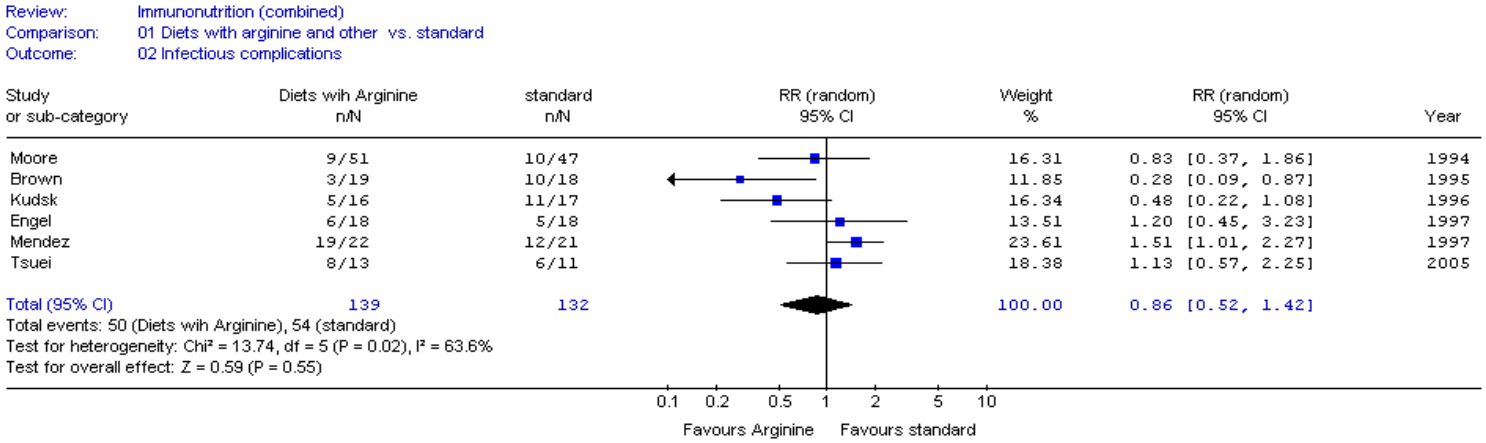


Figure 10. Infection in non-trauma patients

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

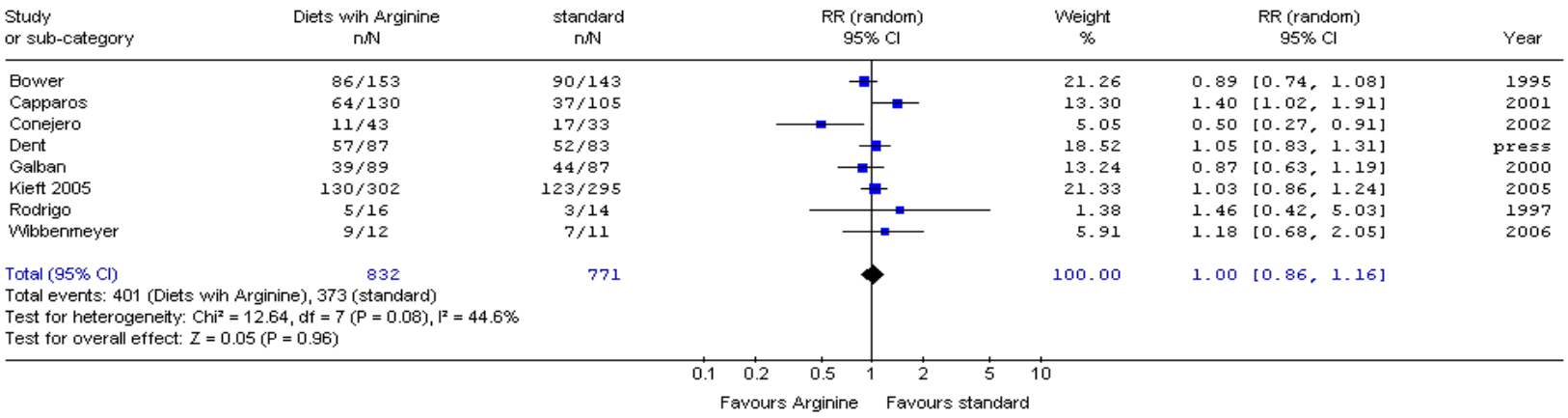


Figure 11.

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

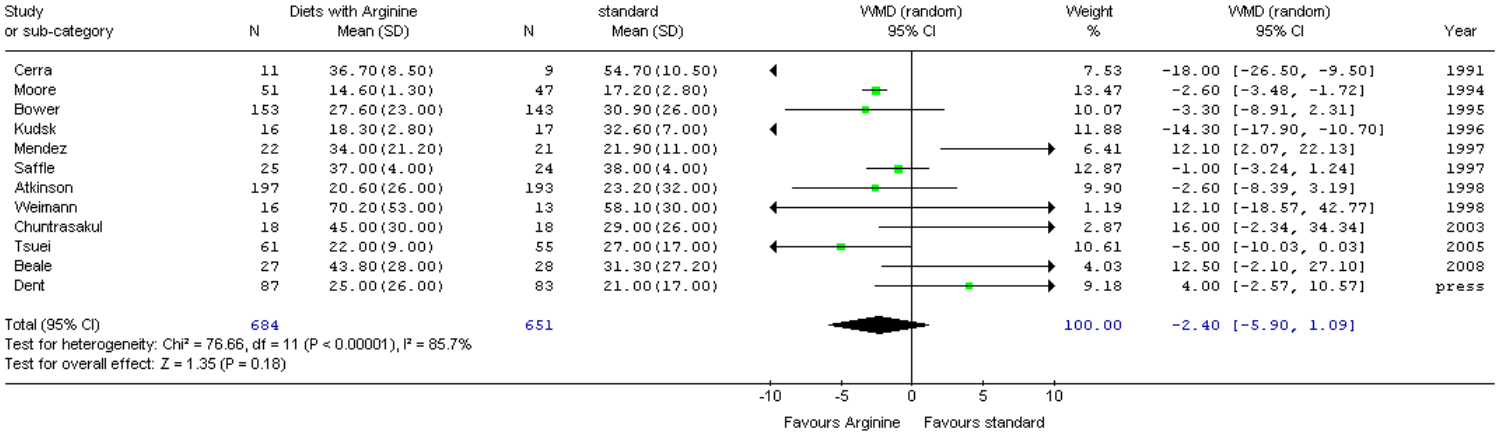


Figure 12.

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

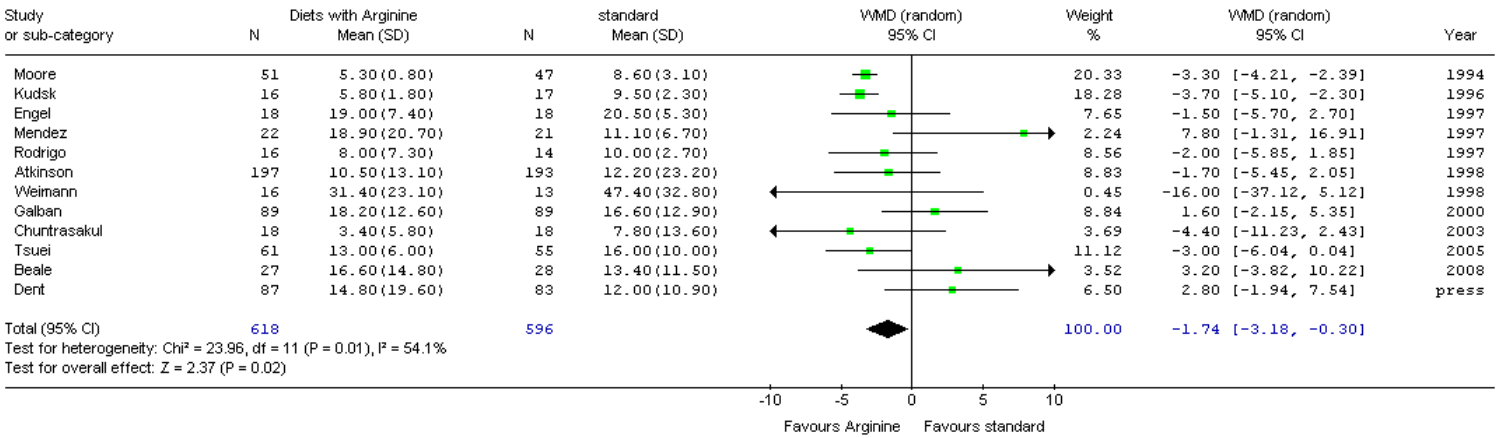
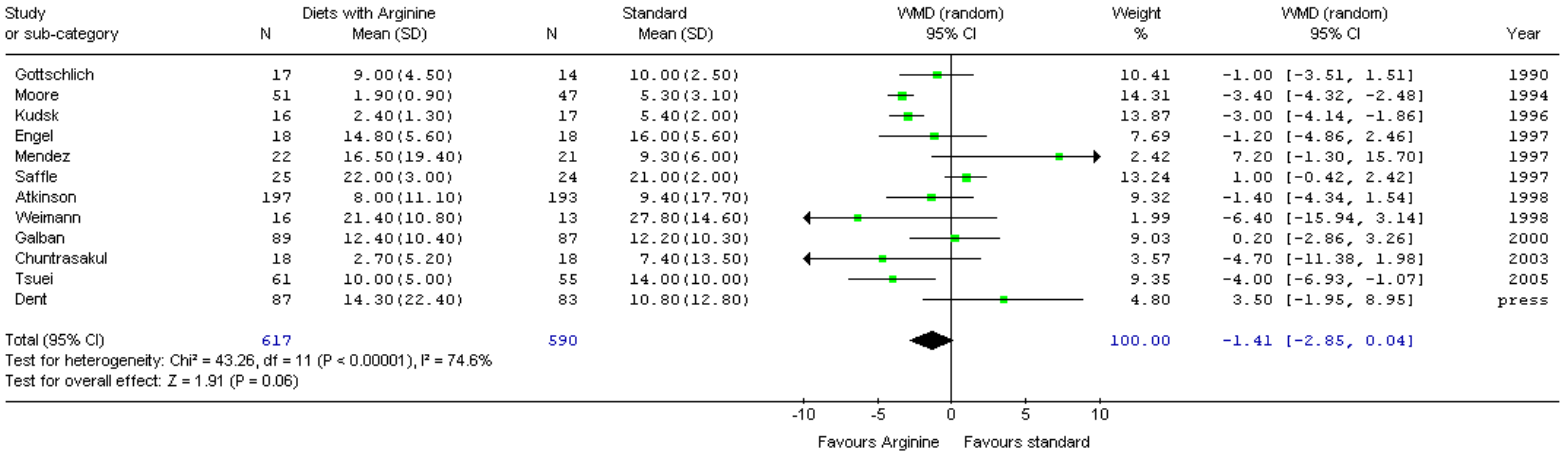


Figure 13.

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



FINAL DRAFT

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

Article inclusion log
Criteria for study selection

Type of study: RCT or Meta-analysis
Population: Critically ill, ventilated patients (no elective surgery patients)
Intervention: 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	Daly	Ann Surg 1988		√	Cancer pts
2	Cerra	Nutrition 1990	√		
3	Gottschlich	JPEN J Parenter Enteral Nutr 1990	√		
4	Cerra	Nutrition 1991		√	Same as Cerra 1990 study
5	Daly	Surgery 1992		√	Cancer pts
6.	Brown	Pharmacotherapy 1994	√		
7	Moore	J Trauma 1994	√		
8	Bower	Crit Care Med 1995	√		
9	Daly	Ann Surg 1995		√	Cancer pts
10	Kemen	Crit Care Med 1995		√	Cancer pts
11	Kudsk	Ann Surg 1996	√		
12	Schilling	Nutrition 1996		√	Elective surgery pts
13	Engel	Anaesthiol Intensiv 1997	√		
14	Gianotti	Arch Surg 1997			Cancer pts
15	Heslin	Annals Surg 1997		√	Elective surgery patients
16	Mendez	J Trauma 1997	√		
17	Rodrigo	Nutr Hosp 1997	√		
18	Saffle	J Trauma 1997	√		Compared Impact to Replete; not immune to non-immune
19	Senkal	Crit Care Med 1997		√	Cancer pts
20	Atkinson	Crit Care Med 1998	√		
21	Braga	Crit Care Med 1998		√	Cancer pts
22	McCarter	JPEN 1998		√	Cancer pts
23	Weimann	Nutrition 1998	√		
24	Beale	Crit Care Med 1999		√	Excluded as elective surgery patients, ICU studies included in ID # 23
25	Braga	Arch Surg 1999		√	Cancer pts
26	Di Carlo	Digestive Surgery 1999		√	Cancer pts
27	Heys	Annals Surgery 1999		√	Excluded as elective surgery patients, ICU studies included in ID # 23
28	Senkal	Arch Surg 1999		√	Cancer pts
29	Snyderman	Laryngoscope 1999		√	Oncologic surgery pts
30	Galban	Crit Care Med 2000	√		
31	Gianotti	Pancreas 2000		√	Surgery pts
32	Riso	Clin Nut 2000		√	Elective surgery patients
33	Caparros	JPEN J Parenter Enteral Nutr 2001	√		
34	Heyland	JAMA 2001		√	All studies from this review were

					included separately
35	Jiang	Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2001		√	Elective surgery pts
36	Tepaske	Lancet 2001		√	Elective surgery patients
37	Preiser	JPEN J Parenter Enteral Nutr 2001		√	No clinical outcomes
38	Van Bokhorst	Am J Clin Nutr 2001		√	Elective surgery patients
39	Hallay	Hepatogastroenterology 2001		√	Excluded as unclear if randomized
40	Braga	Arch Surg 2002		√	Cancer pts, Same as Braga 2002, Gianotti 2003
41	Braga	Surgery 2002		√	Cancer pts, Same as Braga 2002, Gianotti 2003
42	Conejero	Nutrition 2002	√		
43	Gianotti	Gastroenterology 2002		√	Cancer pts, Same as Braga 2002, Gianotti 2003
44	Bertolini	Intensive Care Med 2003	√		
45	Chuntrasakul	J Med Ass Thai 2003	√		
46	Dent	Crit Care Med 2003	√		
47	Montejo	Clinical Nutrition 2003		√	Systematic review, Individual studies looked at
48	Briassoulis G	Int Care Med 2005		√	Pediatrics
49	Farreras	Clin Nutr 2005		√	Cancer pts
50	Kieft	Intensive Care Med 2005	√		
51	Tsuei	J Surgical Research 2005	√		
52	Lobo	Clin Nutr 2006		√	Cancer pts
53	Waitzberg	World J Surg 2006		√	Elective surgery pts
54	Wibbenmeyer	J Burn Care and Rehab 2006	√		
55	Xu	World J Surg 2006		√	Cancer pts
56	De Luis	Eur J Clin Nutr 2007		√	Cancer pts
57	Finco	Surg Endosc		√	Surgery pts
58	Giger	Ann Surg Oncol 2007		√	Cancer pts
59	Helminen	Scan J Surg 2007		√	Elective surgery pts
60	Sakurai	World J Surg 2007		√	Cancer pts
61	Slotwinski	Centr Eur J Immunol 2007		√	Surgery pts
62	Tepaske	JPEN 2007		√	Surgery pts
63	Beale	Crit Care Med 2008	√		
64	Casas-Rodera	Nutr Hosp 2008		√	Cancer pts
65	Klek	Ann Surg 2008		√	Elective surgery pts
66	Klek	Clin Nutr 2008		√	Cancer pts
67	Marik	Int Care Med 2008		√	Systematic review, ICU studies are included

I = included, E = excluded

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