4.1a EN Composition: Diets Supplemented with Arginine and Select Other Nutrients

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 26 studies reviewed, 5 level 1 studies and 21 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 Kuhls 2007 study had two interventions including one comparing enteral nutrition supplemented with arginine plus ß hydroxyl methyl butyrate & glutamine (Juven) to standard enteral nutrition alone, the data for which is included in this section. The data pertaining to the second intervention from this study comparing enteral nutrition supplemented with ß hydroxyl methyl to standard enteral nutrition alone is described in section 6.5 EN Other formulas. There was only one study in which arginine was given without other select nutrients (Tsuei 2004***), hence sensitivity analyses were done without this study.

Mortality: All 26 studies reported on mortality and when the results of the 26 studies (Bertolini 2003 excluded) were aggregated, there was no effect on mortality (RR 1.06, 95% CI 0.93, 1.20, p=0.40, heterogeneity I^2=0%; figure 1a). When a sensitivity analysis was done which excluded the Tsuei study, there also was no effect on mortality (RR 1.05, 95% CI 0.92, 1.21, p=0.46, heterogeneity I^2=4%; figure 1b). 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 had no effect on mortality when including the Tsuei study (RR 1.09, 95% CI 0.95, 1.25, p=0.21, heterogeneity I^2=2%; figure 1a) and excluding the Tsuei study (RR 1.10, 95% CI 0.94, 1.28, p=0.24, heterogeneity I^2=6%; figure 1b); whereas in lower quality studies diets supplemented with arginine and other nutrients were associated with a trend towards a reduction in mortality (RR 0.76, 95% CI 0.49, 1.16, p=0.20, heterogeneity I^2=0%; figure 1a). The difference between these two subgroups was not statistically significant (p=0.11). When the studies of trauma including the Tsuei study (RR 1.04, 95% CI 0.56, 1.93, p=0.91, heterogeneity I^2=0%; figure 2a) and excluding the Tsuei study (RR 1.00, 95% CI 0.53, 1.88, p=1.00, heterogeneity I^2=0%; figure 2b) vs. non-trauma patients (RR 1.07, 95% CI 0.87, 1.30, p=0.52, heterogeneity I^2=29%; figure 2a) were compared, there were no differences in mortality. The difference between these two subgroups was not statistically significant (p=0.93). When the Tsuei study was considered by itself, there was no effect on mortality (RR 2.57, 95% CI 0.12, 57.44, p=0.55).

Infections: Based on the 14 studies that reported on the number of infectious complications, there was no difference in the rate of infectious complications in the analysis that included the Tsuei study (RR 0.99 95% CI, 0.85, 1.15, p=0.88, heterogeneity I^2=48%; figure 3a) and the analysis that excluded the Tsuei study (RR 0.98, 95% CI 0.83, 1.15, p=0.81, heterogeneity I^2=52%; figure 3b). Subgroup analysis also showed no differences in infectious complications when high quality studies including the Tsuei study (RR 0.99, 95% CI 0.83, 1.17, p=0.87, heterogeneity I^2=52%; figure 3a) and excluding the Tsuei study (RR 0.98, 95% CI 0.81, 1.17, p=0.80, heterogeneity I^2=59%; figure 3b) were compared to lower quality studies (RR 0.97, 95% CI 0.65, 1.45, p=0.89, heterogeneity I^2=54%; figure 3a), and when studies of trauma patients including the Tsuei study (RR 0.86, 95% CI 0.52, 1.42, p=0.55, heterogeneity I^2=63%; figure 4a) and excluding the Tsuei study (RR 0.79, 95% CI 0.41, 1.50, p=0.46, heterogeneity I^2=71%;

figure 4b) were compared to studies of non-trauma patients (RR 1.00, 95% CI 0.86, 1.16, p=0.96, heterogeneity I^2=45%; figure 4a). When the Tsuei study was considered by itself, there was no effect on infectious complications (RR 1.13, 95% CI 0.57, 2.25, p=0.73).

Length of stay: Diets supplemented with arginine and other nutrients had no effect on hospital length of stay when the Tsuei study was included in the analysis (WMD -1.02, 95% CI -5.10, 3.07, p=0.63, heterogeneity I^2=84%; figure 5a) and when the Tsuei study was excluded from the analysis (WMD -0.40, 95% CI -4.95, 4.15, p=0.86, heterogeneity I^2=85%; figure 5b); or on ICU length of stay when the Tsuei study was included in the analysis (WMD -0.77, 95% CI -2.46, 0.92, p=0.37, heterogeneity I^2=68%; figure 6a) or when the Tsuei study was excluded from the analysis (WMD -0.44, 95% CI -2.31, 1.42, p=0.64, heterogeneity I^2=70%; figure 6b). When the Tsuei study was considered by itself, there was no effect on hospital length of stay (WMD -5.00, 95% CI -16.17, 6.17, p=0.38) or ICU length of stay (WMD -3.00, 95% CI -9.75, 3.75, p=0.38).

Duration of mechanical ventilation: Diets supplemented with arginine and other nutrients were associated with a significant reduction in mechanical ventilation when the Tsuei study was included in the analysis (WMD -1.99, 95% CI -3.29, -0.69, p=0.003, heterogeneity I^2=52%; figure 7a) and when the Tsuei study was excluded from the analysis (WMD -1.68, 95% CI -3.11, -0.25, p=0.02, heterogeneity I^2=55%; figure 7b). When the Tsuei study was considered by itself, there was no effect on duration of mechanical ventilation (WMD -4.00, 95% CI -10.50, 2.50, p=0.23).

Conclusions:
1) Diets supplemented with arginine and other nutrients have no effect on overall mortality in critically ill patients.
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 have no effect on hospital length of stay and ICU length of stay
4) Diets supplemented with arginine and other nutrients may be associated with a reduction in duration of mechanical ventilation in critically ill patients but the presence of significant heterogeneity limits this inference.

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 # (%)	
				Arginine	Control	Arginine	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)	NR	NR
2) Gottschlich 1990	Critically ill burn patients 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
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)
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)
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)
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)
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	ICU 7/18 (39)	ICU 5/18 (28)	6/18 (33)	5/18 (28)

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)
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 (13)	ICU 1/14 (7)	5/16 (31)	3/14 (21)
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
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 (13)	4/13 (31)	NR	NR
12) Atkinson 1998	Mixed ICU N=390	C.Random: no ITT: yes Blinding: yes (11)	Impact *(see below)* vs. specially prepared isocaloric isonitrogenous diets	95/197 (48)	85/193 (44)	NR	NR
13) Galban 2000	Critically ill septic patients 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)
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)
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)

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)
17) Bertolini 2003**	Patients with severe sepsis from 33 ICUs N=39	C.Random:yes ITT: yes Blinding: no (10)	Perative *(see below)* vs. parenteral nutrition non-isocaloric diets	ICU 8/18(44) 28-day 8/18 (44)	ICU 3/21(14) 28-day 5/21 (24)	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 diets	1/18 (5)	1/18 (5)	NR	NR
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 diets	1/13 (8) RR 2.57, 95% CI 0.12, 57.44, p=0.55	0/11 (0)	8/13 (61) RR 1.13, 95% CI 0.57, 2.25, p=0.73	6/11 (55)
20) Kieft 2005	Mixed ICU patients 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 diets	ICU 84/302 (28) Hospital 114/302 (38) 28-day 93/302 (34)	ICU 78/295 (26) Hospital 106/295 (36) 28-day 82/295 (30)	130/302 (43)	123/295 (42)
21) Pearce 2006	Acute pancreatitis patients N=31	C.Random: yes ITT: no Blinding: double (9)	Complete prototype formula with feed with feed with glutamine, arginine, omega 3 fatty acids and antioxidants vs. control prototype feed isonitrogenous, isocaloric diets	0/15 (0)	3/16 (19)	NR	NR
22) 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 diets	2/12 (17)	0/11	9/12 (75)	7/11 (64)

23) Kuhls 2007****	Trauma patients in ICU Injury Severity Score >18 N=100	C.Random: not sure ITT: no Blinding: double (10)	Standard EN + 3 gms ß hydroxyl methyl butyrate (HMB) + 14 gm arginine + 14 gms glutamine (Juven) vs. standard EN + isonitrogenous placebo supplement 25kcal/kg/day, 1.5g pro/kg/day isonitrogenous, isocaloric diets	3/22 (14)	2/22 (9)	4.0 ± 2.81 (per patient)	4.6 ± 2.81 (per patient)
24) 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 diets	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
25) Khorana 2009	Moderate to severe head injury patients requiring neurosurgery N=40	C.Random: yes ITT: yes Blinding: double (12)	EN formula Neomune (polymeric, 12.5 g/L arg, 6.25 g/L glutamine) vs EN formula Panenteral (polymeric) modified with the addition of protein.	0/20	0/20	Wound infection 0/20 Chest infection 7/20 (35) UTI 0/20 GI bleed 1/20 (5)	Wound infection 0/20 Chest infection 12/20 (60) UTI 1/20 (5) GI bleed 0/20
26) Iamsirisaengthong 2017	Major burn patients (>20% TBSA) N=20	C.Random: no ITT: no Blinding: no (3)	Neomune (25% protein, gln and arg containing) vs blenderized diet (17% protein). Isocaloric, non-isonitrogenous.	Hospital 1/10 (10%)	Hospital 1/10 (10%)	Septic complications 4/10 (40%) Wound Healing (days) 32.3 ± 14.3	Septic complications 7/10 (70%) Wound Healing (days) 38.3 ± 14.9

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

Study	Length of Stay (days)		Duration of Ventilation (days)	
	Arginine	Control	Arginine	Control
1) Cerra 1990	36.7 ± 8.5	54.7 ± 10.5	NR	NR
2) Gottschlich 1990	NR	NR	9 ± 4.5 Mean ± SEM	10 ± 2.5 Mean ± SEM
3) Brown 1994	NR	NR	NR	NR
4) Moore 1994	ICU 5.3 ± 0.8 Hospital 14.6 ± 1.3	ICU 8.6 ± 3.1 Hospital 17.2 ± 2.8	1.9 ± 0.9	5.3 ± 3.1
5) Bower 1995	Hospital 27.6 ± 23	Hospital 30.9 ± 26	NR	NR
6) Kudsk 1996*	ICU 5.8 ± 1.8 Hospital 18.3 ± 2.8	ICU 9.5 ± 2.3 Hospital 32.6 ± 7	2.4 ± 1.3	5.4 ± 2.0
7) Engel 1997	ICU 19 ± 7.4 Hospital NR	ICU 20.5 ± 5.3 Hospital NR	14.8 ± 5.6	16 ± 5.6
8) Mendez 1997	ICU 18.9 ± 20.7 Hospital 34 ± 21.2	ICU 11.1 ± 6.7 Hospital 21.9 ± 11	16.5 ± 19.4	9.3 ± 6

9) Rodrigo 1997	ICU 8 ± 7.3 Hospital NR	ICU 10 ± 2.7 Hospital NR	NR	NR
10) Saffle 1997	Hospital 37 ± 4 (mean ± SEM)	Hospital 38 ± 4 (mean ± SEM)	22 ± 3 (mean ± SEM)	21 ± 2 (mean ± SEM)
11) Weimann 1998	ICU 31.4 ± 23.1 Hospital 70.2 ± 53	ICU 47.4 ± 32.8 Hospital 58.1 ± 30	21.4 ± 10.8	27.8 ± 14.6
12) Atkinson 1998	ICU 10.5 ± 13.1 Hospital 20.6 ± 26	ICU 12.2 ± 23.2 Hospital 23.2 ± 32	8 ± 11.1	9.4 ± 17.7
13) Galban 2000	ICU 18.2 ± 12.6 Hospital NR	ICU 16.6 ± 12.9 Hospital NR	12.4 ± 10.4	12.2 ± 10.3
14) Capparos 2001	ICU 15 (9.8-25) Hospital 29 (16.8-51)	ICU 13 (8.8-20.3) Hospital 26 (17.8-42)	10 (5-18)	9 (5-14)
15) Conejero 2002	14 (4-63)	15(4-102)	14 (5-25)	14 (5-29)
16) Dent 2003	ICU 14.8 ± 19.6 Hospital 25.4 ± 26	ICU 12 ± 10.9 Hospital 20.9 ± 17	14.3 ± 22.4	10.8 ± 12.8
17) Bertolini 2003**	13.5 (9-26)	15 (11-29)	NR	NR

18) Chuntrasakul 2003	ICU 3.4 ± 5.8 Hospital 44.9 ± 30.2	ICU 7.8 ± 13.6 Hospital 28.8 ± 25.7	2.7 ± 5.2	7.4 ± 1.3
19) Tsuei 2004***	ICU 13 ± 6 (13) WMD -3.00, 95% CI -9.75, 3.75, p=0.38 Hospital 22 ± 9 (13) WMD -5.00, 95% CI -16.17, 6.17, p=0.38	ICU 16 ± 10 (11) Hospital 27 ± 17 (11)	10 ± 5 (13) WMD -4.00, 95% CI -10.50, 2.50, p=0.23	14 ± 10 (11)
20) Kieft 2005	ICU 7 (4-14) Hospital 20 (10-35)	ICU 8 (5-16) Hospital 20 (10-34)	6 (3-12)	6 (3-12)
21) Pearce 2006	ICU 11.0 ± 9.5 Hospital 19.1 ± 14.4	ICU 4.0 ± 3.6 Hospital 13.4 ± 11.1	NR	NR
22) Wibbenmeyer 2006	NR	NR	Longer in experimental group; specific numeric data not reported	
23) Kuhls 2007****	ICU 27.8 ± 17.82 (22) Hospital 40.0 ± 23.45 (22)	ICU 22.4 ± 17.35 (22) Hospital 30.3 ± 22.98 (22)	23.1 ± 12.66 (22)	20.9 ± 12.66 (22)
24) Beale 2008	ICU 16.6 ± 14.8 Hospital 43.8 ± 36.6	ICU 13.4 ± 11.5 Hospital 31.3 ± 27.2	NR	NR
25) Khorana 2009	ICU 9.6 days	ICU 9.3 days	NR	NR

26) Iamsirisaengthong 2017	Hospital 35.4 ± 15.2	Hospital 40.4 ± 15.2	NR	NR

C.Random: Concealed randomization NR: Not Reported ITT: intent to treat LOS: Length of stay ICU: intensive care unit

**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 2004: excluded in sensitivity analyses as only study that gave arginine alone.
****Kuhls 2007: data pertaining to* ß hydroxyl methyl butyrate (HMB) supplement vs none not shown here, refer to section 6.5 Other EN Formulas for more details
‡ 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.
Neomune 48 g sachet: 2.5 g arginine, 1.25 g glutamine, fish oil, 12.5 g protein (Protein: 20% arginine, 10% glutamine; Fat: 20% fish oil) vs study's prepared formula: 12.5 g/L arginine, 6.25 g/L glutamine, fish oils, 62.5 g/L of protein

Figure 1a. Mortality (with quality sub-analyses)

Study or Subgroup	Diets with Arginine Events	Diets with Arginine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 High Quality Studies (8+)							
Gottschlich	2	17	1	14	0.3%	1.65 [0.17, 16.33]	1990
Cerra	1	11	1	9	0.2%	0.82 [0.06, 11.33]	1991
Bower	24	153	12	143	3.6%	1.87 [0.97, 3.60]	1995
Kudsk	1	17	1	18	0.2%	1.06 [0.07, 15.62]	1996
Saffle	5	25	3	24	0.9%	1.60 [0.43, 5.97]	1997
Atkinson	95	197	85	193	33.7%	1.09 [0.88, 1.36]	1998
Weimann	2	16	4	13	0.7%	0.41 [0.09, 1.88]	1998
Capparos	27	130	30	105	7.6%	0.73 [0.46, 1.14]	2001
Conejero	14	43	9	33	3.1%	1.19 [0.59, 2.41]	2002
Dent	20	87	8	83	2.7%	2.39 [1.11, 5.11]	2003
Tsuei	1	13	0	11	0.2%	2.57 [0.12, 57.44]	2005
Kieft	114	302	106	295	35.3%	1.05 [0.85, 1.30]	2005
Wibbenmeyer	2	12	0	11	0.2%	4.62 [0.25, 86.72]	2006
Pearce	0	15	3	16	0.2%	0.15 [0.01, 2.71]	2006
Kuhls	3	22	2	22	0.5%	1.50 [0.28, 8.12]	2007
Beale	7	27	7	28	1.9%	1.04 [0.42, 2.56]	2008
Khorana	0	20	0	20		Not estimable	2009
Subtotal (95% CI)		**1107**		**1038**	**91.4%**	**1.09 [0.95, 1.25]**	
Total events	318		272				
Heterogeneity: Tau² = 0.00; Chi² = 15.23, df = 15 (P = 0.43); I² = 2%							
Test for overall effect: Z = 1.26 (P = 0.21)							
1.1.2 Low Quality Studies (<8)							
Moore	1	51	2	47	0.3%	0.46 [0.04, 4.92]	1994
Brown	0	19	0	18		Not estimable	1995
Engel	7	18	5	18	1.8%	1.40 [0.54, 3.60]	1997
Mendez	1	22	1	21	0.2%	0.95 [0.06, 14.30]	1997
Rodrigo	2	16	1	14	0.3%	1.75 [0.18, 17.29]	1997
Galban	17	89	28	87	5.7%	0.59 [0.35, 1.00]	2000
Chuntrasakul	1	18	1	18	0.2%	1.00 [0.07, 14.79]	2003
Iamsirisaengthong	1	10	1	10	0.2%	1.00 [0.07, 13.87]	2017
Subtotal (95% CI)		**243**		**233**	**8.6%**	**0.76 [0.49, 1.16]**	
Total events	30		39				
Heterogeneity: Tau² = 0.00; Chi² = 3.25, df = 6 (P = 0.78); I² = 0%							
Test for overall effect: Z = 1.29 (P = 0.20)							
Total (95% CI)		**1350**		**1271**	**100.0%**	**1.06 [0.93, 1.20]**	
Total events	348		311				
Heterogeneity: Tau² = 0.00; Chi² = 21.05, df = 22 (P = 0.52); I² = 0%							
Test for overall effect: Z = 0.85 (P = 0.40)							
Test for subgroup differences: Chi² = 2.61, df = 1 (P = 0.11), I² = 61.7%							

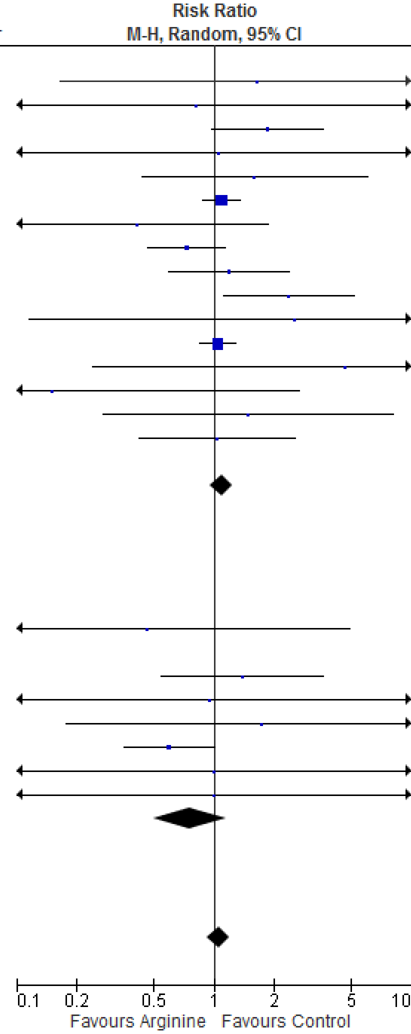

Figure 1b. Mortality (with quality sub-analyses; excluding Tsuei)

Study or Subgroup	Diets with Arginine Events	Diets with Arginine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.6.1 High Quality Studies (8+)							
Gottschlich	2	17	1	14	0.3%	1.65 [0.17, 16.33]	1990
Cerra	1	11	1	9	0.2%	0.82 [0.06, 11.33]	1991
Bower	24	153	12	143	3.6%	1.87 [0.97, 3.60]	1995
Kudsk	1	17	1	18	0.2%	1.06 [0.07, 15.62]	1996
Saffle	5	25	3	24	0.9%	1.60 [0.43, 5.97]	1997
Weimann	2	16	4	13	0.7%	0.41 [0.09, 1.88]	1998
Atkinson	95	197	85	193	33.8%	1.09 [0.88, 1.36]	1998
Capparos	27	130	30	105	7.6%	0.73 [0.46, 1.14]	2001
Conejero	14	43	9	33	3.2%	1.19 [0.59, 2.41]	2002
Dent	20	87	8	83	2.7%	2.39 [1.11, 5.11]	2003
Kieft	114	302	106	295	35.3%	1.05 [0.85, 1.30]	2005
Pearce	0	15	3	16	0.2%	0.15 [0.01, 2.71]	2006
Wibbenmeyer	2	12	0	11	0.2%	4.62 [0.25, 86.72]	2006
Kuhls	3	22	2	22	0.5%	1.50 [0.28, 8.12]	2007
Beale	7	27	7	28	1.9%	1.04 [0.42, 2.56]	2008
Khorana	0	20	0	20		Not estimable	2009
Subtotal (95% CI)		**1094**		**1027**	**91.4%**	**1.10 [0.94, 1.28]**	
Total events	317		272				
Heterogeneity: Tau² = 0.01; Chi² = 14.93, df = 14 (P = 0.38); I² = 6%							
Test for overall effect: Z = 1.17 (P = 0.24)							
1.6.2 Low Quality Studies (<8)							
Moore	1	51	2	47	0.3%	0.46 [0.04, 4.92]	1994
Brown	0	19	0	18		Not estimable	1995
Mendez	1	22	1	21	0.2%	0.95 [0.06, 14.30]	1997
Rodrigo	2	16	1	14	0.3%	1.75 [0.18, 17.29]	1997
Engel	7	18	5	18	1.8%	1.40 [0.54, 3.60]	1997
Galban	17	89	28	87	5.7%	0.59 [0.35, 1.00]	2000
Chuntrasakul	1	18	1	18	0.2%	1.00 [0.07, 14.79]	2003
Iamsirisaengthong	1	10	1	10	0.2%	1.00 [0.07, 13.87]	2017
Subtotal (95% CI)		**243**		**233**	**8.6%**	**0.76 [0.49, 1.16]**	
Total events	30		39				
Heterogeneity: Tau² = 0.00; Chi² = 3.25, df = 6 (P = 0.78); I² = 0%							
Test for overall effect: Z = 1.29 (P = 0.20)							
Total (95% CI)		**1337**		**1260**	**100.0%**	**1.05 [0.93, 1.19]**	
Total events	347		311				
Heterogeneity: Tau² = 0.00; Chi² = 20.73, df = 21 (P = 0.48); I² = 0%							
Test for overall effect: Z = 0.83 (P = 0.41)							
Test for subgroup differences: Chi² = 2.60, df = 1 (P = 0.11), I² = 61.5%							

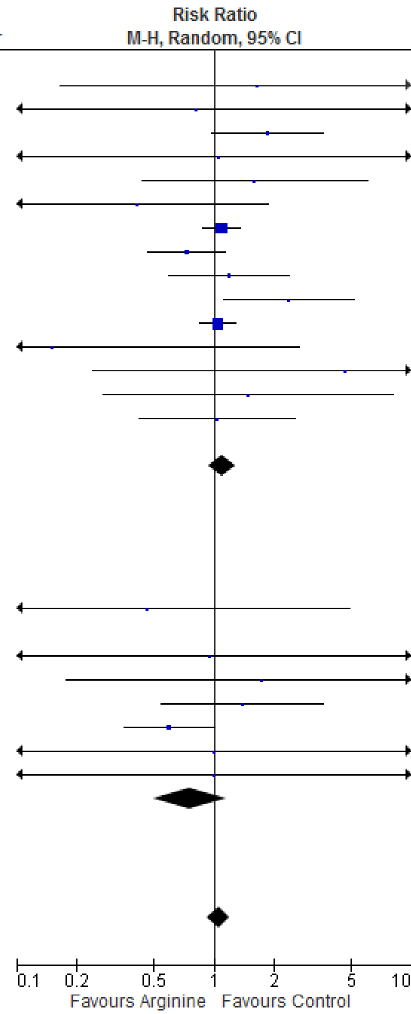

Figure 2a. Mortality (with trauma/non-trauma sub-analyses)

Study or Subgroup	Diets with Arginine Events	Diets with Arginine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.7.1 Trauma patients							
Moore	1	51	2	47	0.3%	0.46 [0.04, 4.92]	1994
Brown	0	19	0	18		Not estimable	1995
Kudsk	1	17	1	18	0.2%	1.06 [0.07, 15.62]	1996
Mendez	1	22	1	21	0.2%	0.95 [0.06, 14.30]	1997
Engel	7	18	5	18	1.8%	1.40 [0.54, 3.60]	1997
Weimann	2	16	4	13	0.7%	0.41 [0.09, 1.88]	1998
Chuntrasakul	1	18	1	18	0.2%	1.00 [0.07, 14.79]	2003
Tsuei	1	13	0	11	0.2%	2.57 [0.12, 57.44]	2005
Kuhls	3	22	2	22	0.5%	1.50 [0.28, 8.12]	2007
Khorana	0	20	0	20		Not estimable	2009
Subtotal (95% CI)		**216**		**206**	**4.0%**	**1.04 [0.56, 1.93]**	
Total events	17		16				
Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 7 (P = 0.90); I² = 0%							
Test for overall effect: Z = 0.12 (P = 0.91)							
1.7.2 Non-trauma patients							
Gottschlich	2	17	1	14	0.3%	1.65 [0.17, 16.33]	1990
Cerra	1	11	1	9	0.2%	0.82 [0.06, 11.33]	1991
Bower	24	153	12	143	3.6%	1.87 [0.97, 3.60]	1995
Rodrigo	2	16	1	14	0.3%	1.75 [0.18, 17.29]	1997
Saffle	5	25	3	24	0.9%	1.60 [0.43, 5.97]	1997
Atkinson	95	197	85	193	33.7%	1.09 [0.88, 1.36]	1998
Galban	17	89	28	87	5.7%	0.59 [0.35, 1.00]	2000
Capparos	27	130	30	105	7.6%	0.73 [0.46, 1.14]	2001
Conejero	14	43	9	33	3.1%	1.19 [0.59, 2.41]	2002
Dent	20	87	8	83	2.7%	2.39 [1.11, 5.11]	2003
Kieft	114	302	106	295	35.3%	1.05 [0.85, 1.30]	2005
Pearce	0	15	3	16	0.2%	0.15 [0.01, 2.71]	2006
Wibbenmeyer	2	12	0	11	0.2%	4.62 [0.25, 86.72]	2006
Beale	7	27	7	28	1.9%	1.04 [0.42, 2.56]	2008
Iamsirisaengthong	1	10	1	10	0.2%	1.00 [0.07, 13.87]	2017
Subtotal (95% CI)		**1134**		**1065**	**96.0%**	**1.06 [0.88, 1.29]**	
Total events	331		295				
Heterogeneity: Tau² = 0.02; Chi² = 18.26, df = 14 (P = 0.20); I² = 23%							
Test for overall effect: Z = 0.64 (P = 0.52)							
Total (95% CI)		**1350**		**1271**	**100.0%**	**1.06 [0.93, 1.20]**	
Total events	348		311				
Heterogeneity: Tau² = 0.00; Chi² = 21.05, df = 22 (P = 0.52); I² = 0%							
Test for overall effect: Z = 0.85 (P = 0.40)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%							

Risk Ratio
M-H, Random, 95% CI

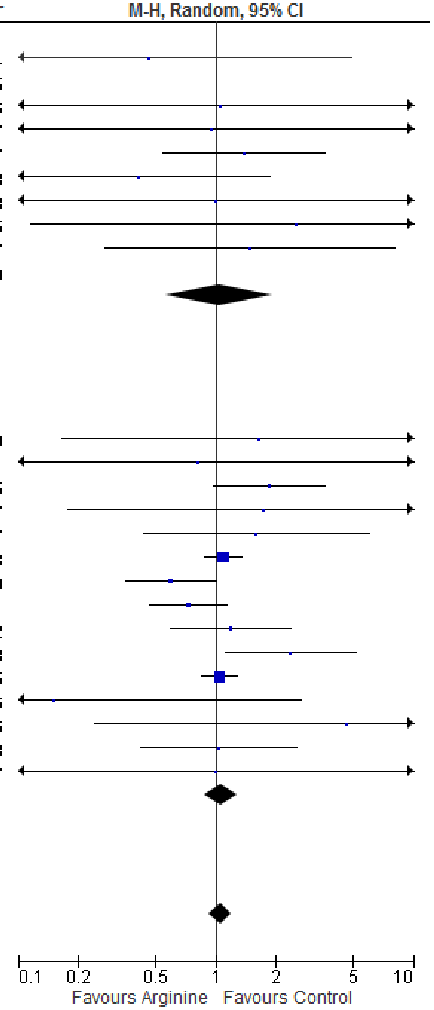

Figure 2b. Mortality in trauma patients (with trauma/non-trauma sub-analyses; excluding Tsuei)

Study or Subgroup	Diets with Arginine Events	Diets with Arginine Total	standard Events	standard Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.8.1 Trauma patients							
Moore	1	51	2	47	0.3%	0.46 [0.04, 4.92]	1994
Brown	0	19	0	18		Not estimable	1995
Kudsk	1	17	1	18	0.2%	1.06 [0.07, 15.62]	1996
Mendez	1	22	1	21	0.2%	0.95 [0.06, 14.30]	1997
Engel	7	18	5	18	1.8%	1.40 [0.54, 3.60]	1997
Weimann	2	16	4	13	0.7%	0.41 [0.09, 1.88]	1998
Chuntrasakul	1	18	1	18	0.2%	1.00 [0.07, 14.79]	2003
Kuhls	3	22	2	22	0.5%	1.50 [0.28, 8.12]	2007
Khorana	0	20	0	20		Not estimable	2009
Subtotal (95% CI)		**203**		**195**	**3.9%**	**1.00 [0.53, 1.88]**	
Total events	16		16				
Heterogeneity: Tau² = 0.00; Chi² = 2.47, df = 6 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.00 (P = 1.00)							
1.8.2 Non-trauma patients							
Gottschlich	2	17	1	14	0.3%	1.65 [0.17, 16.33]	1990
Cerra	1	11	1	9	0.2%	0.82 [0.06, 11.33]	1991
Bower	24	153	12	143	3.6%	1.87 [0.97, 3.60]	1995
Saffle	5	25	3	24	0.9%	1.60 [0.43, 5.97]	1997
Rodrigo	2	16	1	14	0.3%	1.75 [0.18, 17.29]	1997
Atkinson	95	197	85	193	33.8%	1.09 [0.88, 1.36]	1998
Galban	17	89	28	87	5.7%	0.59 [0.35, 1.00]	2000
Capparos	27	130	30	105	7.6%	0.73 [0.46, 1.14]	2001
Conejero	14	43	9	33	3.2%	1.19 [0.59, 2.41]	2002
Dent	20	87	8	83	2.7%	2.39 [1.11, 5.11]	2003
Kieft	114	302	106	295	35.3%	1.05 [0.85, 1.30]	2005
Pearce	0	15	3	16	0.2%	0.15 [0.01, 2.71]	2006
Wibbenmeyer	2	12	0	11	0.2%	4.62 [0.25, 86.72]	2006
Beale	7	27	7	28	1.9%	1.04 [0.42, 2.56]	2008
Iamsirisaengthong	1	10	1	10	0.2%	1.00 [0.07, 13.87]	2017
Subtotal (95% CI)		**1134**		**1065**	**96.1%**	**1.06 [0.88, 1.29]**	
Total events	331		295				
Heterogeneity: Tau² = 0.02; Chi² = 18.26, df = 14 (P = 0.20); I² = 23%							
Test for overall effect: Z = 0.64 (P = 0.52)							
Total (95% CI)		**1337**		**1260**	**100.0%**	**1.05 [0.93, 1.19]**	
Total events	347		311				
Heterogeneity: Tau² = 0.00; Chi² = 20.73, df = 21 (P = 0.48); I² = 0%							
Test for overall effect: Z = 0.83 (P = 0.41)							
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%							

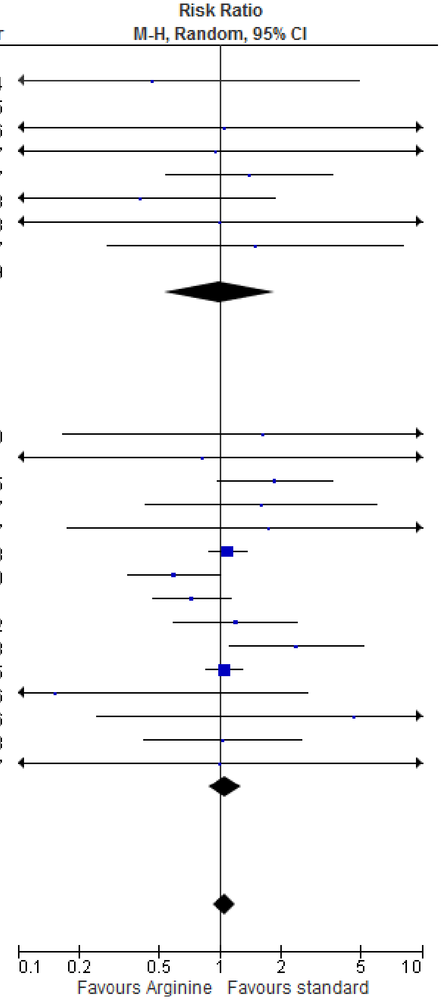

Figure 3a. Infectious complications (with quality sub-analyses)

	Diets wih Arginine		standard			Risk Ratio		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**	**M-H, Random, 95% CI**
1.2.1 High Quality Studies (8+)								
Bower	86	153	90	143	15.1%	0.89 [0.74, 1.08]	1995	
Kudsk	5	16	11	17	3.1%	0.48 [0.22, 1.08]	1996	
Capparos	64	130	37	105	10.8%	1.40 [1.02, 1.91]	2001	
Conejero	11	43	17	33	4.9%	0.50 [0.27, 0.91]	2002	
Dent	57	87	52	83	13.7%	1.05 [0.83, 1.31]	2003	
Kieft 2005	130	302	123	295	15.1%	1.03 [0.86, 1.24]	2005	
Tsuei	8	13	6	11	4.0%	1.13 [0.57, 2.25]	2005	
Wibbenmeyer	9	12	7	11	5.6%	1.18 [0.68, 2.05]	2006	
Subtotal (95% CI)		**756**		**698**	**72.3%**	**0.99 [0.83, 1.17]**		
Total events	370		343					
Heterogeneity: Tau² = 0.03; Chi² = 14.72, df = 7 (P = 0.04); I² = 52%								
Test for overall effect: Z = 0.16 (P = 0.87)								
1.2.2 Low Quality Studies (<8)								
Moore	9	51	10	47	3.1%	0.83 [0.37, 1.86]	1994	
Brown	3	19	10	18	1.8%	0.28 [0.09, 0.87]	1995	
Engel	6	18	5	18	2.2%	1.20 [0.45, 3.23]	1997	
Rodrigo	5	16	3	14	1.5%	1.46 [0.42, 5.03]	1997	
Mendez	19	22	12	21	8.3%	1.51 [1.01, 2.27]	1997	
Galban	39	89	44	87	10.8%	0.87 [0.63, 1.19]	2000	
Subtotal (95% CI)		**215**		**205**	**27.7%**	**0.97 [0.65, 1.45]**		
Total events	81		84					
Heterogeneity: Tau² = 0.12; Chi² = 10.91, df = 5 (P = 0.05); I² = 54%								
Test for overall effect: Z = 0.14 (P = 0.89)								
Total (95% CI)		**971**		**903**	**100.0%**	**0.99 [0.85, 1.15]**		
Total events	451		427					
Heterogeneity: Tau² = 0.03; Chi² = 25.16, df = 13 (P = 0.02); I² = 48%								
Test for overall effect: Z = 0.15 (P = 0.88)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.94), I² = 0%								

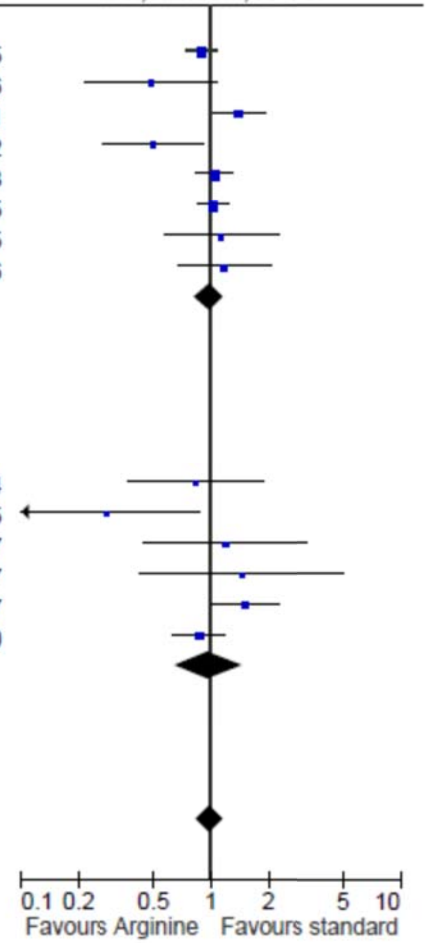

Figure 3b. Infectious complications (with quality sub-analyses; excluding Tsuei)

Study or Subgroup	Diets wih Arginine Events	Diets wih Arginine Total	standard Events	standard Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.9.1 High Quality Studies (8+)							
Bower	86	153	90	143	15.4%	0.89 [0.74, 1.08]	1995
Kudsk	5	16	11	17	3.4%	0.48 [0.22, 1.08]	1996
Capparos	64	130	37	105	11.3%	1.40 [1.02, 1.91]	2001
Conejero	11	43	17	33	5.2%	0.50 [0.27, 0.91]	2002
Dent	57	87	52	83	14.1%	1.05 [0.83, 1.31]	2003
Kieft 2005	130	302	123	295	15.4%	1.03 [0.86, 1.24]	2005
Wibbenmeyer	9	12	7	11	6.0%	1.18 [0.68, 2.05]	2006
Subtotal (95% CI)		**743**		**687**	**70.7%**	**0.98 [0.81, 1.17]**	
Total events	362		337				
Heterogeneity: Tau² = 0.03; Chi² = 14.60, df = 6 (P = 0.02); I² = 59%							
Test for overall effect: Z = 0.26 (P = 0.80)							
1.9.2 Low Quality Studies (<8)							
Moore	9	51	10	47	3.4%	0.83 [0.37, 1.86]	1994
Brown	3	19	10	18	1.9%	0.28 [0.09, 0.87]	1995
Engel	6	18	5	18	2.4%	1.20 [0.45, 3.23]	1997
Rodrigo	5	16	3	14	1.6%	1.46 [0.42, 5.03]	1997
Mendez	19	22	12	21	8.8%	1.51 [1.01, 2.27]	1997
Galban	39	89	44	87	11.3%	0.87 [0.63, 1.19]	2000
Subtotal (95% CI)		**215**		**205**	**29.3%**	**0.97 [0.65, 1.45]**	
Total events	81		84				
Heterogeneity: Tau² = 0.12; Chi² = 10.91, df = 5 (P = 0.05); I² = 54%							
Test for overall effect: Z = 0.14 (P = 0.89)							
Total (95% CI)		**958**		**892**	**100.0%**	**0.98 [0.83, 1.15]**	
Total events	443		421				
Heterogeneity: Tau² = 0.04; Chi² = 25.04, df = 12 (P = 0.01); I² = 52%							
Test for overall effect: Z = 0.24 (P = 0.81)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%							

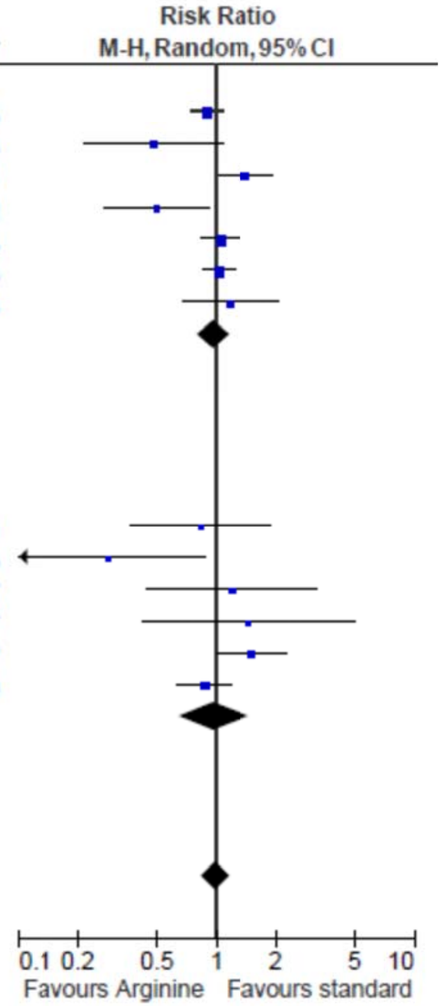

Figure 4a. Infectious complications (with trauma/non-trauma sub-analyses)

Study or Subgroup	Diets wih Arginine Events	Diets wih Arginine Total	standard Events	standard Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.10.1 Trauma Patients							
Moore	9	51	10	47	3.1%	0.83 [0.37, 1.86]	1994
Brown	3	19	10	18	1.8%	0.28 [0.09, 0.87]	1995
Kudsk	5	16	11	17	3.1%	0.48 [0.22, 1.08]	1996
Mendez	19	22	12	21	8.3%	1.51 [1.01, 2.27]	1997
Engel	6	18	5	18	2.2%	1.20 [0.45, 3.23]	1997
Tsuei	8	13	6	11	4.0%	1.13 [0.57, 2.25]	2005
Subtotal (95% CI)		**139**		**132**	**22.5%**	**0.86 [0.52, 1.42]**	
Total events	50		54				
Heterogeneity: Tau² = 0.24; Chi² = 13.74, df = 5 (P = 0.02); I² = 64%							
Test for overall effect: Z = 0.59 (P = 0.55)							
1.10.2 Non-trauma Patients							
Bower	86	153	90	143	15.1%	0.89 [0.74, 1.08]	1995
Rodrigo	5	16	3	14	1.5%	1.46 [0.42, 5.03]	1997
Galban	39	89	44	87	10.8%	0.87 [0.63, 1.19]	2000
Capparos	64	130	37	105	10.8%	1.40 [1.02, 1.91]	2001
Conejero	11	43	17	33	4.9%	0.50 [0.27, 0.91]	2002
Dent	57	87	52	83	13.7%	1.05 [0.83, 1.31]	2003
Kieft 2005	130	302	123	295	15.1%	1.03 [0.86, 1.24]	2005
Wibbenmeyer	9	12	7	11	5.6%	1.18 [0.68, 2.05]	2006
Subtotal (95% CI)		**832**		**771**	**77.5%**	**1.00 [0.86, 1.16]**	
Total events	401		373				
Heterogeneity: Tau² = 0.02; Chi² = 12.64, df = 7 (P = 0.08); I² = 45%							
Test for overall effect: Z = 0.05 (P = 0.96)							
Total (95% CI)		**971**		**903**	**100.0%**	**0.99 [0.85, 1.15]**	
Total events	451		427				
Heterogeneity: Tau² = 0.03; Chi² = 25.16, df = 13 (P = 0.02); I² = 48%							
Test for overall effect: Z = 0.15 (P = 0.88)							
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%							

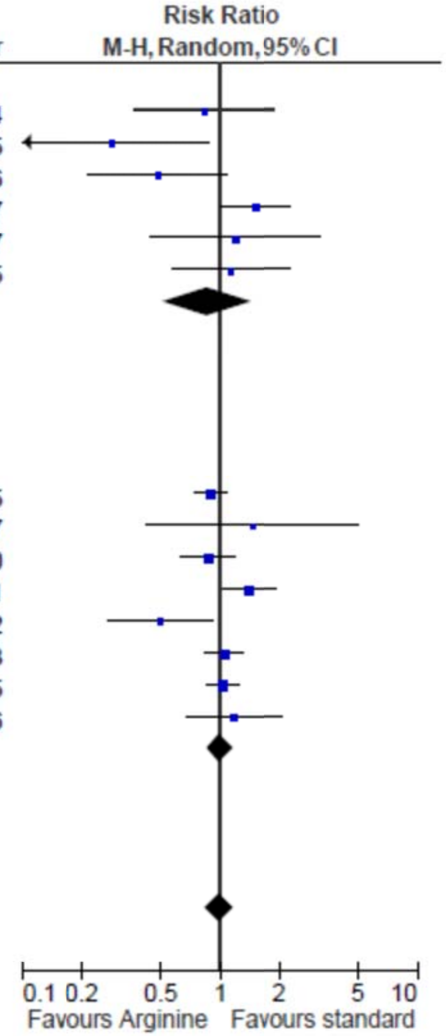

Figure 4b. Infectious complications (with trauma/non-trauma sub-analyses; excluding Tsuei)

	Diets wih Arginine		standard			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
1.11.1 Trauma Patients							
Moore	9	51	10	47	3.4%	0.83 [0.37, 1.86]	1994
Brown	3	19	10	18	1.9%	0.28 [0.09, 0.87]	1995
Kudsk	5	16	11	17	3.4%	0.48 [0.22, 1.08]	1996
Mendez	19	22	12	21	8.8%	1.51 [1.01, 2.27]	1997
Engel	6	18	5	18	2.4%	1.20 [0.45, 3.23]	1997
Subtotal (95% CI)		**126**		**121**	**19.8%**	**0.79 [0.41, 1.50]**	
Total events	42		48				
Heterogeneity: Tau² = 0.36; Chi² = 13.79, df = 4 (P = 0.008); I² = 71%							
Test for overall effect: Z = 0.73 (P = 0.46)							
1.11.2 Non-trauma Patients							
Bower	86	153	90	143	15.4%	0.89 [0.74, 1.08]	1995
Rodrigo	5	16	3	14	1.6%	1.46 [0.42, 5.03]	1997
Galban	39	89	44	87	11.3%	0.87 [0.63, 1.19]	2000
Capparos	64	130	37	105	11.3%	1.40 [1.02, 1.91]	2001
Conejero	11	43	17	33	5.2%	0.50 [0.27, 0.91]	2002
Dent	57	87	52	83	14.1%	1.05 [0.83, 1.31]	2003
Kieft 2005	130	302	123	295	15.4%	1.03 [0.86, 1.24]	2005
Wibbenmeyer	9	12	7	11	6.0%	1.18 [0.68, 2.05]	2006
Subtotal (95% CI)		**832**		**771**	**80.2%**	**1.00 [0.86, 1.16]**	
Total events	401		373				
Heterogeneity: Tau² = 0.02; Chi² = 12.64, df = 7 (P = 0.08); I² = 45%							
Test for overall effect: Z = 0.05 (P = 0.96)							
Total (95% CI)		**958**		**892**	**100.0%**	**0.98 [0.83, 1.15]**	
Total events	443		421				
Heterogeneity: Tau² = 0.04; Chi² = 25.04, df = 12 (P = 0.01); I² = 52%							
Test for overall effect: Z = 0.24 (P = 0.81)							
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%							

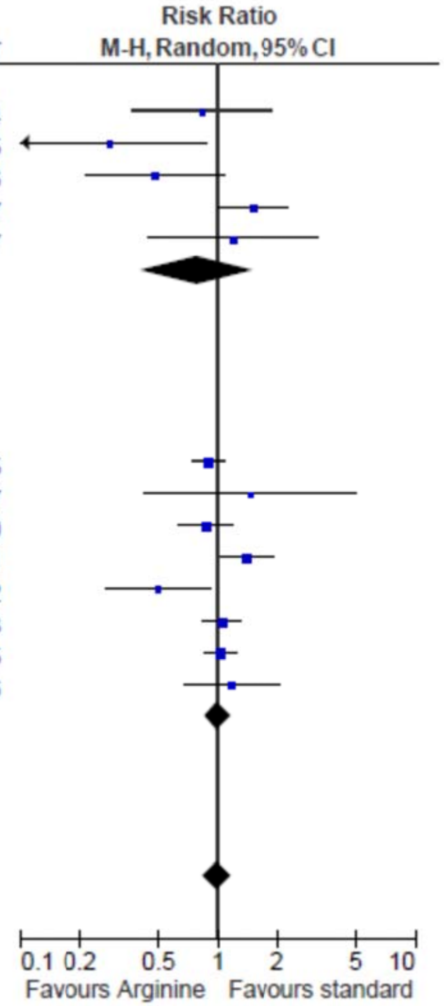

Figure 5a. Hospital LOS

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Cerra	36.7	8.5	11	54.7	10.5	9	7.6%	-18.00 [-26.50, -9.50]	1991
Moore	14.6	1.3	51	17.2	2.8	47	11.3%	-2.60 [-3.48, -1.72]	1994
Bower	27.6	23	153	30.9	26	143	9.3%	-3.30 [-8.91, 2.31]	1995
Kudsk	18.3	2.8	16	32.6	7	17	10.4%	-14.30 [-17.90, -10.70]	1996
Mendez	34	21.2	22	21.9	11	21	6.7%	12.10 [2.07, 22.13]	1997
Atkinson	20.6	26	197	23.2	32	193	9.2%	-2.60 [-8.39, 3.19]	1998
Weimann	70.2	53	16	58.1	30	13	1.5%	12.10 [-18.57, 42.77]	1998
Dent	25.4	26	87	20.9	17	83	8.8%	4.50 [-2.07, 11.07]	2003
Chuntrasakul	44.9	30.2	18	28.8	25.7	18	3.5%	16.10 [-2.22, 34.42]	2003
Tsuei	22	9	61	27	17	55	9.7%	-5.00 [-10.03, 0.03]	2005
Pearce	19.1	14.4	15	13.4	11.1	16	7.3%	5.70 [-3.39, 14.79]	2006
Kuhls	40	23.45	22	30.3	22.98	22	5.0%	9.70 [-4.02, 23.42]	2007
Beale	43.8	28	27	31.3	27.2	28	4.6%	12.50 [-2.10, 27.10]	2008
Iamsirisaengthong	35.4	15.2	10	40.4	15.2	10	5.1%	-5.00 [-18.32, 8.32]	2017
Total (95% CI)			**706**			**675**	**100.0%**	**-1.02 [-5.10, 3.07]**	

Heterogeneity: Tau² = 38.24; Chi² = 81.30, df = 13 (P < 0.00001); I² = 84%
Test for overall effect: Z = 0.49 (P = 0.63)

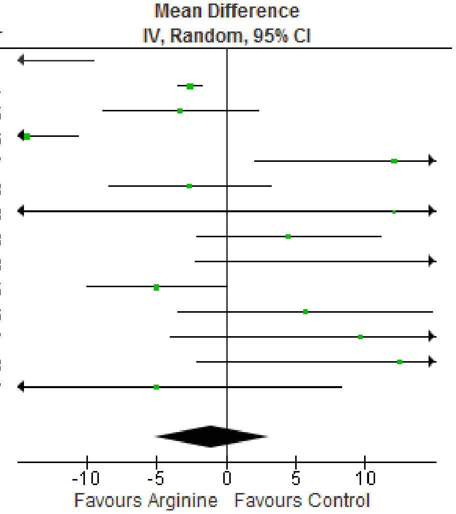

Figure 5b. Hospital LOS (excluding Tsuei)

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Cerra	36.7	8.5	11	54.7	10.5	9	8.5%	-18.00 [-26.50, -9.50]	1991
Moore	14.6	1.3	51	17.2	2.8	47	11.9%	-2.60 [-3.48, -1.72]	1994
Bower	27.6	23	153	30.9	26	143	10.1%	-3.30 [-8.91, 2.31]	1995
Kudsk	18.3	2.8	16	32.6	7	17	11.2%	-14.30 [-17.90, -10.70]	1996
Mendez	34	21.2	22	21.9	11	21	7.6%	12.10 [2.07, 22.13]	1997
Weimann	70.2	53	16	58.1	30	13	1.9%	12.10 [-18.57, 42.77]	1998
Atkinson	20.6	26	197	23.2	32	193	10.0%	-2.60 [-8.39, 3.19]	1998
Chuntrasakul	44.9	30.2	18	28.8	25.7	18	4.1%	16.10 [-2.22, 34.42]	2003
Dent	25.4	26	87	20.9	17	83	9.6%	4.50 [-2.07, 11.07]	2003
Pearce	19.1	14.4	15	13.4	11.1	16	8.1%	5.70 [-3.39, 14.79]	2006
Kuhls	40	23.45	22	30.3	22.98	22	5.7%	9.70 [-4.02, 23.42]	2007
Beale	43.8	28	27	31.3	27.2	28	5.4%	12.50 [-2.10, 27.10]	2008
Iamsirisaengthong	35.4	15.2	10	40.4	15.2	10	5.9%	-5.00 [-18.32, 8.32]	2017
Total (95% CI)			**645**			**620**	**100.0%**	**-0.40 [-4.95, 4.15]**	

Heterogeneity: Tau² = 44.92; Chi² = 80.67, df = 12 (P < 0.00001); I² = 85%
Test for overall effect: Z = 0.17 (P = 0.86)

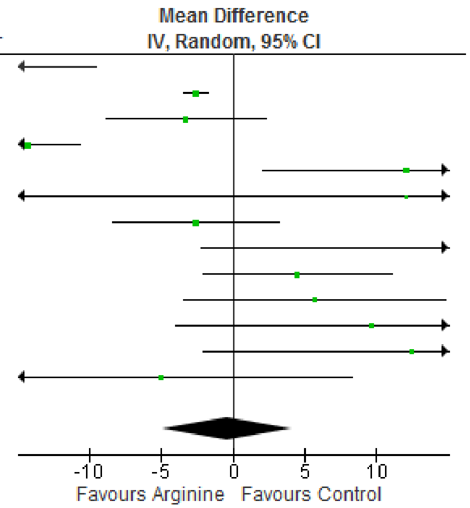

Figure 6a. ICU LOS

	Diets with Arginine			Control				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Moore	5.3	0.8	51	8.6	3.1	47	14.6%	-3.30 [-4.21, -2.39]	1994
Kudsk	5.8	1.8	16	9.5	2.3	17	13.8%	-3.70 [-5.10, -2.30]	1996
Rodrigo	8	7.3	16	10	2.7	14	8.5%	-2.00 [-5.85, 1.85]	1997
Mendez	18.9	20.7	22	11.1	6.7	21	2.8%	7.80 [-1.31, 16.91]	1997
Engel	19	7.4	18	20.5	5.3	18	7.9%	-1.50 [-5.70, 2.70]	1997
Atkinson	10.5	13.1	197	12.2	23.2	193	8.7%	-1.70 [-5.45, 2.05]	1998
Weimann	31.4	23.1	16	47.4	32.8	13	0.6%	-16.00 [-37.12, 5.12]	1998
Galban	18.2	12.6	89	16.6	12.9	89	8.7%	1.60 [-2.15, 5.35]	2000
Dent	14.8	19.6	87	12	10.9	83	6.9%	2.80 [-1.94, 7.54]	2003
Chuntrasakul	3.4	5.8	18	7.8	13.6	18	4.4%	-4.40 [-11.23, 2.43]	2003
Tsuei	13	6	61	16	10	55	10.2%	-3.00 [-6.04, 0.04]	2005
Pearce	11	9.5	15	4	3.6	16	6.4%	7.00 [1.88, 12.12]	2006
Kuhls	27.8	17.82	22	22.4	17.35	22	2.3%	5.40 [-4.99, 15.79]	2007
Beale	16.6	14.8	27	13.4	11.5	28	4.2%	3.20 [-3.82, 10.22]	2008
Total (95% CI)			**655**			**634**	**100.0%**	**-0.77 [-2.46, 0.92]**	

Heterogeneity: Tau² = 4.89; Chi² = 40.26, df = 13 (P = 0.0001); I² = 68%
Test for overall effect: Z = 0.89 (P = 0.37)

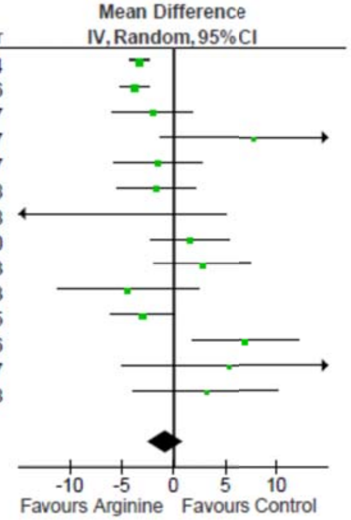

Figure 6b. ICU LOS (excluding Tsuei)

	Diets with Arginine			Control				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Moore	5.3	0.8	51	8.6	3.1	47	15.5%	-3.30 [-4.21, -2.39]	1994
Kudsk	5.8	1.8	16	9.5	2.3	17	14.8%	-3.70 [-5.10, -2.30]	1996
Mendez	18.9	20.7	22	11.1	6.7	21	3.3%	7.80 [-1.31, 16.91]	1997
Engel	19	7.4	18	20.5	5.3	18	8.8%	-1.50 [-5.70, 2.70]	1997
Rodrigo	8	7.3	16	10	2.7	14	9.5%	-2.00 [-5.85, 1.85]	1997
Atkinson	10.5	13.1	197	12.2	23.2	193	9.7%	-1.70 [-5.45, 2.05]	1998
Weimann	31.4	23.1	16	47.4	32.8	13	0.7%	-16.00 [-37.12, 5.12]	1998
Galban	18.2	12.6	89	16.6	12.9	89	9.7%	1.60 [-2.15, 5.35]	2000
Chuntrasakul	3.4	5.8	18	7.8	13.6	18	5.1%	-4.40 [-11.23, 2.43]	2003
Dent	14.8	19.6	87	12	10.9	83	7.9%	2.80 [-1.94, 7.54]	2003
Pearce	11	9.5	15	4	3.6	16	7.3%	7.00 [1.88, 12.12]	2006
Kuhls	27.8	17.82	22	22.4	17.35	22	2.7%	5.40 [-4.99, 15.79]	2007
Beale	16.6	14.8	27	13.4	11.5	28	4.9%	3.20 [-3.82, 10.22]	2008
Total (95% CI)			**594**			**579**	**100.0%**	**-0.44 [-2.31, 1.42]**	

Heterogeneity: Tau² = 5.60; Chi² = 40.21, df = 12 (P < 0.0001); I² = 70%
Test for overall effect: Z = 0.47 (P = 0.64)

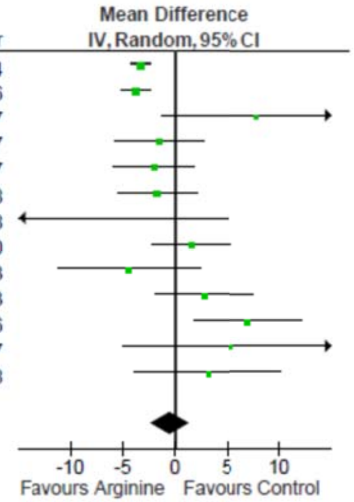

Figure 7a. Ventilated days

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Moore	1.9	0.9	51	5.3	3.1	47	22.8%	-3.40 [-4.32, -2.48]	1994
Kudsk	2.4	1.3	16	5.4	2	17	21.4%	-3.00 [-4.14, -1.86]	1996
Mendez	16.5	19.4	22	9.3	6	21	2.1%	7.20 [-1.30, 15.70]	1997
Engel	14.8	5.6	18	16	5.6	18	8.5%	-1.20 [-4.86, 2.46]	1997
Atkinson	8	11.1	197	9.4	17.7	193	11.1%	-1.40 [-4.34, 1.54]	1998
Weimann	21.4	10.8	16	27.8	14.6	13	1.7%	-6.40 [-15.94, 3.14]	1998
Galban	12.4	10.4	89	12.2	10.3	87	10.6%	0.20 [-2.86, 3.26]	2000
Chuntrasakul	2.7	5.2	18	7.4	13.5	18	3.3%	-4.70 [-11.38, 1.98]	2003
Dent	14.3	22.4	87	10.8	12.8	83	4.6%	3.50 [-1.95, 8.95]	2003
Tsuei	10	5	61	14	10	55	11.2%	-4.00 [-6.93, -1.07]	2005
Kuhls	23.1	12.66	22	20.9	12.66	22	2.7%	2.20 [-5.28, 9.68]	2007
Total (95% CI)			**597**			**574**	**100.0%**	**-1.99 [-3.29, -0.69]**	

Heterogeneity: Tau² = 1.71; Chi² = 20.71, df = 10 (P = 0.02); I² = 52%
Test for overall effect: Z = 3.00 (P = 0.003)

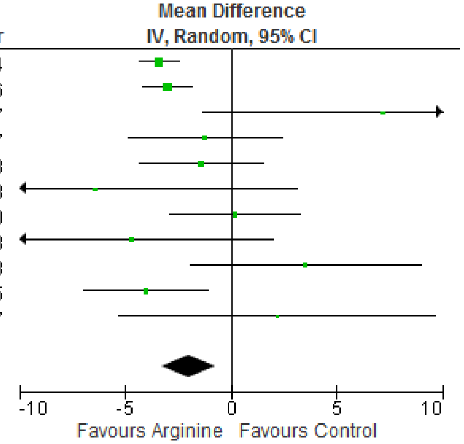

Figure 7b. Ventilated days (excluding Tsuei)

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Moore	1.9	0.9	51	5.3	3.1	47	24.6%	-3.40 [-4.32, -2.48]	1994
Kudsk	2.4	1.3	16	5.4	2	17	23.3%	-3.00 [-4.14, -1.86]	1996
Engel	14.8	5.6	18	16	5.6	18	9.8%	-1.20 [-4.86, 2.46]	1997
Mendez	16.5	19.4	22	9.3	6	21	2.6%	7.20 [-1.30, 15.70]	1997
Weimann	21.4	10.8	16	27.8	14.6	13	2.1%	-6.40 [-15.94, 3.14]	1998
Atkinson	8	11.1	197	9.4	17.7	193	12.7%	-1.40 [-4.34, 1.54]	1998
Galban	12.4	10.4	89	12.2	10.3	87	12.2%	0.20 [-2.86, 3.26]	2000
Dent	14.3	22.4	87	10.8	12.8	83	5.5%	3.50 [-1.95, 8.95]	2003
Chuntrasakul	2.7	5.2	18	7.4	13.5	18	3.9%	-4.70 [-11.38, 1.98]	2003
Kuhls	23.1	12.66	22	20.9	12.66	22	3.2%	2.20 [-5.28, 9.68]	2007
Total (95% CI)			**536**			**519**	**100.0%**	**-1.68 [-3.11, -0.25]**	

Heterogeneity: Tau² = 1.94; Chi² = 20.05, df = 9 (P = 0.02); I² = 55%
Test for overall effect: Z = 2.30 (P = 0.02)

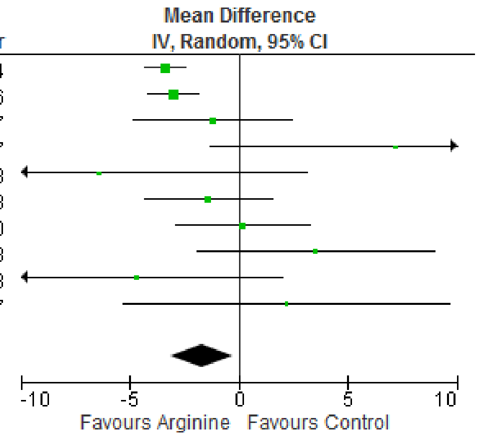

Table 2. Excluded Articles

#	Reason excluded	Citation
1	Cancer pts	Daly JM, Reynolds J, Thom A, Kinsley L, Dietrick-Gallagher M, Shou J, Ruggieri B. Immune and metabolic effects of arginine in the surgical patient. Ann Surg. 1988 Oct;208(4):512-23.
2	Same as Cerra 1990 study	Cerra FB, Lehmann S, Konstantinides N, Dzik J, Fish J, Konstantinides F, LiCari JJ, Holman RT. Improvement in immune function in ICU patients by enteral nutrition supplemented with arginine, RNA, and menhaden oil is independent of nitrogen balance. Nutrition. 1991 May-Jun;7(3):193-9.
3	Cancer pts	Daly JM, Lieberman MD, Goldfine J, Shou J, Weintraub F, Rosato EF, Lavin P. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. Surgery. 1992 Jul;112(1):56-67. Comment in: Surgery. 1993 Sep;114(3):631-2.
4	Cancer pts	Daly JM, Weintraub FN, Shou J, Rosato EF, Lucia M. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. Ann Surg. 1995 Apr;221(4):327-38.
5	Cancer pts	Kemen M, Senkal M, Homann HH, Mumme A, Dauphin AK, Baier J, Windeler J, Neumann H, Zumtobel V. Early postoperative enteral nutrition with arginine-omega-3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact. Crit Care Med. 1995 Apr;23(4):652-9.
6	Elective surgery pts	Schilling J, Vranjes N, Fierz W, Joller H, Gyurech D, Ludwig E, Marathias K, Geroulanos S. Clinical outcome and immunology of postoperative arginine, omega-3 fatty acids, and nucleotide-enriched enteral feeding: a randomized prospective comparison with standard enteral and low calorie/low fat i.v. solutions. Nutrition. 1996 Jun;12(6):423-9.
7	Cancer pts	Gianotti L, Braga M, Vignali A, Balzano G, Zerbi A, Bisagni P, Di Carlo V. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. Arch Surg. 1997 Nov;132(11):1222-9; discussion 1229-30.
8	Elective surgery pts	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.
9	Compared Impact to Replete EN formulas; not immune to non-immune	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.
10	Cancer pts	Senkal M, Mumme A, Eickhoff U, Geier B, Späth G, Wulfert D, Joosten U, Frei A, Kemen M. Early postoperative enteral immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. Crit Care Med. 1997 Sep;25(9):1489-96.
11	Cancer pts	Braga M, Gianotti L, Vignali A, Cestari A, Bisagni P, Di Carlo V. Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. Crit Care Med. 1998 Jan;26(1):24-30.
12	Cancer pts	McCarter MD, Gentilini OD, Gomez ME, Daly JM. Preoperative oral supplement with immunonutrients in cancer patients. JPEN J Parenter Enteral Nutr. 1998 Jul-Aug;22(4):206-11.

13	Systematic review	Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: A systematic review of clinical outcome. Critical Care Medicine 1999;27:2799-805.
14	Cancer pts	Braga M, Gianotti L, Radaelli G, Vignali A, Mari G, Gentilini O, Di Carlo V. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. Arch Surg. 1999 Apr;134(4):428-33. Comment in: Surgery. 2002 Nov;132(5):815-6.
15	Cancer pts	Di Carlo V, Gianotti L, Balzano G, Zerbi A, Braga M. Complications of pancreatic surgery and the role of perioperative nutrition. Dig Surg. 1999;16(4):320-6.
16	Meta-analysis	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.
17	Cancer pts	Senkal M, Zumtobel V, Bauer KH, Marpe B, Wolfram G, Frei A, Eickhoff U, Kemen M. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. Arch Surg. 1999 Dec;134(12):1309-16.
18	Elective surgery pts	Snyderman CH, Kachman K, Molseed L, Wagner R, D'Amico F, Bumpous J, Rueger R. Reduced postoperative infections with an immune-enhancing nutritional supplement. Laryngoscope. 1999 Jun;109(6):915-21.
19	Elective surgery pts	Gianotti L, Braga M, Gentilini O, Balzano G, Zerbi A, Di Carlo V. Artificial nutrition after pancreaticoduodenectomy. Pancreas. 2000 Nov;21(4):344-51.
20	Elective surgery pts	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	Excluded as unclear if randomized	Hallay J, Kovacs G, Szatmari K, Bako A, Szentkereszty Z, Lakos G, Sipka S, Sapy P. Early jejunal nutrition and changes in the immunological parameters of patients with acute pancreatitis. Hepatogastroenterology 2001;48(41):1488-92.
22	Systematic review	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. Journal of the American Medical Association 2001;286:944-53.
23	Elective surgery pts	Jiang ZM, Gu ZY, Chen FL, Wang XR, Li ZJ, Xu Y, Li R. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. [The role of immune enhanced enteral nutrition on plasma amino acid, gut permeability and clinical outcome (a randomized, double blind, controlled, multi-center clinical trail with 120 cases)] [Article in Chinese] 2001 Oct;23(5):515-8.
24	No clinical outcomes	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.
25	Elective surgery pts	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.
26	Elective surgery pts	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.
27	Cancer pts, Same as Braga 2002, Gianotti 2003	Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg. 2002 Feb;137(2):174-80.

28	Cancer pts, Same as Braga 2002, Gianotti 2003	Braga M, Gianotti L, Vignali A, Carlo VD. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. Surgery. 2002 Nov;132(5):805-14.
29	Elective surgery pts	de Luis DA, Aller R, Izaola O, Cuellar L, Terroba MC. Postsurgery enteral nutrition in head and neck cancer patients. Eur J Clin Nutr. 2002 Nov;56(11):1126-9.
30	Cancer pts, Same as Braga 2002, Gianotti 2003	Gianotti L, Braga M, Nespoli L, Radaelli G, Beneduce A, Di Carlo V. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. Gastroenterology. 2002 Jun;122(7):1763-70.
31	Elective surgery pts	de Luis DA, Izaola O, Cuellar L, Terroba MC, Arranz M, Fernandez N, Aller R. Effect of c-reactive protein and interleukins blood levels in postsurgery arginine-enhanced enteral nutrition in head and neck cancer patients. Eur J Clin Nutr. 2003 Jan;57(1):96-9.
32	Systematic review	Montejo JC, Zarazaga A, López-Martínez J, Urrútia G, Roqué M, Blesa AL, Celaya S, Conejero R, Galbán C, García de Lorenzo A, Grau T, Mesejo A, Ortiz-Leyba C, Planas M, Ordóñez J, Jiménez FJ; Immunonutrition in the intensive care unit. A systematic review and consensus statement. Spanish Society of Intensive Care Medicine and Coronary Units. Clin Nutr. 2003 Jun;22(3):221-33.
33	Elective surgery pts	de Luis DA, Izaola O, Cuellar L, Terroba MC, Aller R. Randomized clinical trial with an enteral arginine-enhanced formula in early postsurgical head and neck cancer patients. Eur J Clin Nutr. 2004 Nov;58(11):1505-8.
34	Pediatrics	Briassoulis G, Filippou O, Kanariou M, Hatzis T. Comparitive effects of early randomized immune or non-immune-enhancing enteral nutrition on cytokine production in children with septic shock.Intensive Care Med. 2005 Jun;31(6):851-8.
35	Elective surgery pts	de Luis DA, Izaola O, Aller R, Cuellar L, Terroba MC. A randomized clinical trial with oral Immunonutrition (omega3-enhanced formula vs. arginine-enhanced formula) in ambulatory head and neck cancer patients. Ann Nutr Metab. 2005 Mar-Apr;49(2):95-9.
36	Elective surgery pts	de Luis DA, Arranz M, Aller R, Izaola O, Cuellar L, Terroba MC. Immunoenhanced enteral nutrition, effect on inflammatory markers in head and neck cancer patients. Eur J Clin Nutr. 2005 Jan;59(1):145-7.
37	Cancer pts	Farreras N, Artigas V, Cardona D, Rius X, Trias M, González JA. Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. Clin Nutr. 2005 Feb;24(1):55-65.
38	Cancer pts	Lobo DN, Williams RN, Welch NT, Aloysius MM, Nunes QM, Padmanabhan J, Crowe JR, Iftikhar SY, Parsons SL, Neal KR, Allison SP, Rowlands BJ. Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled, double-blind study. Clin Nutr. 2006 Oct;25(5):716-26. Epub 2006 Jun 13.
39	Not ICU pts	Sakurai Y, Oh-Oka Y, Kato S, Suzuki S, Hayakawa M, Masui T, Yoshida I, Tonomura S, Mitsutaka S, Nakamura Y, Uyama I, Komori Y, Ochiai M. Effects of long-term continuous use of immune-enhancing enteral formula on nutritional and immunologic status in non-surgical patients. Nutrition. 2006 Jul-Aug;22(7-8):713-21.
40	Elective surgery pts	Waitzberg DL, Saito H, Plank LD, Jamieson GG, Jagannath P, Hwang TL, Mijares JM, Bihari D. Postsurgical infections are reduced with specialized nutrition support. World J Surg. 2006 Aug;30(8):1592-604.
41	Cancer pts	Xu J, Zhong Y, Jing D, Wu Z. Preoperative enteral immunonutrition improves postoperative outcome in patients with gastrointestinal cancer. World J Surg. 2006 Jul;30(7):1284-9.

42	Cancer pts	de Luis DA, Izaola O, Cuellar L, Terroba MC, Martin T, Aller R. Clinical and biochemical outcomes after a randomized trial with a high dose of enteral arginine formula in postsurgical head and neck cancer patients. Eur J Clin Nutr. 2007 Feb;61(2):200-4. Epub 2006 Aug 23.
43	Surgery pts	Finco C, Magnanini P, Sarzo G, Vecchiato M, Luongo B, Savastano S, Bortoliero M, Barison P, Merigliano S. Prospective randomized study on perioperative enteral immunonutrition in laparoscopic colorectal surgery. Surg Endosc. 2007 Jul;21(7):1175-9. Epub 2007 Mar 14.
44	Cancer pts	Giger U, Büchler M, Farhadi J, Berger D, Hüsler J, Schneider H, Krähenbühl S, Krähenbühl L. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. Ann Surg Oncol. 2007 Oct;14(10):2798-806. Epub 2007 Jul 15.
45	Elective surgery pts	Helminen H, Raitanen M, Kellosalo. Immunonutrition in elective gastrointestinal surgery patients. J. Scand J Surg. 2007;96(1):46-50.
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