4.1a. EN Composition: Diets Supplemented with Arginine and Select Other Nutrients* May 2015

2015 Recommendation: ***Based on 5 level 1 studies and 22 level 2 studies, we do not recommend diets supplemented with arginine and other select nutrients* be used for critically ill patients.***

2015 Discussion: The committee noted the inclusion of one new small study in head injury patients (n =40, Khorana 2009), the data from which did not alter the effect on mortality. Other outcomes from this study were not reported in a manner that allowed aggregation with existing data. There continues to be no overall signal of benefit or of harm in all ICU patients or in the subgroup of studies of trauma patients. The committee agreed that the previous concerns from the updates in 2009 and 2013 regarding the potential for harm (increased mortality) associated with the use of diets supplemented with arginine and other nutrients harm in septic patients (Bower 1995, Dent 2003, Bertolini 2003) were still relevant. Hence the recommendation for caution against the use of diets supplemented with arginine and other select nutrients* remain unchanged. It was emphasized that this recommendation does not apply to the elective surgery population where the evidence is contrary to critically ill patients and the use of such formulas is associated with a significant reduction in infections (1).

(1) Drover JW, Dhaliwal R, Weitzel L, Wischmeyer PE, Ochoa JB, Heyland DK. Perioperative use of arginine-supplemented diets: a systematic review of the evidence. J Am Coll Surg. 2011 Mar;212(3):385-99

2013 Recommendation: ***Based on 4 level 1 studies and 22 level 2 studies, we do not recommend diets supplemented with arginine and other select nutrients* be used for critically ill patients.***

2013 Discussion: The committee noted that with the addition of 2 new RCTs (Pearce 2006 and Kuhls 2007) there were no changes in the treatment effect on mortality or infections. 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. As in 2009, 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.

Semi Quantitative Scoring

Value	Definition	2013 Score (0,1,2,3)	2015 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	**0**	**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**	**1**
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	**2**	**2**
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	**2**	**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**	**3**
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	**2**	**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**	**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**	**2**
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	**2**	**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**	**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)**

4.1a. 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 25 studies reviewed, 5 level 1 studies and 20 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 25 studies reported on mortality and when the results of the 25 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 0.75, 95% CI 0.49, 1.15, p=0.19, heterogeneity I^2=0%; figure 1a). The difference between these two subgroups was not statistically significant (p=0.10). 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 & duration of mechanical ventilation: 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 -1.38, 95% CI -4.73, 1.97, p=0.42, heterogeneity I^2=84%; figure 5a) and when the Tsuei study was excluded from the analysis (WMD -0.89, 95% CI -4.53, 2.74, p=0.63, 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 trend towards a reduction in mechanical ventilation when the Tsuei study was included in the analysis (WMD -1.30, 95% CI -2.72, 0.12, p=0.07, heterogeneity I^2=73%; figure 7a) and when the Tsuei study was excluded from the analysis (WMD -1.02, 95% CI -2.53, 0.49, p=0.19, heterogeneity I^2=74%; 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, ICU length of stay and may possibly reduce duration of mechanical ventilation in critically ill patients.

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

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	10 ± 2.5
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	**Hospital** 38 ± 4	22 ± 3	21 ± 2
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

**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
C.Random: Concealed randomization NR: Not Reported ITT: intent to treat
‡ 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
Optimental: 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
Crucial: 10 g/L arginine, ω 3 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	3.7%	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	33.6%	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	7.7%	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	35.1%	1.05 [0.85, 1.30]	2005
Tsuei	1	13	0	11	0.2%	2.57 [0.12, 57.44]	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	0.6%	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**	**91.5%**	**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
Subtotal (95% CI)		**233**		**223**	**8.5%**	**0.75 [0.49, 1.15]**	
Total events	29		38				
Heterogeneity: Tau² = 0.00; Chi² = 3.21, df = 5 (P = 0.67); I² = 0%							
Test for overall effect: Z = 1.31 (P = 0.19)							
Total (95% CI)		**1340**		**1261**	**100.0%**	**1.06 [0.93, 1.20]**	
Total events	347		310				
Heterogeneity: Tau² = 0.00; Chi² = 21.05, df = 21 (P = 0.46); I² = 0%							
Test for overall effect: Z = 0.84 (P = 0.40)							
Test for subgroup differences: Chi² = 2.65, df = 1 (P = 0.10), I² = 62.3%							

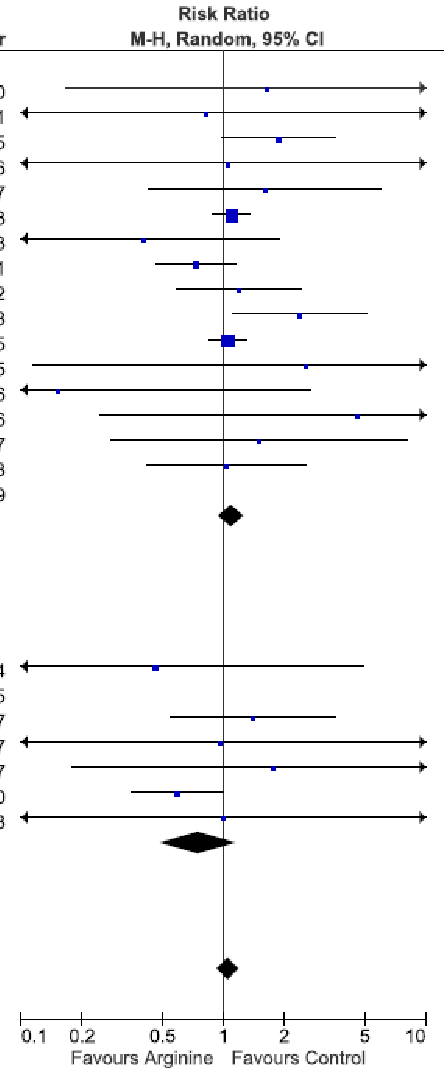


Figure 1b. Mortality (with quality sub-analyses; excluding Tsuei)

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	0.4%	1.65 [0.17, 16.33]	1990
Cerra	1	11	1	9	0.3%	0.82 [0.06, 11.33]	1991
Bower	24	153	12	143	4.3%	1.87 [0.97, 3.60]	1995
Kudsk	1	17	1	18	0.3%	1.06 [0.07, 15.62]	1996
Saffle	5	25	3	24	1.1%	1.60 [0.43, 5.97]	1997
Atkinson	95	197	85	193	31.3%	1.09 [0.88, 1.36]	1998
Weimann	2	16	4	13	0.8%	0.41 [0.09, 1.88]	1998
Capparos	27	130	30	105	8.8%	0.73 [0.46, 1.14]	2001
Conejero	14	43	9	33	3.8%	1.19 [0.59, 2.41]	2002
Dent	20	87	8	83	3.2%	2.39 [1.11, 5.11]	2003
Kieft	114	302	106	295	32.4%	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	0.7%	1.50 [0.28, 8.12]	2007
Beale	7	27	7	28	2.3%	1.04 [0.42, 2.56]	2008
Khorana	0	20	0	20		Not estimable	2009
Subtotal (95% CI)		**1094**		**1027**	**90.0%**	**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	0.3%	0.95 [0.06, 14.30]	1997
Engel	7	18	5	18	2.1%	1.40 [0.54, 3.60]	1997
Rodrigo	2	16	1	14	0.4%	1.75 [0.18, 17.29]	1997
Galban	17	89	28	87	6.6%	0.59 [0.35, 1.00]	2000
Chuntrasakul	1	18	1	18	0.3%	1.00 [0.07, 14.79]	2003
Subtotal (95% CI)		**233**		**223**	**10.0%**	**0.75 [0.49, 1.15]**	
Total events	29		38				
Heterogeneity: Tau² = 0.00; Chi² = 3.21, df = 5 (P = 0.67); I² = 0%							
Test for overall effect: Z = 1.31 (P = 0.19)							
Total (95% CI)		**1327**		**1250**	**100.0%**	**1.05 [0.92, 1.21]**	
Total events	346		310				
Heterogeneity: Tau² = 0.00; Chi² = 20.73, df = 20 (P = 0.41); I² = 4%							
Test for overall effect: Z = 0.73 (P = 0.46)							
Test for subgroup differences: Chi² = 2.64, df = 1 (P = 0.10), I² = 62.1%							

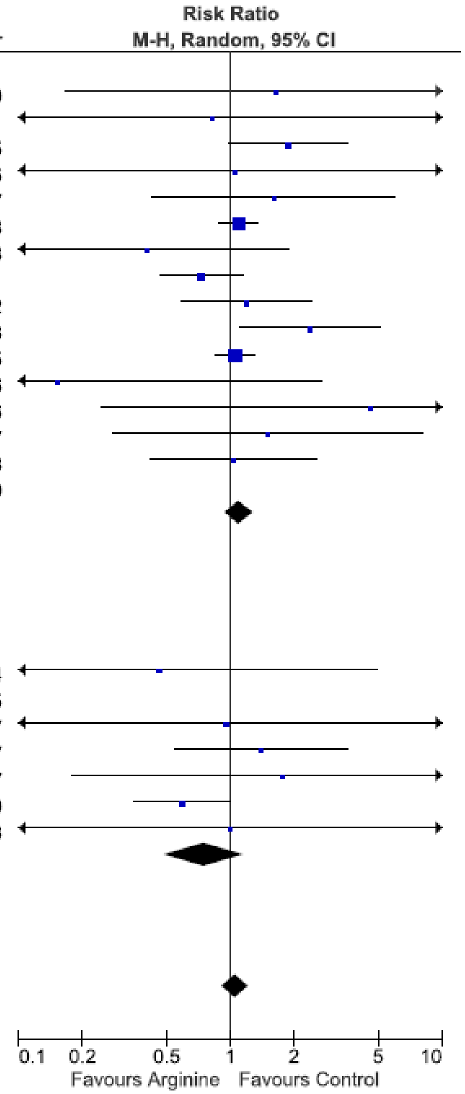


Figure 2a. Mortality (with trauma/non-trauma sub-analyses)

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	0.6%	1.50 [0.28, 8.12]	2007
Khorana	0	20	0	20		Not estimable	2009
Subtotal (95% CI)		**216**		**206**	**4.1%**	**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	3.7%	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	33.6%	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	7.7%	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	35.1%	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
Beale	7	27	7	28	1.9%	1.04 [0.42, 2.56]	2008
Subtotal (95% CI)		**1124**		**1055**	**95.9%**	**1.07 [0.87, 1.30]**	
Total events	330		294				
Heterogeneity: Tau² = 0.03; Chi² = 18.26, df = 13 (P = 0.15); I² = 29%							
Test for overall effect: Z = 0.64 (P = 0.52)							
Total (95% CI)		**1340**		**1261**	**100.0%**	**1.06 [0.93, 1.20]**	
Total events	347		310				
Heterogeneity: Tau² = 0.00; Chi² = 21.05, df = 21 (P = 0.46); I² = 0%							
Test for overall effect: Z = 0.84 (P = 0.40)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%							

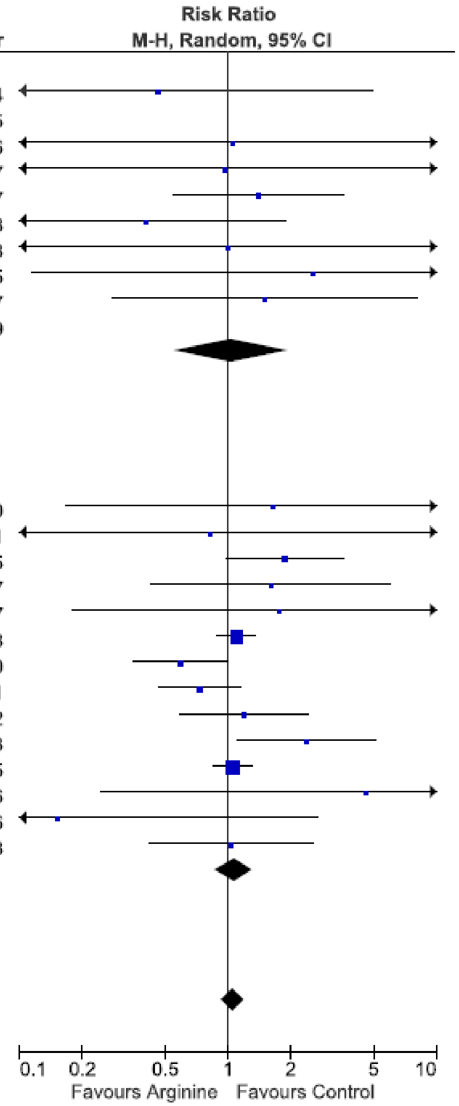


Figure 2b. Mortality in trauma patients (with trauma/non-trauma sub-analyses; excluding Tsuei)

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	0.3%	1.06 [0.07, 15.62]	1996
Engel	7	18	5	18	2.1%	1.40 [0.54, 3.60]	1997
Mendez	1	22	1	21	0.3%	0.95 [0.06, 14.30]	1997
Weimann	2	16	4	13	0.8%	0.41 [0.09, 1.88]	1998
Chuntrasakul	1	18	1	18	0.3%	1.00 [0.07, 14.79]	2003
Kuhls	3	22	2	22	0.7%	1.50 [0.28, 8.12]	2007
Khorana	0	20	0	20		Not estimable	2009
Subtotal (95% CI)		**203**		**195**	**4.7%**	**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	0.4%	1.65 [0.17, 16.33]	1990
Cerra	1	11	1	9	0.3%	0.82 [0.06, 11.33]	1991
Bower	24	153	12	143	4.3%	1.87 [0.97, 3.60]	1995
Rodrigo	2	16	1	14	0.4%	1.75 [0.18, 17.29]	1997
Saffle	5	25	3	24	1.1%	1.60 [0.43, 5.97]	1997
Atkinson	95	197	85	193	31.3%	1.09 [0.88, 1.36]	1998
Galban	17	89	28	87	6.6%	0.59 [0.35, 1.00]	2000
Capparos	27	130	30	105	8.8%	0.73 [0.46, 1.14]	2001
Conejero	14	43	9	33	3.8%	1.19 [0.59, 2.41]	2002
Dent	20	87	8	83	3.2%	2.39 [1.11, 5.11]	2003
Kieft	114	302	106	295	32.4%	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	2.3%	1.04 [0.42, 2.56]	2008
Subtotal (95% CI)		**1124**		**1055**	**95.3%**	**1.07 [0.87, 1.30]**	
Total events	330		294				
Heterogeneity: Tau² = 0.03; Chi² = 18.26, df = 13 (P = 0.15); I² = 29%							
Test for overall effect: Z = 0.64 (P = 0.52)							
Total (95% CI)		**1327**		**1250**	**100.0%**	**1.05 [0.92, 1.21]**	
Total events	346		310				
Heterogeneity: Tau² = 0.00; Chi² = 20.73, df = 20 (P = 0.41); I² = 4%							
Test for overall effect: Z = 0.73 (P = 0.46)							
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%							

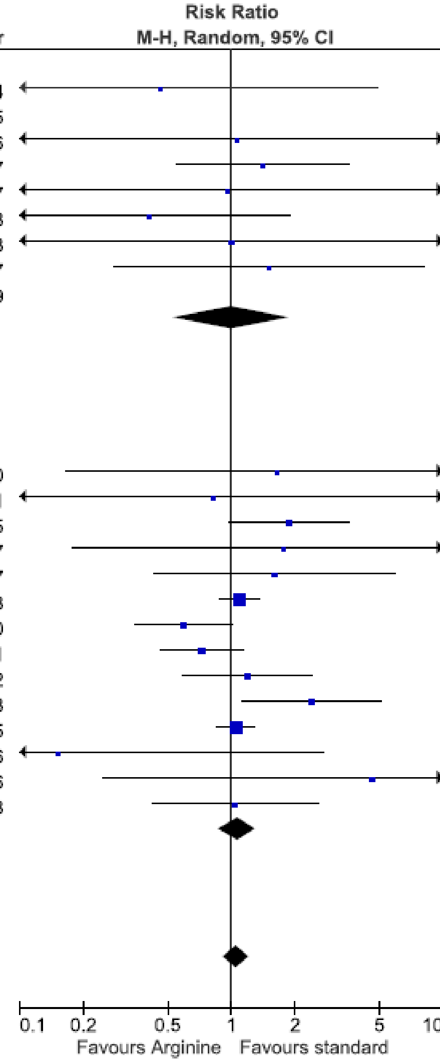


Figure 3a. Infectious complications (with quality sub-analyses)

	Diets wih Arginine		standard			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
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%							

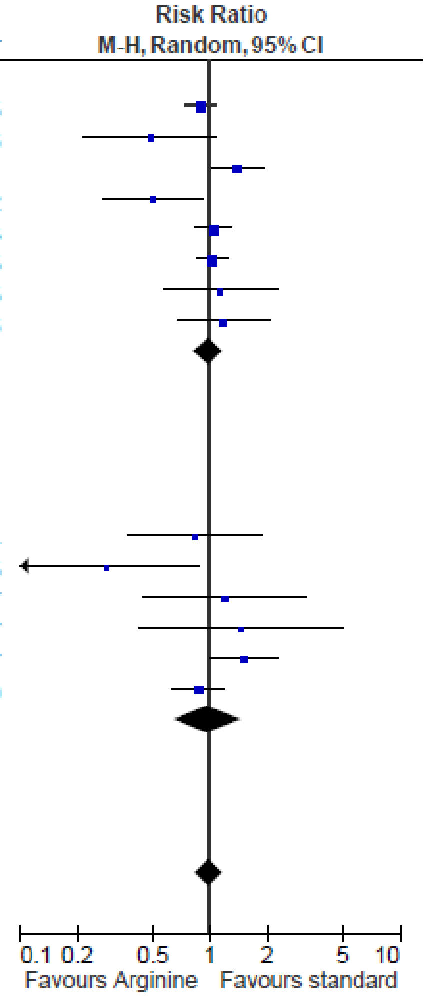


Figure 3b. Infectious complications (with quality sub-analyses; excluding Tsuei)

	Diets wih Arginine		standard			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	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%							

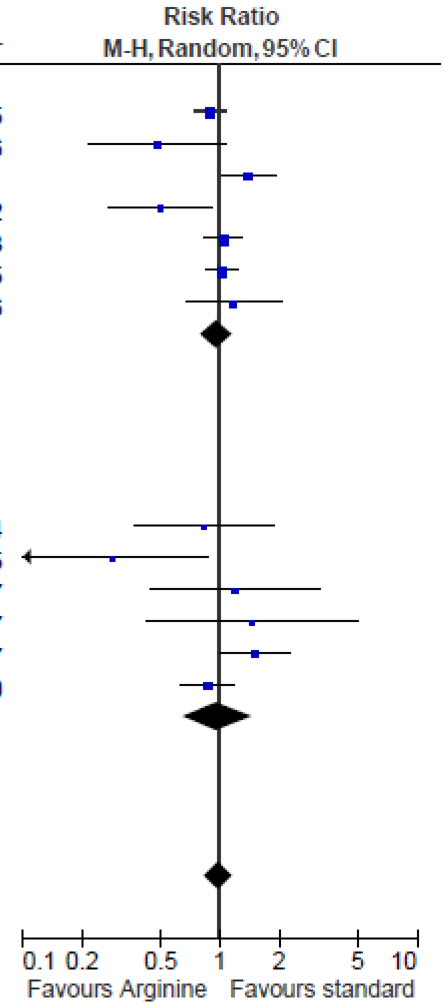


Figure 4a. Infectious complications (with trauma/non-trauma sub-analyses)

	Diets wih Arginine		standard			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	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%							

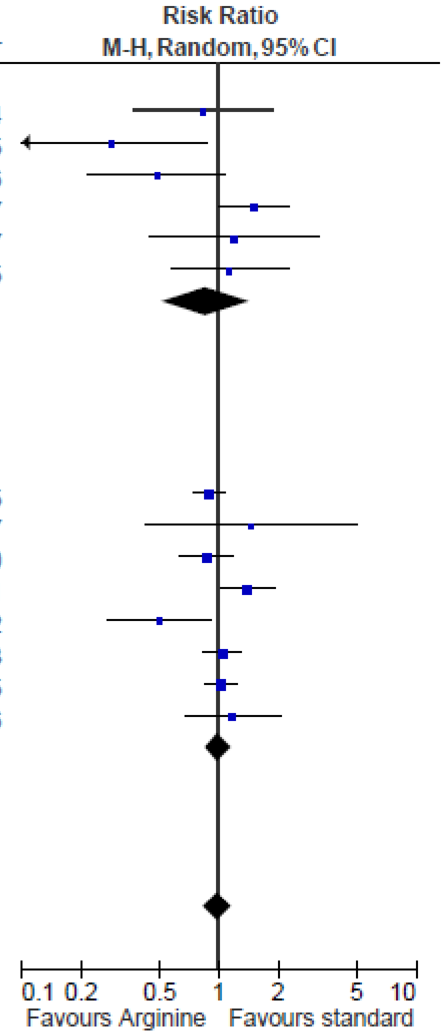


Figure 4b. Infectious complications (with trauma/non-trauma sub-analyses; excluding Tsuei)

	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%							

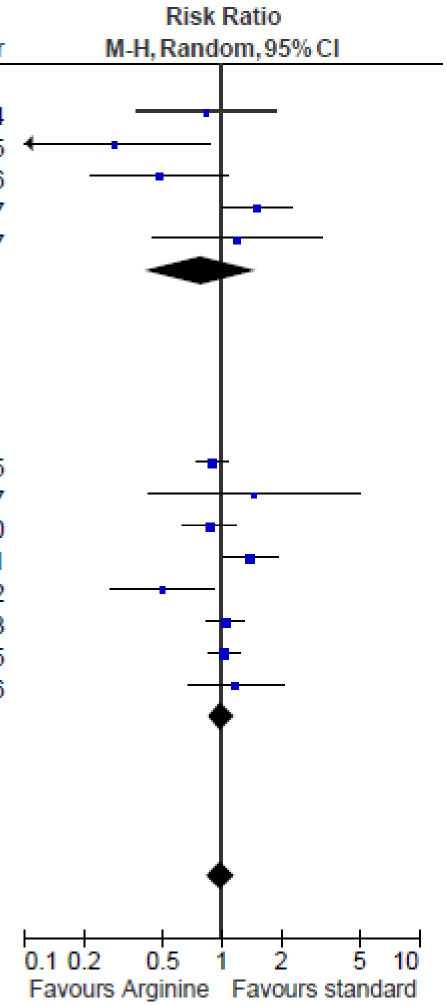
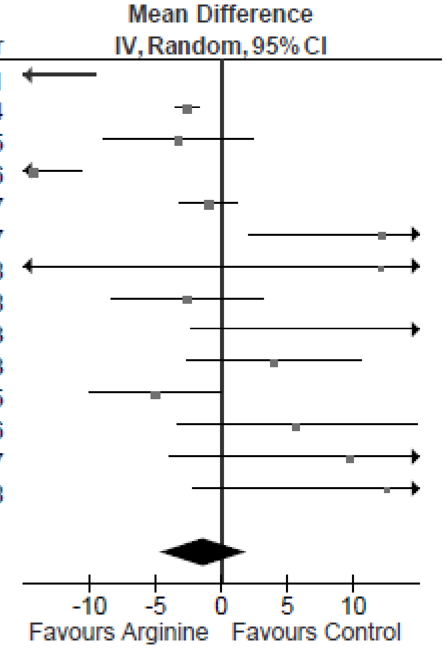


Figure 5a. Hospital LOS

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	6.8%	-18.00 [-26.50, -9.50]	1991
Moore	14.6	1.3	51	17.2	2.8	47	12.0%	-2.60 [-3.48, -1.72]	1994
Bower	27.6	23	153	30.9	26	143	9.0%	-3.30 [-8.91, 2.31]	1995
Kudsk	18.3	2.8	16	32.6	7	17	10.6%	-14.30 [-17.90, -10.70]	1996
Saffle	37	4	25	38	4	24	11.5%	-1.00 [-3.24, 1.24]	1997
Mendez	34	21.2	22	21.9	11	21	5.8%	12.10 [2.07, 22.13]	1997
Weimann	70.2	53	16	58.1	30	13	1.1%	12.10 [-18.57, 42.77]	1998
Atkinson	20.6	26	197	23.2	32	193	8.9%	-2.60 [-8.39, 3.19]	1998
Chuntrasakul	45	30	18	29	26	18	2.6%	16.00 [-2.34, 34.34]	2003
Dent	25	26	87	21	17	83	8.2%	4.00 [-2.57, 10.57]	2003
Tsuei	22	9	61	27	17	55	9.5%	-5.00 [-10.03, 0.03]	2005
Pearce	19.1	14.4	15	13.4	11.1	16	6.4%	5.70 [-3.39, 14.79]	2006
Kuhls	40	23.45	22	30.3	22.98	22	4.0%	9.70 [-4.02, 23.42]	2007
Beale	43.8	28	27	31.3	27.2	28	3.7%	12.50 [-2.10, 27.10]	2008
Total (95% CI)			**721**			**689**	**100.0%**	**-1.38 [-4.73, 1.97]**	

Heterogeneity: $Tau^2 = 24.16$; $Chi^2 = 83.24$, df = 13 ($P < 0.00001$); $I^2 = 84\%$
Test for overall effect: Z = 0.81 (P = 0.42)



Revised Figure 5b. Hospital LOS (excluding Tsuei)

	Diets with Arginine			Control				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	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	12.9%	-2.60 [-3.48, -1.72]	1994
Bower	27.6	23	153	30.9	26	143	9.9%	-3.30 [-8.91, 2.31]	1995
Kudsk	18.3	2.8	16	32.6	7	17	11.5%	-14.30 [-17.90, -10.70]	1996
Mendez	34	21.2	22	21.9	11	21	6.5%	12.10 [2.07, 22.13]	1997
Saffle	37	4	25	38	4	24	12.4%	-1.00 [-3.24, 1.24]	1997
Atkinson	20.6	26	197	23.2	32	193	9.8%	-2.60 [-8.39, 3.19]	1998
Weimann	70.2	53	16	58.1	30	13	1.3%	12.10 [-18.57, 42.77]	1998
Dent	25	26	87	21	17	83	9.1%	4.00 [-2.57, 10.57]	2003
Chuntrasakul	45	30	18	29	26	18	3.0%	16.00 [-2.34, 34.34]	2003
Pearce	19.1	14.4	15	13.4	11.1	16	7.2%	5.70 [-3.39, 14.79]	2006
Kuhls	40	23.45	22	30.3	22.98	22	4.6%	9.70 [-4.02, 23.42]	2007
Beale	43.8	28	27	31.3	27.2	28	4.2%	12.50 [-2.10, 27.10]	2008
Total (95% CI)			**660**			**634**	**100.0%**	**-0.89 [-4.53, 2.74]**	

Heterogeneity: $Tau^2 = 26.39$; $Chi^2 = 82.47$, df = 12 ($P < 0.00001$); $I^2 = 85\%$

Test for overall effect: Z = 0.48 (P = 0.63)

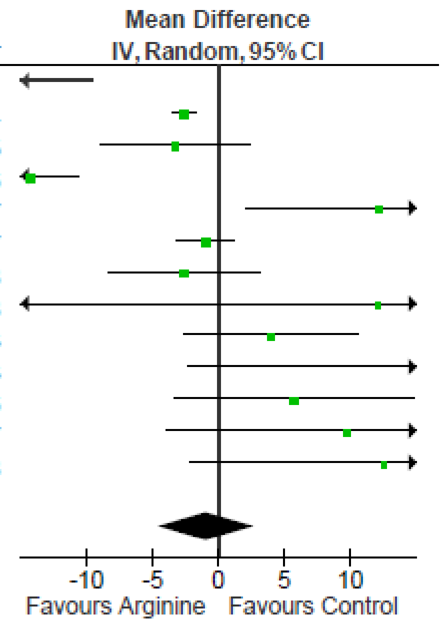


Figure 6a. ICU LOS

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference 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)

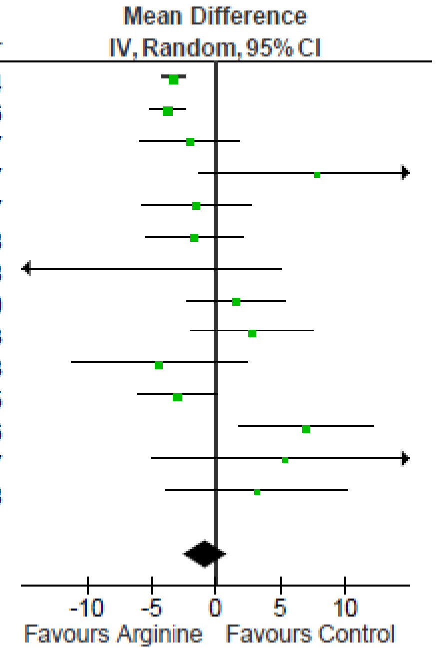
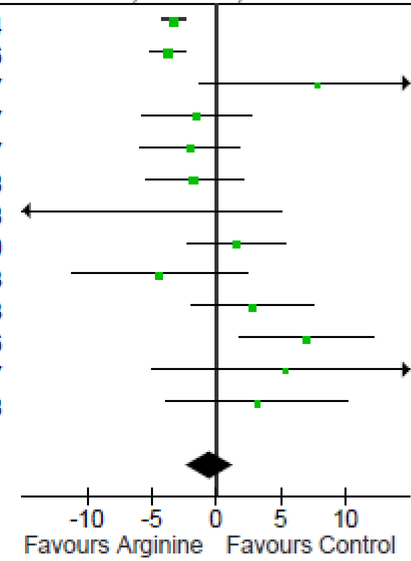


Figure 6b. ICU LOS (excluding Tsuei)

	Diets with Arginine			Control				Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
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: $Tau^2 = 5.60$; $Chi^2 = 40.21$, df = 12 (P < 0.0001); $I^2 = 70\%$
Test for overall effect: Z = 0.47 (P = 0.64)

Figure 7a. Ventilated days

	Diets with Arginine			Control				Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Gottschlich	9	4.5	17	10	2.5	14	10.1%	-1.00 [-3.51, 1.51]	1990	
Moore	1.9	0.9	51	5.3	3.1	47	13.9%	-3.40 [-4.32, -2.48]	1994	
Kudsk	2.4	1.3	16	5.4	2	17	13.5%	-3.00 [-4.14, -1.86]	1996	
Mendez	16.5	19.4	22	9.3	6	21	2.4%	7.20 [-1.30, 15.70]	1997	
Saffle	22	3	25	21	2	24	12.9%	1.00 [-0.42, 2.42]	1997	
Engel	14.8	5.6	18	16	5.6	18	7.5%	-1.20 [-4.86, 2.46]	1997	
Weimann	21.4	10.8	16	27.8	14.6	13	1.9%	-6.40 [-15.94, 3.14]	1998	
Atkinson	8	11.1	197	9.4	17.7	193	9.1%	-1.40 [-4.34, 1.54]	1998	
Galban	12.4	10.4	89	12.2	10.3	87	8.8%	0.20 [-2.86, 3.26]	2000	
Chuntrasakul	2.7	5.2	18	7.4	13.5	18	3.5%	-4.70 [-11.38, 1.98]	2003	
Dent	14.3	22.4	87	10.8	12.8	83	4.7%	3.50 [-1.95, 8.95]	2003	
Tsuei	10	5	61	14	10	55	9.1%	-4.00 [-6.93, -1.07]	2005	
Kuhls	23.1	12.66	22	20.9	12.66	22	2.9%	2.20 [-5.28, 9.68]	2007	
Total (95% CI)			**639**			**612**	**100.0%**	**-1.30 [-2.72, 0.12]**		

Heterogeneity: $Tau^2 = 3.57$; $Chi^2 = 44.55$, df = 12 ($P < 0.0001$); $I^2 = 73\%$
Test for overall effect: Z = 1.79 (P = 0.07)

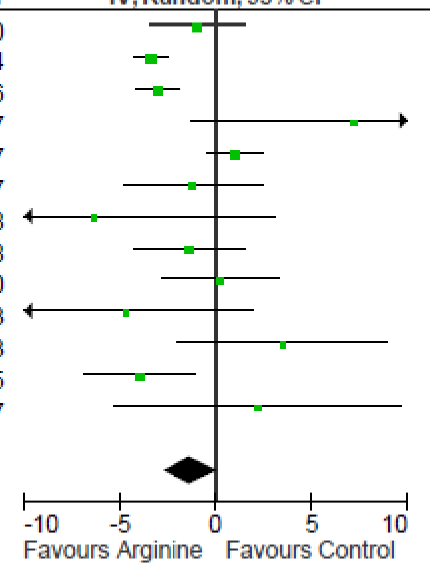


Figure 7b. Ventilated days (excluding Tsuei)

	Diets with Arginine			Control				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Gottschlich	9	4.5	17	10	2.5	14	11.1%	-1.00 [-3.51, 1.51]	1990
Moore	1.9	0.9	51	5.3	3.1	47	15.1%	-3.40 [-4.32, -2.48]	1994
Kudsk	2.4	1.3	16	5.4	2	17	14.7%	-3.00 [-4.14, -1.86]	1996
Engel	14.8	5.6	18	16	5.6	18	8.3%	-1.20 [-4.86, 2.46]	1997
Saffle	22	3	25	21	2	24	14.0%	1.00 [-0.42, 2.42]	1997
Mendez	16.5	19.4	22	9.3	6	21	2.6%	7.20 [-1.30, 15.70]	1997
Atkinson	8	11.1	197	9.4	17.7	193	10.0%	-1.40 [-4.34, 1.54]	1998
Weimann	21.4	10.8	16	27.8	14.6	13	2.2%	-6.40 [-15.94, 3.14]	1998
Galban	12.4	10.4	89	12.2	10.3	87	9.7%	0.20 [-2.86, 3.26]	2000
Dent	14.3	22.4	87	10.8	12.8	83	5.2%	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	3.3%	2.20 [-5.28, 9.68]	2007
Total (95% CI)			**578**			**557**	**100.0%**	**-1.02 [-2.53, 0.49]**	

Heterogeneity: $Tau^2 = 3.72$; $Chi^2 = 42.90$, df = 11 ($P < 0.0001$); $I^2 = 74\%$
Test for overall effect: Z = 1.32 (P = 0.19)