6.2 Enteral Nutrition (Other): Prebiotics/Probiotics/Synbiotics May 27th 2009

Recommendation:

There are insufficient data to make a recommendation on the use of Prebiotics/Probiotics/Synbiotics in critically ill patients.

Discussion: The committee noted the inconsistent effect of Prebiotics/Probiotocs/Synbiotics on mortality and the lack of a treatment effect on other clinical outcomes. There was inconsistency between studies in the method of reporting other outcomes such as septic morbidity, complications and diarrhea. Also there was a huge variation in the type of probiotics used, the use of prebiotics and the choice of a control group. Given this and the potential for increased harm in critically ill patients as evidenced by the recent PROPATRIA trial (1) and previous concerns specifically saccharomyces boulardii (2), the committee decided there was not enough evidence to support the use of Prebiotics/Probiotocs/Synbiotics. However, it was noted that their use may be associated with a trend towards a reduction in diarrhea in the critically ill population.

(1) Besselink MG at al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Feb 23;371(9613):651-9.

(2) Lherm T, Monet C, Nougiere B, Soulier M, Larbi D, Le Gall C, Caen D, Malbrunot C. Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. Intensive Care Med. 2002 Jun;28(6):797-801.

Values	Definition	Score 0, 1, 2 or 3
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	0
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	1
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	2
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	1
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings =3.	2
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	1

6.2 Enteral Nutrition (Other): Prebiotics/Probiotics/Synbiotics May 27th 2009

Question: Does the addition of Prebiotics/Probiotics/Synbiotics to enteral feeding result in better outcomes in critically ill patients?

Summary of evidence: There were 1 level 1 and 11 level 2 studies that were reviewed. Two trials studied the effects of addition of *saccharomyces boulardii* to enteral nutrition on diarrhea, one studied the effects of Trevis ™ (combination of probiotics+ prebiotics), three studied the effects of Synbiotic 2000 (combination of probiotics and prebiotics), one studied Ecologic 641 (probiotics) plus prebiotics (Besselink 2008), 4 studies used probiotics of varying strains while one study used a prebiotic supplemented enteral formula. In one study, Synbiotics were compared to a prebiotics (vs. placebo/conventional therapy), hence the data from this trial was not included in the meta-analysis (Olah 2007). Bleichner et al only reported on diarrhea while the other studies reported on clinical outcomes. In most of the studies patients received either enteral or parenteral nutrition, but no further details were provided.

Mortality: When the data from all the studies were aggregated, the use of Prebiotics/Probiotics/Synbiotics had no effect on mortality (RR = 0.89, 95% CI 0.68, 1.17, p =0.52, no heterogeneity present) (figure 1). In one study (Besselink 2008, The PROPRATRIA study), there was a significantly higher mortality in the group receiving the probiotics (p 0.010). When 4 of the 12 studies that reported on ICU mortality were aggregated, Prebiotics/Probiotics/Synbiotics were associated with a trend towards a reduction in mortality (RR = 0.74, 95 % CI 0.50, 1.09, p = 0.12, no heterogeneity present) (figure 2).

Infections, LOS, ventilator days: When the data from all the trials were aggregated, the use of Prebiotics/Probiotics/Synbiotics had no effect on infectious complications (RR 0.89, 95 % CI 0.68, 1.17, p =0.40) (figure 3). One study showed a significant reduction in ICU length of stay with the use of Synbiotic 2000 (Kotzampassi 2006), one showed a trend towards a reduction (Besselink 2008) while 6 other studies did not. Duration of ventilation was significantly reduced in the group that received Synbiotic 2000 in one study (Kotzampassi 2006) but not in the other study using Synbiotic 2000 (Knight 2008), and no differences were seen between the groups in the study of Lactobacillus casei rhamnosum (Forestier 2008).

Other: In the Besselink study, there was a significantly higher incidence of need for surgical intervention (p=0.05), organ failures (p=0.02) and bowel ischemia (p =0.004) associated with the use of pre/probiotics. Other outcomes such as diarrhea, immune function, normalization of CRP, etc were also recorded. Only two studies reported the number of patients with diarrhea and this was significantly reduced in one study using Synbiotic 2000 (Kotzampassi 2006) but was no different in the other study using Sacccharomyces boulardii (Bleichner 1997). When the % total days with diarrhea were studied, there was a significant reduction in the groups receiving Saccharomyces boulardii in both studies (Bleichner 1997, Tempe 1983) but there was no difference in diarrhea rates in one study (Alberda 2007). When the data from the 4 studies that reported on the # patients with diarrhea were aggregated, the use of pro/prebiotics was associated with a reduction in diarrhea (RR 0.67, 95% CI 0.45, 1.00, p = 0.05) (Figure 4). In the

study by Jain et al, gastric colonization with multiple organisms and potentially pathogenic bacteria was significantly reduced in the probiotic group. In one study, the administration of ProViva (L. Planatarum 299v) was associated with a late attenuation of the systemic inflammatory response when compared to the control group (McNaught 2005). Klarin et al examined rectal biopsies and concluded that Lactobacillus Planatarum 299v adhered to intestinal mucosa in critically ill patients.

Conclusions:

1) The addition of Prebiotics/Probiotics/Synbiotics to enteral nutrition has no effect on overall mortality.
2) The addition of Prebiotics/Probiotics/Synbiotics to enteral nutrition has no effect on infectious complications.
4) The addition of Prebiotics/Probiotics/Synbiotics to enteral nutrition may reduce may reduce diarrhea.

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 Prebiotics/Probiotics/Synbiotics in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%) Intervention	Mortality # (%) Control	Other	P value
Probiotics vs. placebo/conventional therapy							
1) Tempe 1983	ICU patients N =40	C.Random: yes ITT: yes Blinding: double (10)	EN + saccharomyces boulardii (SB, probiotic) vs EN + placebo (sterile solution)	3/20 (15)	3/20 (15)	EN + SB EN + placebo # days with diarrhea 34/389 (9) 63/373 (17)	<0.001
2) Bleichner 1997	Mixed from 11 ICUs N=128	C.Random: not sure ITT: yes Blinding: double (13)	EN + saccharomyces boulardii (SB, probiotic)) vs EN + placebo (powder)	NR	NR	EN + SB EN + placebo # patients with diarrhea 18/64 (28) 24/64 (38) # days with diarrhea 91 (14) 134 (20)	0.26 <0.01
3) Jain 2004	ICU patients N = 90	C.Random: no ITT: yes Blinding: double (10)	Trevis™ (Lactobacillus acidophilus La5, Bifidobacterium lactis Bb12, Streptococcus thermophilus, Lactobacillus bulgaricus, probiotics) + Raflitose (prebiotic oligofructose) vs. placebo (powdered sucrose capsules). All patients received EN or PN.	22/45 (49)	20/45 (45)	Trevis™ Placebo # multiple organisms Day 8 9/23 (39) 18/24 (75) # potentially pathogenic organisms day 8 10/23 (43) 18/24 (75)	NR 0.05
4) McNaught 2005	ICU patients N = 103	C.Random: no ITT: no Blinding: no (5)	Proviva (Lactobacillus plantarum 299v, probiotic) vs. conventional therapy. All patients received EN or PN as needed.	18/52 (35)	18/51 (35)	NR	
5) Klarin 2005	Critically ill patients tolerating enteral nutrition requiring broad spectrum antibiotics N =17	C.Random: no ITT: no Blinding: no (6)	Lactobacillus plantarum 299v (Lp 299v, probiotic) mixed in fermented oatmeal added to enteral feeds vs. standard enteral nutrition. Some patients needed parenteral nutrition.	ICU 1/8 (12) hospital 2/8 (25)	ICU 2/7 (29) hospital 2/7 (29)	Lp 299v Standard Patients with positive cultures 6/8 (75) 5/7 (71) Patients with bacterial conversion in rectal biopsies 3/8 (38) 0/7	NS 0.03
6) Kotzampassi 2006	Multiple Trauma patients from 5 ICUs N = 77	C.Random: no ITT: no Blinding: double blind (9)	Synbiotic 2000 Forte (10^{10} cfu each; Pediococcus pentoseceus 5-33:3, Leuconostoc mesenteroides 32-77:1, L. paracasei ssp paracasei 19 and L. plantarum 2362 {probiotics} and inulin, oat bran, pectin and resistant starch {prebiotics}) vs. Placebo (Maltodextrin). Mixed in tap water.	ICU 5/35 (14)	ICU 9/30 (30)	Synbiotic Forte Placebo Ventilator Days 16.7 ± 9.5 29.7 ± 16.5 Patients with diarrhea 5/35 (14) 10/30 (30)	0.001 0.04

Study	Population	Methods (score)	Intervention	Mortality # (%) Intervention	Mortality # (%) Control	Other	P value
7) Alberda 2007	ICU patients N =28	C.Random: no ITT: yes Blinding: double (10)	VSL # 3 (viable Lactobacillus casei, L. planatarum, L. acidophulus, L. delbrueckii, Bifidobacterium longum, breve & infantis) vs. sonicates (nonviable) vs. placebo with EN with fibre.	ICU 1/10* (10)	ICU 1/9 (11)	Diarrhea rates 1/10 (14) 2/9 (23) Immune function Increased in the group receiving viable probiotics MODS score No differences	NS <0.05 NS
8) Karakan 2007	Patients with Severe Acute Pancreatitis N = 30	C.Random: not sure ITT: yes Blinding: double (9)	Prebiotic supplemented EN (soluble fibres + insoluble fibres) vs. EN with fibre. Both received supplemental PN	Hospital 2/15 (13)	Hospital 4/15 (27)	Total complications 7/15 (47) 9/15 (60) Multi organ failure 1/15 (7) 2/15 (13) Duration to normal CRP 7 ± 2 10 ± 3	<0.05 NS <0.05
9) Forestier 2008	Mixed ICU patients N = 208	C.Random: not sure ITT: no Blinding: double (6)	Lactobacillus casei rhamnosum vs. placebo (growth medium without bacteria). Both given po or NG tube.	NR	NR	Patients with + pseudomonas at any site 6/102 (6) 17/106 (16) Ventilation 12 (1-90) 9 (1-88)	0.02
10) Besselink 2008	Acute Pancreatitis patients from 15 ICUs N = 298	C.Random: not sure ITT: yes Blinding: double (11)	Ecologic 641 (Lactobacillus acidophilus, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum & Bifidobacterium lactis plus cornstarch + maltodextrins vs. placebo (cornstarch + maltodextrins). Both given via NJ	Hospital 14/152 (16)	Hospital 9/144 (6)	Surgical intervention 28/152 (18) 14/144 (10) Any organ failure 41/152 (27) 23/144 (16) Bowel Ischemia 9/152 (6) 0/144	0.05 0.02 0.004
11) Knight 2008	Mixed ICU pts N= 300	C.Random: yes ITT: no Blinding: double (10)	EN + Synbiotic 2000 FORTE BID for at least 2 days vs. EN + Placebo	ICU 28/130 (22) Hospital 35/130 (27)	ICU 34/129 (26) Hospital 42/129 (33)	Diarrhea rates 7/130 (5) 9/129 (7)	NS
Probiotics vs. Prebiotics							
12) Olah 2007	Severe Acute Pancreatitis patients N = 83	C.Random: no ITT: no Blinding: no (9)	Synbiotic 2000 (same as Synbiotic 2000 Forte, see above {probiotics+prebiotics}) vs. oat bran, pectin and resistant starch {prebiotics}). Both given via NJ.	ICU 2/33 (6)	ICU 6/29 (21)	Synbiotic Forte Placebo SIRS 3/33 (9) 5/15 (17) Multi-Organ Failure 5/33 (15) 9/29 (31) Multi-Organ Failure + SIRS 8/33 (24) 14/29 (48)	NR 0.14 <0.05

Table 2. Randomized studies evaluating Prebiotics/Probiotics/Synbiotics in critically ill patients

Study	Length of Stay		Infections	
	Intervention	Control	Intervention	Control
Placebo controlled trials or conventional therapy				
1) Tempe 1983	NR	NR	NR	NR
2) Bleichner 1997	NR	NR	NR	NR
3) Jain 2004	Hospital LOS 14 (9-29) ICU LOS 7 (3-16)	Hospital LOS 15 (9-26) ICU LOS 5 (3-14)	Septic Complications 33/45 (73)	Septic Complications 26/45 (58)
4) McNaught 2005	NR	NR	Septic morbidity 21/52 (40)	Septic morbidity 22/51 (43)
5) Klarin 2005	ICU LOS 12 (4-37)	ICU LOS 11 (4-49)	NR	NR
6) Kotzampassi 2006	ICU LOS 27.7 ± 15.2	ICU LOS 41.3 ± 20.5	Severe Sepsis 6/35 (17) Septic Complications 17/35 (49)	Severe Sepsis 12/30 (40) Septic Complications 23/30 (77)
7) Alberda 2007	NR	NR	NR	NR
8) Karakan 2007	ICU LOS 6 ± 2 Hospital LOS 10 ± 4	ICU LOS 6 ± 2 Hospital LOS 15 ± 6	Sepsis 1/15 (7)	Sepsis 2/15 (13)
9) Forestier 2008	ICU LOS 14 (3-91)	ICU LOS 13.5 (3-88)	Pseudomonas VAP 3/102 (3)	Pseudomonas VAP 8/106 (8)
10) Besselink 2008	ICU LOS 6.6 ± 17 Hospital LOS 28.9 ± 41.5	ICU LOS 3.0 ± 9.3 Hospital LOS 23.5 ± 25.9	Infections 46/152 (30)	Infections 41/144 (28)
11) Knight 2008	ICU 6 (3-11)	ICU 7 (3-14)	VAP 12/130 (9)	VAP 17/129 (13)
Probiotics vs. Prebiotics				
12) Olah 2007	Hospital LOS (mean) 14. 9	Hospital LOS (mean) 19.7	Septic Complications 4/33 (12)	Septic Complications 8/29 (28)

C.Random: Concealed randomization
ITT: Intent to treat

NR: Not reported
LOS days, Ventilator days and Cost: not reported
* only data for the viable bacteria reported here (non viable group not included here)

NR: Not reported
NS: Non significant

SB: Saccharomyces boulardii
Presumed hospital mortality unless otherwise specified

Figure 1.

Review: Probiotics
Comparison: 01 Probiotics vs. Placebo/None
Outcome: 01 Mortality

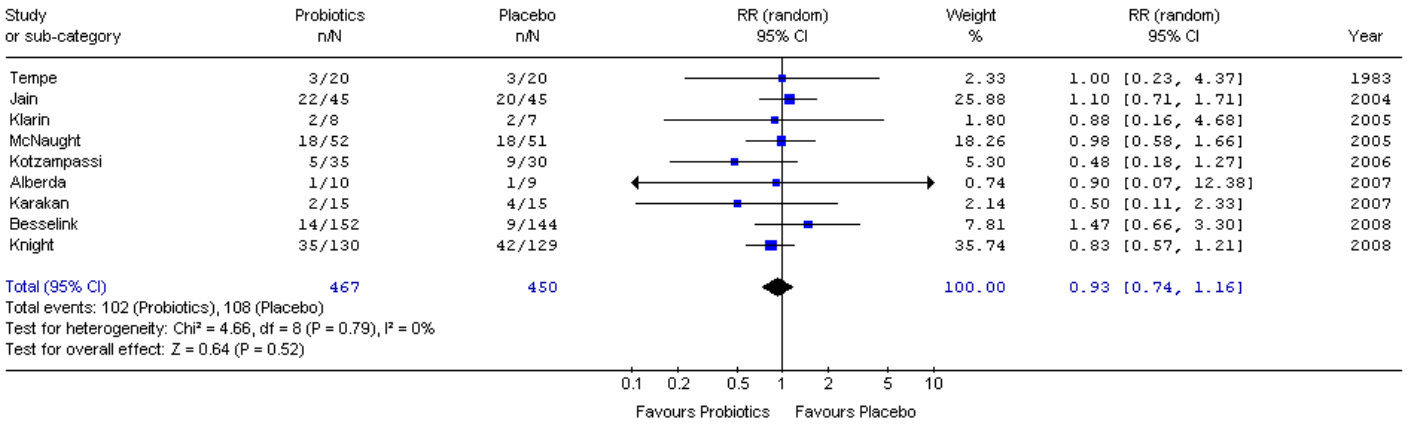


Figure 2

Review: Probiotics
Comparison: 01 Probiotics vs. Placebo/None
Outcome: 02 ICU Mortality

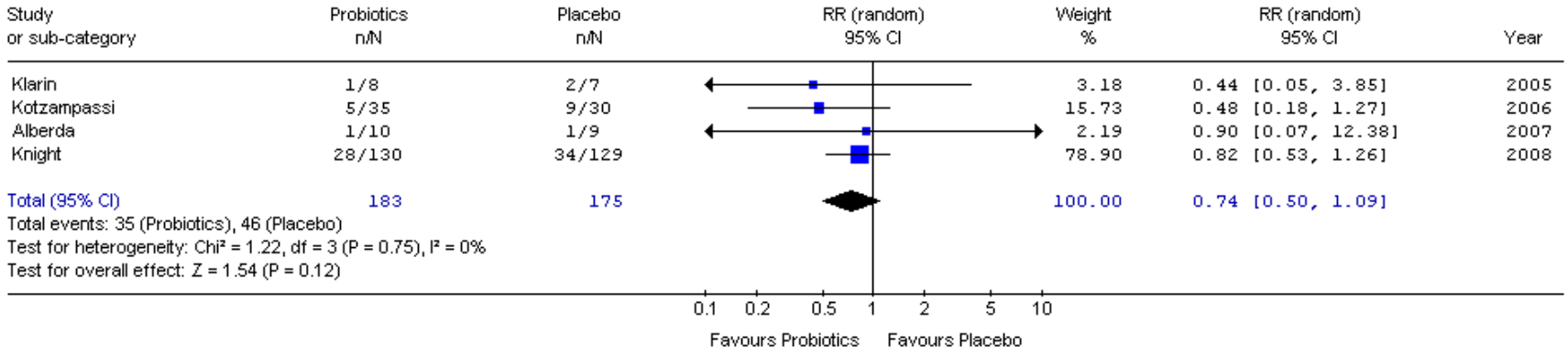


Figure 3

Review: Probiotics
Comparison: 01 Probiotics vs. Placebo/None
Outcome: 04 Infectious Complications

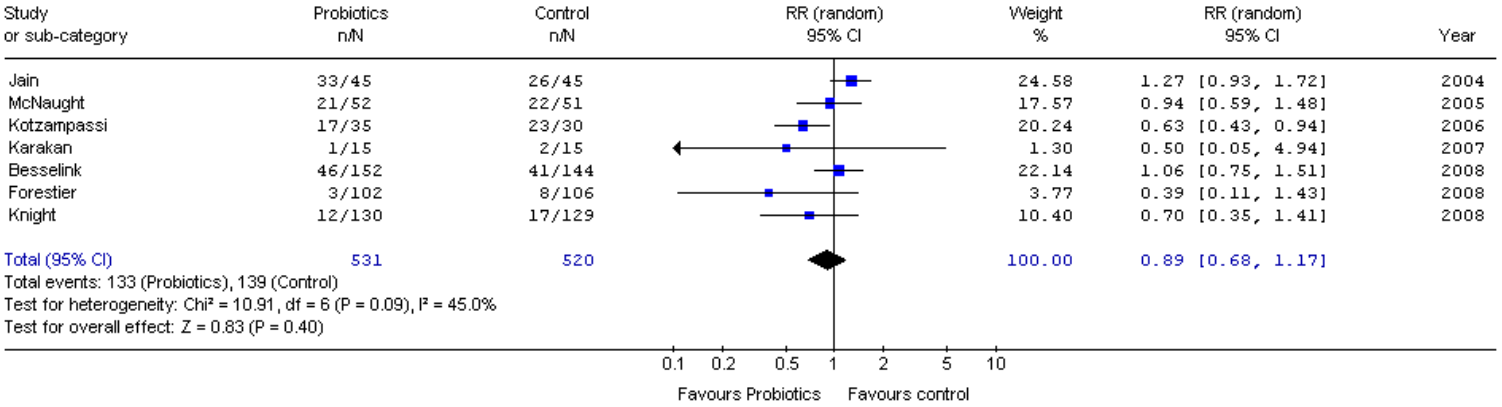
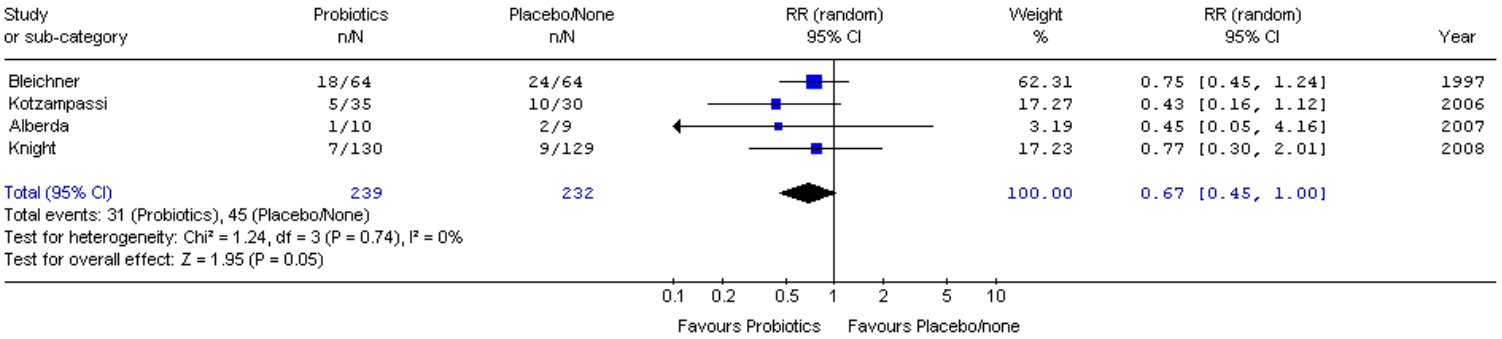


Figure 4.

Review: Probiotics
Comparison: 01 Probiotics vs. Placebo/None
Outcome: 03 Diarrhea



TOPIC:_6.2 Enteral Nutrition (Other): Prebiotics/Probiotics/Synbiotics

Article inclusion log

Criteria for study selection

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

	Author	Journal	I	E	Why Rejected
1	Tempe	Sem Hop Paris 1983	√		
2	De Felippe	Surg Gynecol Obstet 1993		√	Not EN
3	Bleichner	Int Care Med 1997	√		
4	McNaught	Gut 2002		√	Elective surgery pts
5	Olah	British Journal of Surgery 2002		√	Not ICU pts
6	Rayes	Nutrition 2002		√	Elective surgery pts
7	Rayes	Transplantation 2002		√	Liver transplant pts
8	Andersen	Gut 2004		√	Elective surgery pts
9	Falcao	Clinical Science 2004		√	Glutamine + probiotics
10	Jain	Clin Nut 2004	√		
11	Dendukuri	CMAJ 2005		√	Systematic review, Not ICU pts
12	Kanawaza	Langenbecks Arch Surg 2005		√	Not ICU pts
13	Klarin	Critical Care 2005	√		
14	McNaught	Clin Nut 2005	√		
15	Rayes	American Journal of Trans 2005		√	Transplant pts
16	Voudouris	Critical Care Abstracts, 25th International Symposium on Intensive Care and Emergency Medicine 2005		√	Contacted authors, unable to retrieve data
17	Gommersall	ANZCA 2006		√	Abstract only, unable to get data from authors
18	Kotzampassi	World J Surg 2006	√		
19	Alberda	Am J Clin Nutr 2007	√		
20	Beausoleil	Can J Gastroenterol 2007		√	Not ICU pts
21	Hickson	BMJ 2007		√	Not ICU pts
22	Karakan	World J Gastroenterol 2007	√		
23	Olah	Hepato-Gastro 2007	√		
24	Qin	Eur J Clin Nutr 2007		√	Not ICU pts
25	Rayes	Annals of Surgery 2007		√	Surgery pts
26	Spindler-Vesel	JPEN 2007		√	Too many interventions [synbiotics, prebiotics, glutamine & peptide]
27	Watkinson	Clinical Nutrition 2007		√	Systematic review, Individual studies looked at
28	Forestier	Crit Care 2008	√		
29	Besselink	Lancet 2008	√		
30	Klarin	Critical Care 2008		√	Probiotics given as an oral swab, not ingested
31	Knight	Intensive Care Medicine 2008	√		

I = included, E = excluded

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