6.2 Enteral Nutrition (Other): Probiotics

Question: Does the addition of probiotics to enteral feeding result in better outcomes in critically ill patients?

Summary of evidence: There were 4 level 1 and 29 level 2 studies that were reviewed. Of the 33 included trials, 22 enrolled heterogeneous critically ill (medical and surgical) ICU patients (Tempe 1983, Heimburger 1994, Bleichner 1997, Kecskes 2003, Jain 2004, Klarin 2005, McNaught 2005, Alberda 2007, Forestier 2008, Klarin 2008, Knight 2008, Barraud 2010, Morrow 2010, Frohmader 2010, Ferrie 2011, Lopez de Toro 2014, Sanaie 2014, Rongrungruang 2015, Zeng 2016, Malik 2016, de Castro Soares 2017 and Shariatpanahi 2018), 6 enrolled patients with acute pancreatitis (Li 2007, Olah 2007, Besselink 2008, Sharma 2011, Cui 2013, Wang 2013), 1 enrolled trauma patients (Kotzampassi 2006), 2 enrolled head injury patients (Tan 2011 and Wan 2019) and 2 enrolled burn patients (Schlotterer 1987, Lu 2004). Three trials studied the effects of the addition of *saccharomyces boulardii* to enteral nutrition, four studied the effects of Lactobacillus plantarum, three studied the effects of Lactobacillus rhamnosus, one studied Lactobacillus casei, three studied the effects of VSL #3, one studied the effects of Trevis ™ (combination of probiotics+ prebiotics), four studied the effects of Synbiotic 2000 (combination of probiotics and prebiotics), one studied Ecologic 641 (probiotics) plus prebiotics (Besselink 2008), one studied Biovicerin (sporulated B. cereus), and twelve studies used probiotics of varying strains . One study compared a kitchen made formula made with honey (as a prebiotic contains oligosarccharides or bifidogenic factor) to one without (Shariatpanahi 2018), hence the data from this trial was not included in the meta-analyses. Bleichner 1997 and de Castro Soares 2017 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 the 25 trials that reported on 28 day, 1 month, hospital or ICU mortality were aggregated, probiotics were associated with a trend towards a reduction in overall mortality (RR 0.88, 95% CI 0.73, 1.07, p=0.20, test for heterogeneity I^2=23%; figure 1). Probiotics had no effect on hospital mortality when the data from 18 trials were pooled (RR 1.01, 95% CI 0.84, 1.21, p=0.92, heterogeneity I^2=0%; figure 2) and no effect on ICU mortality pooling results from 8 trials (RR 0.90, 95% CI 0.70, 1.17, p=0.44, heterogeneity I^2=0%; figure 3).

Overall infections and VAP: Infectious outcome data were reported in 20 trials and the pooled results show that probiotics were associated with a significant reduction in infectious complications (RR 0.80, 95% CI 0.70, 0.91, p=0.0007, test for heterogeneity I^2=26%; figure 4). When the data from the 9 trials reporting VAP were pooled, probiotics were associated with a trend towards a decrease in the incidence of VAP (RR 0.80, 95% CI 0.64, 1.00; p=0.05, heterogeneity I^2=41%; figure 5).

Subgroup analyses: Several subgroup analyses were done to elucidate the effects of probiotics on overall infections (see figure 6).The details are as follows:

Dose of probiotics: Subgroup analyses showed a trend towards a reduction in overall infections in trials using high dose probiotics (≥5 x 10^9 CFU/day) (0.87, 95% CI 0.75, 1.02, p = 0.09, test for heterogeneity I^2=26%) and a significant reduction in the trials using a lower dose (<5 x 10^9 CFU/day) (RR 0.69, 95% CI 0.58, 0.83, p<0.0001; test for heterogeneity I^2=0%), p-value for the difference between groups: p=0.05).

Lactobacillus plantarum: Subgroup analyses showed that *L. plantarum,* either alone or in combination with other probiotics, was associated with a significant reduction in overall infections (RR 0.71, 95% CI 0.58, 0.86, p=0.0007, test for heterogeneity I^2=0%). A significant reduction in overall infections was also seen in the trials that did not include *L. plantarum* (RR 0.84, 95% CI 0.72, 0.98, p=0.03, test for heterogeneity I^2=32%). The test for subgroup differences was p=0.18.

***Lactobacillus rhamnosus* GG:** Subgroup analyses showed that effect of trials using LGG was not significantly different from trials that did not include LGG (RR 0.76, 95% CI 0.53, 1.11, p=0.15 compared to RR 0.80, 95% CI 0.69, 0.93, p=0.003, test for difference between subgroups: p=0.80).

Higher mortality: The median mortality rate (28 day or hospital mortality or ICU mortality if 28 day/hospital not reported) in the control groups of all studies was 19%. Subgroup analyses showed that probiotics were associated with a significant reduction in overall infections among patients with higher risk of death (>19% mortality in the control group) (RR 0.77, 95 % CI 0.65, 0.92, p=0.004). There was no significant effect in overall infections observed for trials of patients with a lower mortality (≤19% mortality) in the control group (RR 0.88, 95% CI 0.69, 1.11, p=0.27) and the test of subgroup differences was not significant (p=0.67).

Methodological score: The median method score was 9. We compared trials with a methods score of less than 9 with those with a score of 9 or more. Trials with a higher score showed a significant reduction in overall infections (RR 0.80, 95% CI 0.65, 0.99, p= 0.04) as did trials with a lower methods score (RR 0.76, 95% CI 0.65, 0.88, p=0.0003). There were no significant differences between the subgroups (p=0.64).

Length of Stay: Probiotics had no impact on hospital LOS when data from 13 trials were pooled (WMD -0.63, 95% CI -3.61, 2.36, p=0.68, test for heterogeneity I^2=74%; figure 7). There was a trend towards a decrease in ICU LOS when results of 15 trials were pooled (WMD -3.39, 95% CI -7.49, -0.71, p=0.11, test for heterogeneity I^2 =93%; figure 8).

Other: The impact on diarrhea, reported variably as days of diarrhea, diarrhea rates and/or duration of diarrhea was reported in 15 trials. Pooling results from 9 trials that reported patients who developed diarrhea, probiotics had no effect (RR 0.96, 95% CI 0.82, 1.13, p=0.62; heterogeneity I^2=3%; figure 9). Data were too sparse to aggregate other reported individual infections (see table 1).

Conclusions:
1) The addition of probiotics to enteral nutrition has no effect on overall, hospital or ICU mortality.
2) The addition of probiotics to enteral nutrition is associated with a reduction in overall infectious complications.
3) Probiotic supplementation may be associated with a reduction in the incidence of VAP.
4) The addition of probiotics to enteral nutrition has no effect on hospital LOS but may be associated with a reduction in ICU LOS.
5) The addition of probiotics to enteral nutrition has no effect on 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 Probiotics in critically ill patients

	Study	Population	Methods Score	Type of Probiotic/Intervention		
				Delivery Vehicle	Intervention/Dose/Duration	Control
1	**Tempe 1983**	ICU patients N=40	C.Random: yes ITT: yes Blinding: double Score: 10 Viability (intervention): NR	EN tube	EN (unknown) + Ultra-Levure (*Saccharomyces boulardii)*, 10^{10}/1L solution for 11-21 days	EN (unknown) + Placebo (sterile solution)
2	**Schlotterer 1987**	Burn patients N=18	C.Random: no ITT: no Blinding: double Score: 8 Viability (intervention): NR	NG tube	EN (Polydiet or Nutrigil) + *Saccharomyces boulardi* 500 mg QID for 8-28 days	EN (Polydiet or Nutrigil) + Placebo
3	**Heimburger 1994**	Mixed ICU patients 83% received antibiotics N=62	C.Random: no ITT: no Blinding: double Score: 9 Viability (intervention): NR	EN tube	EN (standard) + 1g of Lactinex (*Lactobacillus acidophilus & Lactobaccilus bulgaricus*) 10^8 live cells TID for 5-10 days	EN (standard) + placebo (0.5g dextrose + 0.5g lactose)
4	**Bleichner 1997**	Mixed ICU patients N=128	C.Random: not sure ITT: yes Blinding: double Score: 13 Viability (intervention): NR	EN tube	EN (unknown) + *Saccharomyces boulardii* 500 mg QID for 21 days or until EN stopped	EN (unknown) + Placebo (powder)
5	**Kecskes 2003**	ICU patients on antibiotics N=45	C.Random: no ITT: no Blinding: double Score: 8 Viability (intervention): yes	NJ tube	EN (Nutrison fibre) + fermented oatmeal formula with *Lactobacillus plantarum* 299 10^9 BID and fibre for 7 days	EN (Nutrison fibre) + heat killed Lactobacillus plantarum 299 BID + fibre (non-viable)
6	**Jain 2004**	ICU patients N=90	C.Random: no ITT: yes Blinding: double Score: 10 Viability (intervention): NR	Oral or NG tube	EN or PN + Trevis™ 1 capsule TID + 7.5g Raftilose (oligofructose) BID until hospital discharge	EN or PN + Placebo (powdered sucrose capsules)

7	**Lu 2004**	Burn patients N=40	C.Random: no ITT: yes Blinding: double Score: 9 Viability (intervention): NR	NR	EN + synbiotics Medipham (Sweden) ($1x10^{10}$ each: *Pediococcus pentosaceus, Leuconostoc mesenteroides, Lactobacillus paracasei, Lactobacillus plantarum* + 2.5 g each: beta-glucan, inulin, pectin, stabilizing starch for 21 days	EN + prebiotics only (2.5 g each: beta-glucan, inulin, pectin, stabilizing starch)
8	**Klarin 2005**	Critically ill patients on antibiotics N=17	C.Random: no ITT: no Blinding: no Score: 6 Viability (intervention): NR	Mixed in fermented oatmeal, given via NG tube	EN + *Lactobacillus plantarum* 299v, 10^9/day 50ml every 6 hours x 3 days then 25 ml every 6 hours until ICU discharge	EN (Impact or Nutrodrip Fibre). Some patients needed PN
9	**McNaught 2005**	ICU patients on antibiotics N=130	C.Random: no ITT: yes Blinding: no Score: 7 Viability (intervention): NR	Oral, NJ tube	EN or PN + Proviva, (oatmeal & fruit drink) 5 x 10^7 CFU/ml of *L. plantarum 299v* X 500 mls until hospital discharge or beyond	EN or PN alone
10	**Kotzampassi 2006**	Multiple trauma patients from 5 ICUs N=77	C.Random: no ITT: no Blinding: double Score: 8 Viability (intervention): NR VAP determination: clinical	Endoscopic gastrostomy or NG tube	EN or PN + Synbiotic 2000 Forte 10^{11}, 1 sachet/day for 15 days until ICU discharge	EN or PN + Placebo (Maltodextrin), mixed in tap water
11	**Alberda 2007**	ICU patients N=28	C.Random: no ITT: yes; Blinding: double Score: 10 Viability (intervention): No for VSL # 3; Yes for bacteria sonicates	NG tube	Jevity Plus (EN) (10 g fructooligosaccharides/1000 mL and 12 g of soluble and insoluble fiber blend) + VSL # 3, 1 package BID, 9×10^{11}/day for 7 days until ICU discharge or EN discontinuation	Jevity Plus + Placebo
12	**Li 2007**	Severe acute pancreatitis patients N=25	C.Random: no ITT: yes Blinding: no Score: 7 Viability (intervention): NR	Given enterally	Jinshuangqi (1 capsule is 0.5 g, consist of $0.5*10^7$ CFU *Bifidobacterium longum,* $0.5*10^6$ *lactobacillus bulgaricus and* $0.5*10^6$ *Streptococcus thermophilus*) 2.0 g TID on basis of traditional treatment Duration: NR	Traditional treatment

13	**Olah 2007**	Severe acute pancreatitis patients N=83	C.Random: no ITT: no Blinding: no Score: 9 Viability (intervention): NR	NJ tube	EN (Nutricion Fibre) + Synbiotic 2000, 4 X 10^{10} CFU for 7 days	EN (Nutricion Fibre) + 10g plant fibres ((2.5 g each of Betaglucan, Inulin, Pectin & Resistant starch) (Prebiotics) BID for at least 2 days
14	**Forestier 2008**	Mixed ICU patients, 50% on antibiotics N=208	C.Random: not sure ITT: no Blinding: double Score: 8 Viability (intervention): NR VAP determination: objective	NG tube or Oral (after tube removal)	*Lactobacillus casei rhamnosum*, 10^9 CFU BID until ICU discharge	Placebo (growth medium never exposed to bacteria).
15	**Besselink 2008**	Acute pancreatitis patients from 15 ICUs N=298	C.Random: not sure ITT: yes Blinding: double Score:11 Viability (intervention): NR VAP determination: clinical	NJ tube or Oral	EN (Nutrison Multifibre) + Ecologic 641 10^{10} CFU BID for 28 days	EN (Nutrison Multifibre) + Placebo (cornstarch + maltodextrins)
16	**Klarin 2008**	ICU patients from 5 ICUs, on antibiotics for c. Difficile N=68	C.Random: yes ITT: no Blinding: double Score: 10 Viability (intervention): NR	Mixed in fermented oatmeal added to enteral feeds NG tube	299 *Lactobacillus plantarum,* 8 x 10^8 CFU/ml given as 6 x 100 ml doses every 12h & after 50 ml given BID until ICU discharge	Same oatmeal gruel mixed with lactic acid
17	**Knight 2009**	General ICU patients N=300	C.Random: yes ITT: no Blinding: double Score: 10 Viability (intervention): NR VAP determination: clinical	NJ or OG (orogastric) tube	EN (Nutrition Energy) + Synbiotic 2000 FORTE 4 x10^{11} species/sachet BID for 28 days or ICU discharge	EN (Nutrison Energy) + Placebo
18	**Barraud 2010**	Mechanically ventilated ICU patients, 80% on antibiotics N=167	C.Random: yes ITT: yes; Blinding: double Score: 12 Viability (intervention): NR VAP determination: objective	NG tube	EN (Fresubin) + Ergyphilus 2 x 10^{10} per capsule/day + potato starch 5 caps/day for 28 days	EN (fresubin) + Placebo capsules (excipient of potato starch)

19	**Morrow 2010**	ICU patients N=146	C.Random: no; ITT: yes; Blinding: double; Score:10 Viability (intervention): yes VAP determination: objective	Oropharynx and NG tube	EN (routine care) + *Lactobacillus rhamnosus* GG, $2X10^9$ BID as lubricant and mixed with water until extubation	EN (routine care) + inert plant starch inulin (prebiotic) BID as lubricant and mixed with water
20	**Frohmader 2010**	General ICU patients on antibiotics N=45	C.Random: yes ITT: yes Blinding: double Score: 11 Viability (intervention): yes	NG or NJ tube	EN (Standard) + VSL #3 mixed in nutritional supplement (Sustagen), BID until hospital discharge	EN (Standard) + placebo mixed in nutritional supplement (Sustagen), BID
21	**Ferrie 2011**	Critically ill patients with diarrhea, N=36	C.Random: no ITT: yes Blinding: double Score: 10 Viability (intervention): yes	NG tube	EN (Standard) + Culturelle *(Lactobacillus rhamnosus GG),* 10^{10} species/capsule + 280 mg inulin powder for 7 days	EN (Standard) + Raftiline, gelatin capsule with 280 mg inulin powder (prebiotic)
22	**Sharma 2011**	Acute pancreatitis patients N=50	C.Random: yes ITT: yes Blinding: double Score:11 Viability (intervention): yes	Oral, NJ or NG	EN (standard) or oral 4 sachets each $2.5 X 10^9$ *Lactobacillus acidophilus, Bifidobacterium longus*, *Bifidobacterium bifidum* & *Bifidobacterium infantalis* + 25 gms fructose for 7 days	EN (Standard) + placebo
23	**Tan 2011**	Closed head injury patients N=52	C.Random: yes ITT: yes Blinding: single Score:10 Viability (intervention): yes VAP determination: clinical	NG tube	EN (standard) total of 10^9 bacteria i.e. 7 sachets each $0.5 x 10^8$ *Bifidobacterium longum,* $0.5 X 10^71$ *Lactobacillus bulgaricus* and $0.5 X 10^7$ *Streptococcus thermophilus* for 21 days	EN (standard)
24	**Cui 2013**	Severe acute pancreatitis N=70	C.Random: no ITT: yes Blinding: no Score:9 Viability (intervention): yes	EN	EN + *bifidobacterium*, 4 capsules (each 210 mg, ($12.4 x 10^9$ per gram), hence $2.604 x 10^9$ per 240 mg) every 12 hours, given through nasal gastric tube. Total dose per day $20.832 x 10^9$.	EN

25	**Wang 2013**	Severe acute pancreatitis with intestinal ileus or abdominal distention. N=183	C.Random: no ITT: yes Blinding: no Score: 6 Viability (intervention): NR	SBFT	EN (standard) + capsules 0.5g TID containing *Bacillus subtilis and Enterococcus faecium* (5.0×10^7 *Bacillus subtilis* and 4.5×10^8 *Enterococcus faecium* per 250 g capsule). Unclear timeframe.	EN (standard)
26	**Lopez de Toro 2014**	Medical and surgical ICU pts with multi-organ failure N=89	C.Random: yes ITT: yes Blinding: no Score:11 Viability (intervention): NR	EN	EN + synbiotic drink with *streptococcus thermophilus, lactobacillus bulgaricus, lactobacillus casei, lactobacillus acidophilus, bifidobacterium*, Escherichia coli, coliformes x 7 days (max 4.8×10^9 UFC/ml).	EN and PN
27	**Sanaie 2014**	Critically ill pts, SIRS, expected LOS $\geq$7 days N=40	C.Random: yes ITT: yes Blinding: double Score:9 Viability (intervention): yes	NG tube	EN (standard) + 2 sachets VSL#3 BID x 7 days.	EN (standard) + placebo
28	**Rongungruang 2015**	Critically ill medical pts, no VAP at enrollment N=150	C.Random: no ITT: no Blinding: no Score:4 Viability (intervention): NR	EN and oral	80 ml fermented dairy product (8×10^9 cfu *Lactobacillus casei* [Shirota strain]) for oral care + 80 ml of the fermented dairy product via EN once daily for 28 days after extubated. EN feeding NR.	Standard care
29	**Zeng 2016**	Mixed ICU patients. N=250	C.Random: no ITT: no Blinding: single Score:8 Viability (intervention): yes	NG tube	EN + probiotic capsules 0.5g 3 times a day (active *Bacillus subtilis* and *Enterococcus faecalis*, concentration 4.5×10^9 per 0.25g and 0.5×10^9 per 0.25 g, respectively)	EN (standard)
30	**Malik 2016**	Mixed ICU patients, not taking microbial cell preparation prior to enrollment N=60	C.Random: yes ITT: no Blinding: double Score:9 Viability (intervention): NR	NG tube	EN + 3g packet (30 billion CFU of highly compatible, acid and bile resistant strains of *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium bifidium, Bifidobacterium longum, Bifidobacterium infantus*. Given twice daily for 7 days.	EN + placebo

31	**de Castro Soares 2017**	ICU pts with diarrhea receiving antibiotics N=60	C.Random: yes ITT: no Blinding: double Score:8 Viability (intervention): NR	Feeding tube	EN + four vials of *B. cereus* (Biovicerin) q6h (each vial contains $5x10^6$ sporulated B cereus in liquid suspension.	EN + fibre (30g/day [10g q8h] of soluble fibre with 60% guar gum and 40% inulin.
32	**Shariatpanahi 2018**	ICU pts expected to stay for ≥7days N=37	C.Random: no ITT: no Blinding: double Score:5 Viability (intervention): NR	NG tube	Kitchen formula with 50% CHO (10 % from natural honey as a prebiotic), 20% protein and 30% lipid. Given enterally for 7 days.	Kitchen formula with 50% CHO (no honey), 20% protein and 30% lipid.
33	**Wan 2020**	Patients with severe traumatic brain injury (Glasgow Coma Scale 3-8) N=76	C.Random: no ITT: yes Blinding: no Score:7 Viability (intervention): NR	NG or oral	EN with probiotics tablets (210mg/per tablet) combining *Bifidobacterium longum, Lactobacillus bulgaricus, and Enterococcus faecalis* ≥1.0 x 10^7 CFU. Given 6 tablets, 2X/day for 15 days	EN (standard).

C Random: concealed randomization
EN: enteral nutrition
NJ: nasojejunal
NG: nasogastric
OG: orogastric
FOS: fructooligosaccharides
CFU: Colony forming units
NR: not reported

Trevis™: 1 capsule= *Lactobacillus acidophilus La5, Bifidobacterium lactis Bb12, Streptococcus thermophilus, Lactobacillus bulgaricus, 4 x 10^9/total*

Synbiotic 2000 Forte: 10^{11} CFU of each: *Pediococcus pentoseceus 5-33:3, Leuconostoc mesenteroides 32-77:1, L. paracasei ssp paracasei 19, L. plantarum* 2362 & 2.5 g each of: inulin, oat bran, pectin and resistant starch

Ergyphilus: 10^{10} *Lactobaccilus rhamnosus GG, Lactobacillus casei, Lactobacillus acidophilus, Bifidobacterium bifidus,*

VSL # 3: > 10^{10} *Bifidobacterium longum, Bifidobacterium breve, >$10^{10/g}$ Bifidobacterium infantis, >$10^{11/g}$ Lactobacillus acidophulus, plantarum, casei, bulgaris & Streptococcus thermophilus*

Jinshuangqi: *Bifidobacterium longum > $10^{7\ CFU}$, Lactobacillus bulgaricus > $10^{6\ CFU}$ & Streptococcus Thermophilus > $10^{6\ CFU}$*

Ecologic 641: *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum & Bifidobacterium lactis (each has 10^{10} bacteria)*

Synbiotic 2000: *10^{10} CFU of each: Pediococcus pentoseceus 5-33:3, Leuconostoc mesenteroides 32-77:1, L. paracasei ssp paracasei 19, L. plantarum 2362 &* 2.5 g each of: betaglucan, inulin, pectin and resistant starch

Golden Bifid: *Bifidobacterium bifidum, Lactobacillus bulgaricus and Streptococcus thermophilus triple human probiotics supplemented oligosaccharides FOS (bifidus factor)*

Table 1. Randomized studies evaluating Probiotics in critically ill patients (continued)

	Study	Mortality		Infections		Length of Stay		Diarrhea	
		Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
1	Tempe 1983	3/20 (15)	3/20 (15)	NR	NR	NR	NR	**Diarrhea days** 34/389 (9)	**Diarrhea days** 63/373 (17)
2	Schlotterer 1987	NR	NR	NR	NR	NR	NR	**Diarrhea days** 3/150 (2)	**Diarrhea days** 19/143 (13)
3	Heimburger 1994	NR	NR	NR	NR	NR	NR	**Diarrhea** 5/16 (31)	**Diarrhea** 2/18 (11)
4	Bleichner 1997	NR	NR	NR	NR	NR	NR	**Diarrhea** 18/64 (28)[i] **Days w/ diarrhea** 91/648 (14)	**Diarrhea** 24/64 (38) **Days w/ diarrhea** 134/683 (20)
5	Kecskes 2003	**Hospital** 1/22 (5)	**Hospital** 2/23 (9)	**Septic Complications** 1/22 (5)	**Septic Complications** 7/23 (30)	**Hospital** 13.7 ± 8.7	**Hospital** 21.4 ± 17.9	NR	NR
6	Jain 2004	**Hospital** 22/45 (49)	**Hospital** 20/45 (45)	**Septic Complications** 33/45 (73)	**Septic Complications** 26/45 (58)	**Hospital** 24.0 ± 31.5 **ICU** 11.9 ± 13.1	**Hospital** 18.7 ± 13.5 **ICU** 9.0 ± 8.9	NR	NR
7	Lu 2004	**Hospital** 2/20 (10)	**Hospital** 1/20 (5)	**Infectious Complications** 8/20 (40)	**Infectious Complications** 11/20 (55)	NR	NR	NR	NR
8	Klarin 2005	**Hospital** 2/8 (25) **ICU** 1/8 (12)	**Hospital** 2/7 (29) **ICU** 2/7 (29)	NR	NR	**Hospital** 48.3 ± 30.4 **ICU** 14.2 ± 10.6	**Hospital** 34.3 ± 15.4 **ICU** 16.3 ± 15.7	NR	NR

9	**McNaught 2005**	18/52 (35)	18/51 (35)	**Septic morbidity** 21/52 (40)	**Septic morbidity** 22/51 (43)	**ICU** 5 (2-9)	**ICU** 4 (2-7)	NR	NR
10	**Kotzampassi 2006**	**ICU** 5/35 (14)	**ICU** 9/30 (30)	**Infections** 22/35 (63) **VAP** 19/35 (54) **Septic Complications** 17/35 (49) **Central venous line infections** 13/35 (37) **Wound Infections** 6/35 (17) **UTI** 6/35 (17)	**Infections** 27/30 (90) **VAP** 24/30 (80) **Septic Complications** 23/30 (77) **Central venous line infections** 20/30 (66) **Wound Infections** 8/30 (26) **UTI** 13/30 (43)	**ICU** 27.7 ± 15.2	**ICU** 41.3 ± 20.5	**Diarrhea** 5/35 (14)	**Diarrhea** 10/30 (30)
11	**Alberda 2007**	**ICU** 1/10 (10)	**ICU** 1/9 (11)	NR	NR	NR	NR	**Diarrhea** 1/10 (14)	**Diarrhea** 2/9 (23)
12	**Li 2007**	NR	NR	**Infections** 8/14 (58)	**Infections** 10/11 (91)	**Hospital** 42 ± 5.0	**Hospital** 49 ± 6.8	NR	NR
13	**Olah 2007**	**Hospital** 2/33 (6)	**Hospital** 6/29 (21)	**Infections** 9/33 (27) **Septic Complications** 7/33 (12) **Pancreatic Abscess** 2/33 (6) **Infected Pancreatic Necrosis** 2/33 (6) **UTI** 3/33 (9)	**Infections** 15/29 (52) **Septic Complications** 17/29 (28) **Pancreatic Abscess** 2/29 (7) **Infected Pancreatic Necrosis** 6/29 (21) **UTI** 3/33 (9)	**Hospital** 14.9 ± 3.3	**Hospital** 19.7 ± 4.5	NR	NR

14	**Forestier 2008**	NR	NR	**VAP** 19/102 (19)	**VAP** 21/106 (20)	**ICU** 22.5 ± 20.6	**ICU** 19.7 ± 16.7	NR	NR
15	**Besselink 2008**	24/152 (16)	9/144 (6)	**Infections** 46/152 (30) **VAP** 24/152 (16) **Bacteremia** 33/152 (22) **Infected necrosis** 21/152 (14) **Urosepsis** 1/52 (2)	**Infections** 41/144 (28) **VAP** 16/144 (11) **Bacteremia** 22/144 (15) **Infected necrosis** 14/144 (10) **Urosepsis** 2/144 (1)	**Hospital** 28.9 ± 41.5 **ICU** 6.6 ± 17	**Hospital** 23.5 ± 25.9 **ICU** 3.0 ± 9.3	**Diarrhea** 25/152 (16)	**Diarrhea** 28/144 (19)
16	**Klarin 2008**	**Hospital** 3/22 (5) **ICU** 2/22 (9)	**Hospital** 2/22 (0) **ICU** 2/22 (9)	**c. difficile+ fecal samples** 0/71	**c. difficile+ fecal samples** 4/80	**Hospital** 25.8 ± 19.4 **ICU** 8.0 ± 5.4	**Hospital** 50.3 ± 75.2 **ICU** 11.6 ± 14	NR	NR
17	**Knight 2009**	**Hospital** 35/130 (27) **ICU** 28/130 (22)	**Hospital** 42/129 (33) **ICU** 34/129 (26)	**VAP** 12/130 (9)	**VAP** 17/129 (13)	**ICU** 6 (3-11)	**ICU** 7 (3-14)	**Diarrhea** 7/130 (5)	**Diarrhea** 9/129 (7)
18	**Barraud 2010**	**ICU** 21/87 (24) **28 days** 22/87 (25) **90 days** 27/87 (31)	**ICU** 21/80 (26) **28 days** 19/80 (24) **90 days** 24/80 (30)	**All infections** 30/87 (34) **Infection > 96 hr** 26/87 (30) **VAP** 23/87 (26) **Catheter related BSI** 3/87 (4) **UTI** 4/87 (5)	**All infections** 30/80 (38) **Infection > 96 hr** 29/80 (36) **VAP** 15/80 (19) **Catheter related BSI** 11/80 (14) **UTI** 4/89 (5)	**Hospital** 26.6 ± 22.3 **ICU** 18.7 ± 12.4	**Hospital** 28.9 ± 26.4 **ICU** 20.2 ± 20.8	**Diarrhea** 48/87 (55)	**Diarrhea** 42/80 (53)

19	**Morrow 2010**	12/68 (18)	15/70 (21)	**VAP** 13/73 (18)	**VAP** 28/73 (38)	**Hospital** 21.4 ± 14.9 (68) **ICU** 14.8 ± 11.8 (68)	**Hospital** 21.7 ± 17.4 (70) **ICU** 14.6 ± 11.6 (70)	**Non C. Difficile Diarrhea** 42/68 (62) **C. difficile diarrhea** 4/68 (6)	**Non C. Difficile Diarrhea** 44/70 (63) **C. difficile diarrhea** 13/70 (19)
20	**Frohmader 2010**	5/20 (25)	3/25 (12)	NR	NR	**ICU** 7.3 ± 5.7	**ICU** 8.1 ± 4	**Diarrhea episodes/pt/day** 0.53 ± 0.54	**Diarrhea episodes/pt/day** 1.05 ± 1.08
21	**Ferrie 2011**	**Hospital** 2/18 (11) **6 months** 7/18 (39)	**Hospital** 2/18 (11) **6 months** 5/18 (28)	**Infections** 14/18 (78)	**Infections** 16/18 (89)	**Hospital** 54.50 ± 31.26 **ICU** 32.04 ± 24.46	**Hospital** 59.04 ± 33.92 **ICU** 29.75 ± 18.81	**Duration of Diarrhea** 3.83 ± 2.39 **Loose stools/day** 1.58 ± 0.88	**Duration of Diarrhea** 2.56 ± 1.85 **Loose stools/day** 1.10 ± 0.79
22	**Sharma 2011**	**Hospital** 2/24 (8)	**Hospital** 2/26 (8)	NR	NR	**Hospital** 13.23 ± 18.19 **ICU** 4.94 ± 9.54	**Hospital** 9.69 ±9.69 **ICU** 4.0 ± 5.86	NR	NR
23	**Tan 2011**	**28 day** 3/26 (12)	**28 day** 5/26 (19)	**Infections** 9/26 (35) **VAP** 7/26 (27)	**Infections** 15/26 (58) **VAP** 13/26 (50)	**ICU** 6.8 ± 3.8 (26)	**ICU** 10.7 ± 7.3 (26)	NR	NR
24	**Cui 2013**	**Hospital** 1/23 (4)	**Hospital** 1/25 (4)	**N/A**	N/A	**Hospital** 10.4 ± 3.9 (23)	**Hospital** 13.4 ± 5.2 (25)	NR	NR
25	**Wang 2013**	1/62 (8.1)	3/61 (9.8**)**	**Pancreatic sepsis** 8/62 (13) **MODS** 7/62 (11.3)	**Pancreatic sepsis** 13/61 (21) **MODS** 15/61 (25)	NR	NR	NR	NR

26	**Lopez de Toro 2014**	**Hospital** 19/46 (41) **ICU** 15/46 (33)	**Hospital** 18/43 (42) **ICU** 14/43 (33)	**Hospital acquired infections** 9/46 (20)	**Hospital acquired infections** 13/43 (30)	**Hospital** 18.5 (10-36) **ICU** 9 (3-19)	**Hospital** 24.5 (10-38) **ICU** 8 (2.5-16.5)	NR	NR
27	**Sanaie 2014**	**28 day** 2/20 (10)	**28 day** 5/20 (25)	**Bacteremia** 2/20(10)	**Bacteremia** 5/20(25)	**ICU** 13.85 ± 6.96	**ICU** 14.16 ± 5.97	NR	NR
28	**Rongungruang 2015**	**28 day** 18/75 (24) **90 day** 25/75 (33)	**28 day** 17/75 (23) **90 day** 26/75 (35)	**VAP** 18/75 (24)	**VAP** 22/75 (29)	**ICU** 30.5 (4-98) **Hospital** 20 (2-106)	**ICU** 19 (5-30) **Hospital** 19 (3-171)	**Diarrhea** 19/75 (25)	**Diarrhea** 14/75 (19)
30	**Zeng 2016**	**Hospital** 26/118 (22.0) **ICU** 15/118 (13)	**Hospital** 25/117 (21.4) **ICU** 9/117 (8)	**Clinically diagnosed VAP** 48/118 (41) **Micro confirmed VAP** 43/118 (36)	**Clinically diagnosed VAP** 62/117 (53) **Micro confirmed VAP** 59/117 (50)	**ICU** 18 [IQR 14-32] **Hospital** 13.5 ± 12.4	**ICU** 22 [IQR 11-56] **Hospital** 10.6 ± 10.2	NR	NR
31	**Malik 2016**	NR	NR	NR	NR	**ICU** 10.9 ± 3.9 (24)	**ICU** 15.8 ± 7.8 (25)	NR	NR
32	**De Castro Soares 2017**	NR	NR	NR	NR	NR	NR	**Days to cease Diarrhea** 2.5 ± 1.3	**Days to cease Diarrhea** 3.7 ± 1.1 P=0.011
33	**Shariatpanahi 2018**	**ICU** 3/16 (18.8)	**ICU** 4/16 (25)	NR	NR	**ICU** 5.5±1.2	**ICU** 7.3±1.3	**# patients with diarrhea** 1/16 (6.3)	**# patients with diarrhea** 3/16 (18.8)
34	**Wan 2020**	**1 month** 5/38 (13)	**1 month** 7/38 (18)	**Sepsis** 4/38 (11) **Pulmonary infection** 17/38 (45)	**Sepsis** 3/38 (8) **Pulmonary infection** 28/38 (74)	**ICU** 10.32±5.31	**ICU** 14.24±6.79	NR	NR

NR: Not Reported
VAP: Ventilator Associated Pneumonia
UTI: Urinary Tract Infection
ICU: Intensive Care Unit
BSI: Blood Stream Infection

Figure 1. Overall Mortality

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Tempe 1983	3	20	3	20	1.6%	1.00 [0.23, 4.37]	1983
Kecskes 2003	1	22	2	23	0.7%	0.52 [0.05, 5.36]	2003
Jain 2004	22	45	20	45	10.0%	1.10 [0.71, 1.71]	2004
Lu 2004	2	20	1	20	0.7%	2.00 [0.20, 20.33]	2004
Klarin 2005	2	8	2	7	1.3%	0.88 [0.16, 4.68]	2005
McNaught 2005	18	52	18	51	8.3%	0.98 [0.58, 1.66]	2005
Kotzampassi 2006	5	35	9	30	3.3%	0.48 [0.18, 1.27]	2006
Alberda 2007	1	10	1	9	0.5%	0.90 [0.07, 12.38]	2007
Olah 2007	2	33	6	29	1.5%	0.29 [0.06, 1.34]	2007
Besselink 2008	24	152	9	144	5.3%	2.53 [1.22, 5.25]	2008
Klarin 2008	3	22	2	22	1.3%	1.50 [0.28, 8.12]	2008
Knight 2009	35	130	42	129	11.7%	0.83 [0.57, 1.21]	2009
Frohmader 2010	5	20	3	25	2.0%	2.08 [0.56, 7.68]	2010
Morrow 2010	12	68	15	70	5.9%	0.82 [0.42, 1.63]	2010
Barraud 2010	21	87	19	80	8.0%	1.02 [0.59, 1.75]	2010
Sharma 2011	2	24	2	26	1.0%	1.08 [0.17, 7.10]	2011
Ferrie 2011	2	18	2	18	1.1%	1.00 [0.16, 6.35]	2011
Tan 2011	3	26	5	26	2.0%	0.60 [0.16, 2.26]	2011
Cui 2013	1	23	1	25	0.5%	1.09 [0.07, 16.39]	2013
Wang 2013	1	62	3	61	0.7%	0.33 [0.04, 3.07]	2013
Lopez de Toro 2014	19	46	18	20	11.8%	0.46 [0.32, 0.67]	2014
Sanaie 2014	2	20	5	20	1.5%	0.40 [0.09, 1.83]	2014
Rongrungruang 2015	18	75	17	75	7.3%	1.06 [0.59, 1.89]	2015
Zeng 2016	26	118	25	117	9.1%	1.03 [0.63, 1.68]	2016
Wan 2020	5	38	7	38	2.9%	0.71 [0.25, 2.05]	2020
Total (95% CI)		**1174**		**1130**	**100.0%**	**0.88 [0.73, 1.07]**	
Total events	235		237				

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 31.25$, df = 24 (P = 0.15); $I^2 = 23\%$
Test for overall effect: Z = 1.27 (P = 0.20)

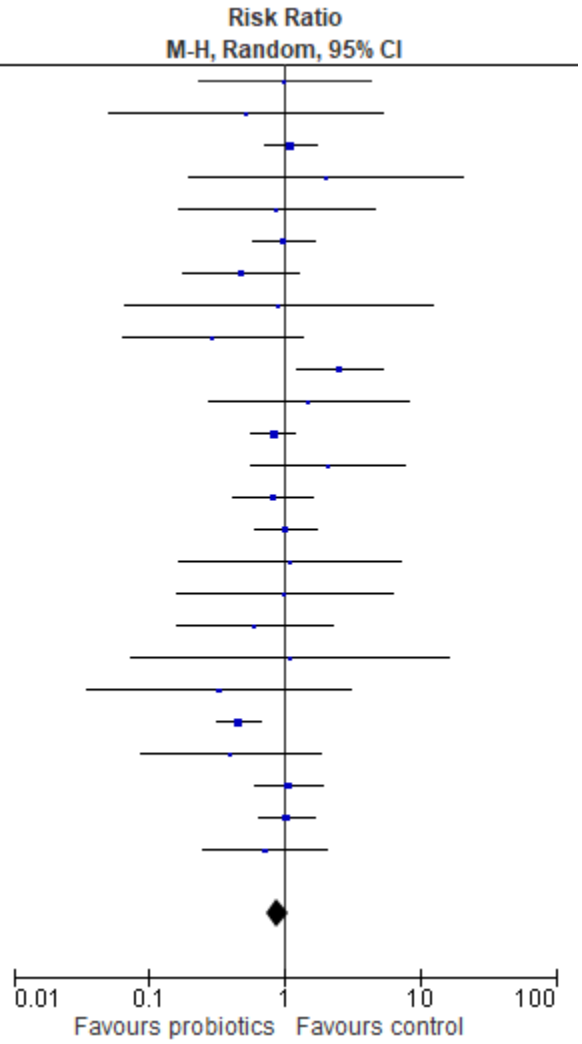


Figure 2. Hospital Mortality

Study or Subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Tempe 1983	3	20	3	20	1.5%	1.00 [0.23, 4.37]	1983
Kecskes 2003	1	22	2	23	0.6%	0.52 [0.05, 5.36]	2003
Jain 2004	22	45	20	45	16.2%	1.10 [0.71, 1.71]	2004
Lu 2004	2	20	1	20	0.6%	2.00 [0.20, 20.33]	2004
Klarin 2005	2	8	2	7	1.1%	0.88 [0.16, 4.68]	2005
McNaught 2005	18	52	18	51	11.4%	0.98 [0.58, 1.66]	2005
Olah 2007	2	33	6	29	1.4%	0.29 [0.06, 1.34]	2007
Besselink 2008	24	152	9	144	5.9%	2.53 [1.22, 5.25]	2008
Klarin 2008	3	22	2	22	1.1%	1.50 [0.28, 8.12]	2008
Knight 2009	35	130	42	129	22.3%	0.83 [0.57, 1.21]	2009
Frohmader 2010	5	20	3	25	1.9%	2.08 [0.56, 7.68]	2010
Morrow 2010	12	68	15	70	6.8%	0.82 [0.42, 1.63]	2010
Sharma 2011	2	24	2	26	0.9%	1.08 [0.17, 7.10]	2011
Ferrie 2011	2	18	2	18	0.9%	1.00 [0.16, 6.35]	2011
Cui 2013	1	23	1	25	0.4%	1.09 [0.07, 16.39]	2013
Wang 2013	1	62	3	61	0.6%	0.33 [0.04, 3.07]	2013
Lopez de Toro 2014	19	46	18	43	13.0%	0.99 [0.60, 1.61]	2014
Zeng 2016	26	118	25	117	13.4%	1.03 [0.63, 1.68]	2016
Total (95% CI)		**883**		**875**	**100.0%**	**1.01 [0.84, 1.21]**	
Total events	180		174				

Heterogeneity: Tau² = 0.00; Chi² = 13.24, df = 17 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)

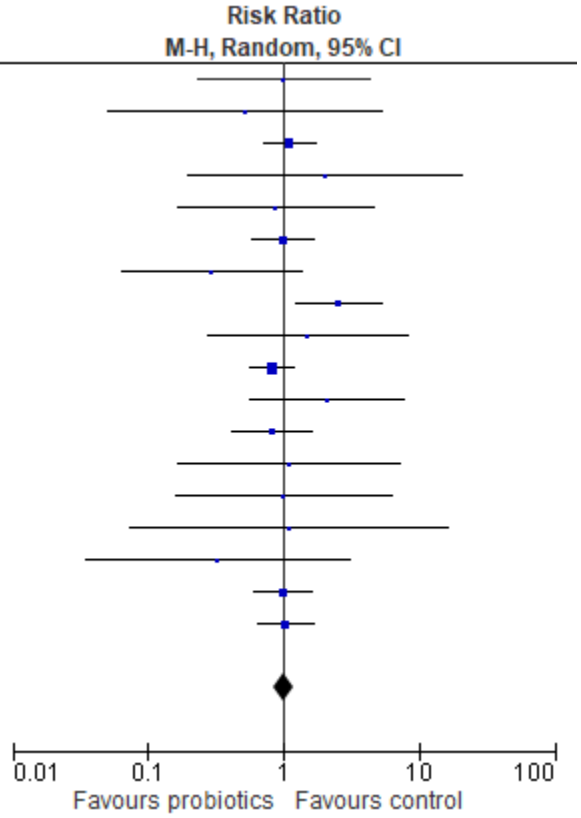


Figure 3. ICU Mortality

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Klarin 2005	1	8	2	7	1.4%	0.44 [0.05, 3.85]	2005
Kotzampassi 2006	5	35	9	30	7.0%	0.48 [0.18, 1.27]	2006
Alberda 2007	1	10	1	9	1.0%	0.90 [0.07, 12.38]	2007
Klarin 2008	2	22	2	22	1.9%	1.00 [0.15, 6.48]	2008
Knight 2009	28	130	34	129	34.9%	0.82 [0.53, 1.26]	2009
Barraud 2010	21	87	21	80	24.4%	0.92 [0.54, 1.55]	2010
Lopez de Toro 2014	15	46	14	43	18.6%	1.00 [0.55, 1.82]	2014
Zeng 2016	15	118	9	117	10.8%	1.65 [0.75, 3.63]	2016
Total (95% CI)		**456**		**437**	**100.0%**	**0.90 [0.70, 1.17]**	
Total events	88		92				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.68$, df = 7 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 0.77 (P = 0.44)

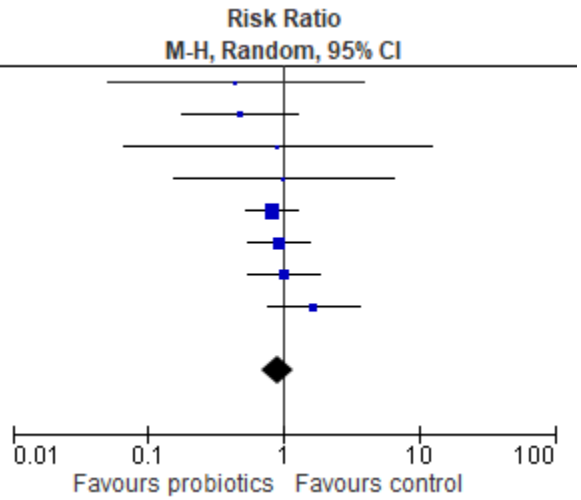


Figure 4. Overall Infections

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kecskes 2003	1	22	7	23	0.4%	0.15 [0.02, 1.12]	2003
Lu 2004	8	20	11	20	3.2%	0.73 [0.37, 1.42]	2004
Jain 2004	33	45	26	45	9.7%	1.27 [0.93, 1.72]	2004
McNaught 2005	21	52	22	51	5.8%	0.94 [0.59, 1.48]	2005
Kotzampassi 2006	22	35	27	30	10.6%	0.70 [0.53, 0.93]	2006
Li 2007	8	14	10	11	5.2%	0.63 [0.38, 1.03]	2007
Olah 2007	9	33	15	29	3.2%	0.53 [0.27, 1.02]	2007
Forestier 2008	19	102	21	106	4.3%	0.94 [0.54, 1.64]	2008
Besselink 2008	46	152	41	144	8.2%	1.06 [0.75, 1.51]	2008
Knight 2009	12	130	17	129	2.9%	0.70 [0.35, 1.41]	2009
Barraud 2010	30	87	30	80	6.9%	0.92 [0.61, 1.38]	2010
Morrow 2010	13	73	28	73	4.1%	0.46 [0.26, 0.82]	2010
Tan 2011	9	26	15	26	3.6%	0.60 [0.32, 1.12]	2011
Ferrie 2011	14	18	16	18	10.1%	0.88 [0.65, 1.18]	2011
Wang 2013	8	62	13	61	2.3%	0.61 [0.27, 1.36]	2013
Lopez de Toro 2014	9	46	13	43	2.6%	0.65 [0.31, 1.36]	2014
Sanaie 2014	2	20	5	20	0.7%	0.40 [0.09, 1.83]	2014
Rongrungruang 2015	18	75	22	75	4.6%	0.82 [0.48, 1.40]	2015
Zeng 2016	48	118	62	117	10.8%	0.77 [0.58, 1.01]	2016
Wan 2020	4	38	3	38	0.8%	1.33 [0.32, 5.56]	2020
Total (95% CI)		**1168**		**1139**	**100.0%**	**0.80 [0.70, 0.91]**	
Total events	334		404				

Heterogeneity: Tau² = 0.02; Chi² = 25.58, df = 19 (P = 0.14); I² = 26%
Test for overall effect: Z = 3.40 (P = 0.0007)

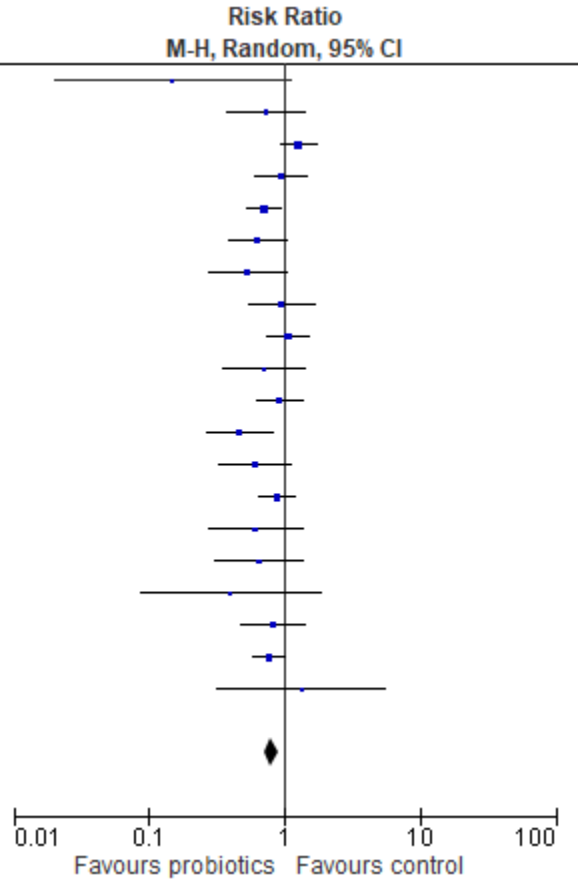


Figure 5. VAP

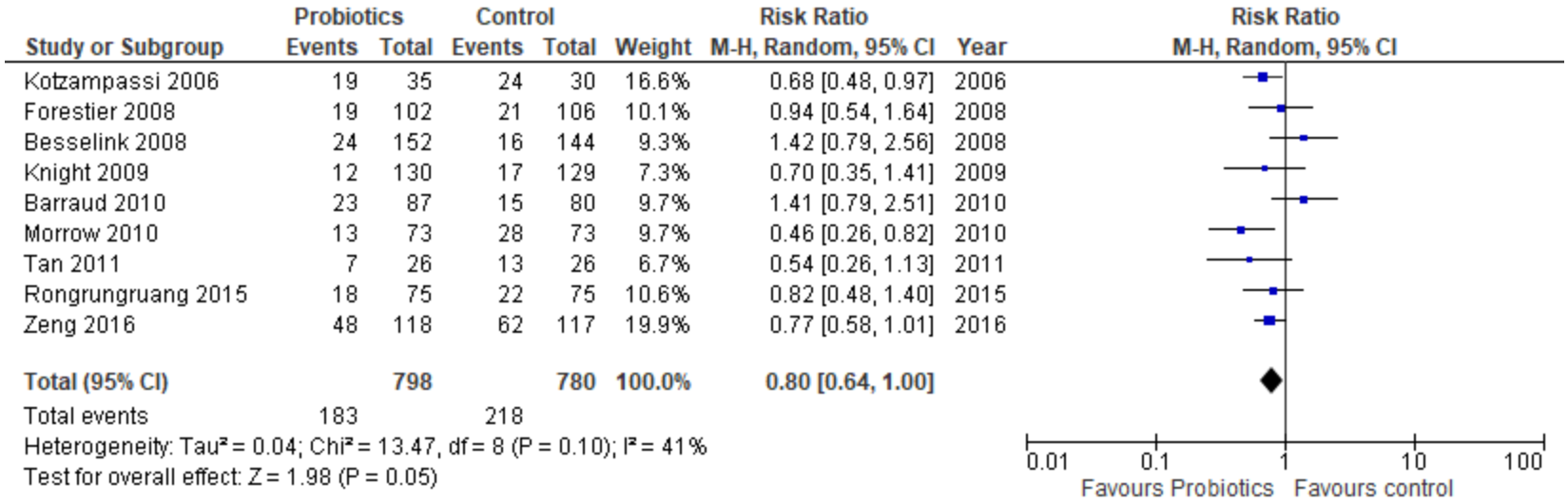
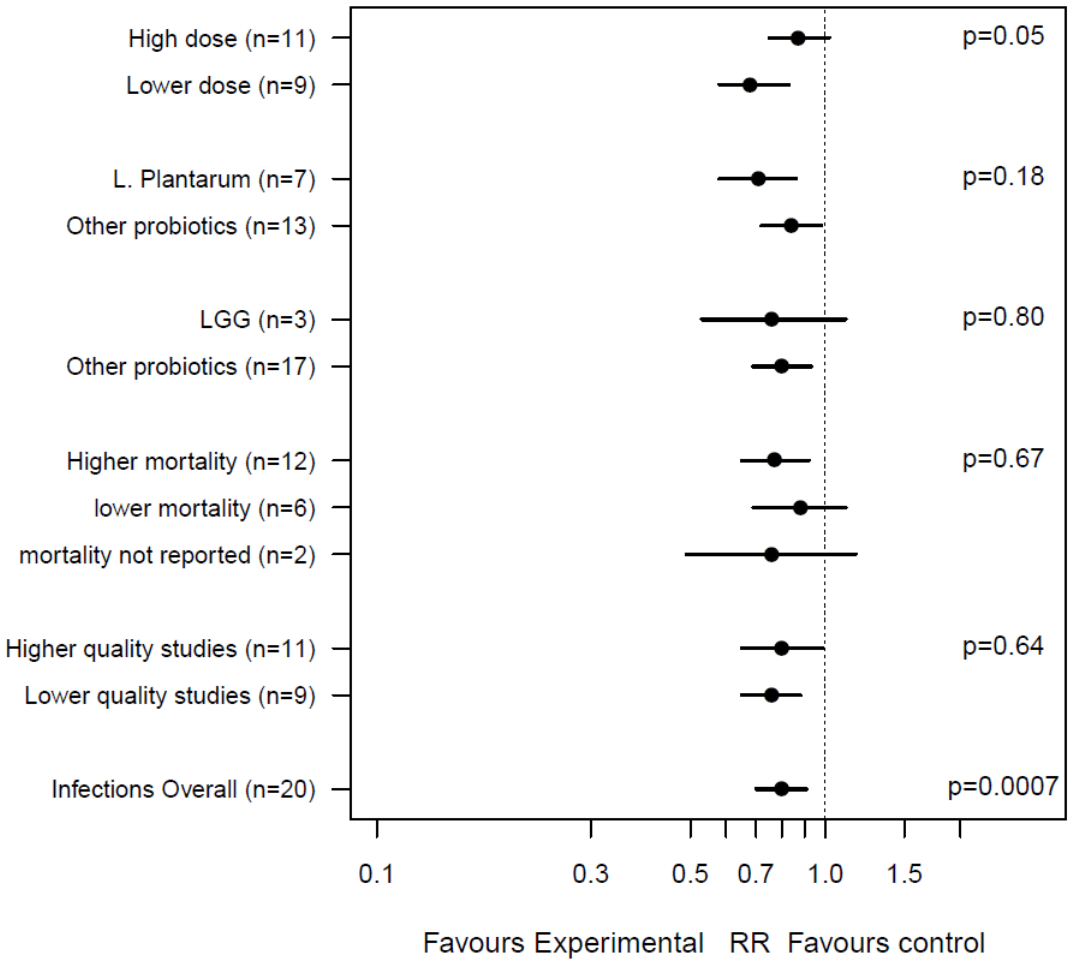

Probiotics
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
Year
M-H, Random, 95% CI
Kotzampassi 2006 19 35 24 30 16.6% 0.68 [0.48, 0.97] 2006
Forestier 2008 19 102 21 106 10.1% 0.94 [0.54, 1.64] 2008
Besselink 2008 24 152 16 144 9.3% 1.42 [0.79, 2.56] 2008
Knight 2009 12 130 17 129 7.3% 0.70 [0.35, 1.41] 2009
Barraud 2010 23 87 15 80 9.7% 1.41 [0.79, 2.51] 2010
Morrow 2010 13 73 28 73 9.7% 0.46 [0.26, 0.82] 2010
Tan 2011 7 26 13 26 6.7% 0.54 [0.26, 1.13] 2011
Rongrungruang 2015 18 75 22 75 10.6% 0.82 [0.48, 1.40] 2015
Zeng 2016 48 118 62 117 19.9% 0.77 [0.58, 1.01] 2016
Total (95% CI) 798 780 100.0% 0.80 [0.64, 1.00]
Total events 183 218
Heterogeneity: Tau² = 0.04; Chi² = 13.47, df = 8 (P = 0.10); I² = 41%
Test for overall effect: Z = 1.98 (P = 0.05)
0.01
0.1
1
10
100
Favours Probiotics
Favours control

Figure 6. Effect of Probiotics on Infections: Subgroup Analyses



Legend: Numbers in brackets indicate the number of studies.
RR: Risk ratio
p values for the subgroups indicate the differences in the subgroup effect of probiotics on infections.
LGG= *Lactobacillus rhamnosus* GG

Figure 7. Hospital Length of Stay

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kecskes 2003	13.7	8.7	22	21.4	17.9	23	6.8%	-7.70 [-15.87, 0.47]	2003
Jain 2004	24	31.5	45	18.7	13.5	45	5.4%	5.30 [-4.71, 15.31]	2004
Klarin 2005	48.3	30.4	52	34.3	15.4	51	5.9%	14.00 [4.72, 23.28]	2005
Olah 2007	14.9	3.3	33	19.7	4.5	29	13.1%	-4.80 [-6.79, -2.81]	2007
Li 2007	42	5	14	49	6.8	11	10.3%	-7.00 [-11.80, -2.20]	2007
Besselink 2008	28.9	41.5	152	23.5	25.9	144	7.1%	5.40 [-2.44, 13.24]	2008
Klarin 2008	25.8	19.4	22	50.3	75.2	22	0.8%	-24.50 [-56.95, 7.95]	2008
Barraud 2010	26.6	22.3	87	28.9	26.4	80	7.5%	-2.30 [-9.74, 5.14]	2010
Morrow 2010	21.4	14.9	68	21.7	17.4	70	9.6%	-0.30 [-5.70, 5.10]	2010
Ferrie 2011	54.5	31.26	18	59.04	33.92	18	1.7%	-4.54 [-25.85, 16.77]	2011
Sharma 2011	13.23	18.19	24	9.69	9.69	26	6.8%	3.54 [-4.64, 11.72]	2011
Cui 2013	10.4	3.9	23	13.4	5.2	25	12.6%	-3.00 [-5.59, -0.41]	2013
Zeng 2016	13.5	12.4	118	10.6	10.2	117	12.3%	2.90 [-0.00, 5.80]	2016
Total (95% CI)			**678**			**661**	**100.0%**	**-0.63 [-3.61, 2.36]**	

Heterogeneity: $Tau^2 = 16.56$; $Chi^2 = 46.08$, df = 12 ($P < 0.00001$); $I^2 = 74\%$

Test for overall effect: $Z = 0.41$ ($P = 0.68$)

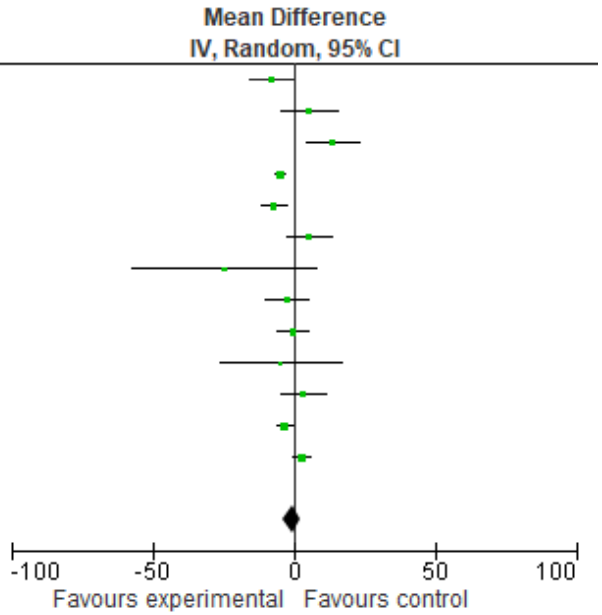


Figure 8. ICU LOS

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Jain 2004	11.9	13.1	45	9	8.9	45	7.1%	2.90 [-1.73, 7.53]	2004
Klarin 2005	14.2	10.6	8	16.3	15.7	7	4.1%	-2.10 [-15.86, 11.66]	2005
Kotzampassi 2006	27.7	15.2	35	41.3	20.5	30	5.7%	-13.60 [-22.50, -4.70]	2006
Besselink 2008	6.6	17.1	152	30	9.3	144	7.4%	-23.40 [-26.51, -20.29]	2008
Klarin 2008	8	5.4	22	11.6	14	22	6.6%	-3.60 [-9.87, 2.67]	2008
Forestier 2008	22.5	20.6	102	19.7	16.7	106	6.9%	2.80 [-2.31, 7.91]	2008
Frohmader 2010	7.3	5.7	20	8.1	4	25	7.5%	-0.80 [-3.75, 2.15]	2010
Barraud 2010	18.7	12.4	87	20.2	20.8	80	6.9%	-1.50 [-6.75, 3.75]	2010
Morrow 2010	14.8	11.8	68	14.6	11.6	70	7.2%	0.20 [-3.71, 4.11]	2010
Ferrie 2011	32.04	24.46	18	29.75	18.81	18	4.0%	2.29 [-11.96, 16.54]	2011
Tan 2011	6.8	3.8	26	10.7	7.3	26	7.4%	-3.90 [-7.06, -0.74]	2011
Sharma 2011	4.94	9.54	24	4	5.86	26	7.1%	0.94 [-3.49, 5.37]	2011
Sanaie 2014	13.85	6.96	20	14.16	5.97	20	7.2%	-0.31 [-4.33, 3.71]	2014
Malik 2016	10.9	3.9	24	15.8	7.8	25	7.4%	-4.90 [-8.33, -1.47]	2016
Wan 2020	10.32	5.31	38	14.24	6.79	38	7.5%	-3.92 [-6.66, -1.18]	2020
Total (95% CI)			**689**			**682**	**100.0%**	**-3.39 [-7.49, 0.71]**	

Heterogeneity: Tau² = 56.51; Chi² = 187.40, df = 14 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.62 (P = 0.11)

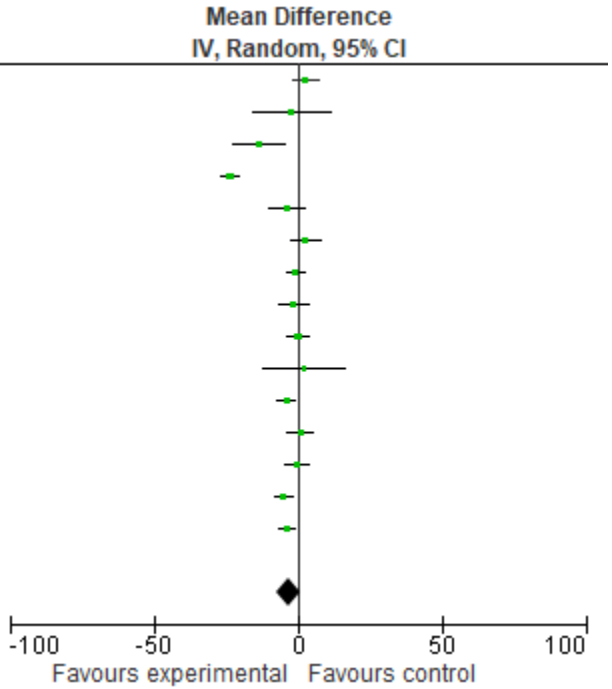
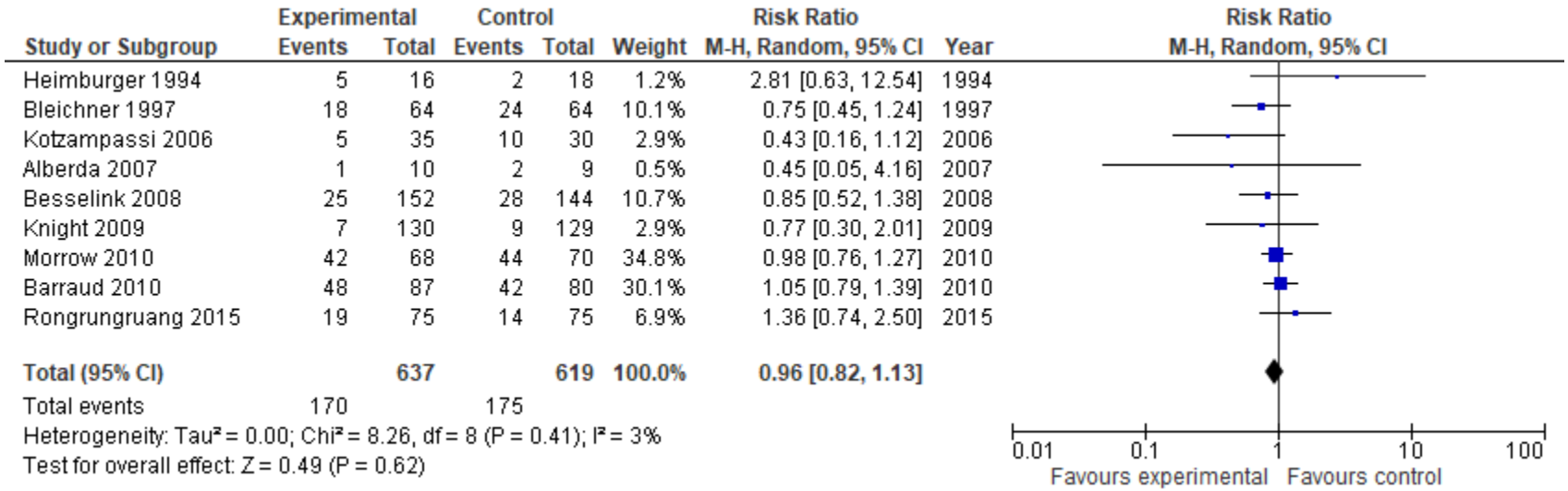


Figure 9. Diarrhea



Included Studies

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No	Reason	Citation
1.	Not EN fed patients	de Felippe Júnior J, da Rocha e Silva Júnior M, Maciel FM, Soares Ade M, Mendes NF. Infection prevention in patients with severe multiple trauma with the immunomodulator beta 1-3 polyglucose (glucan). Surg Gynecol Obstet. 1993 Oct;177(4):383-8.
2.	Not ICU pts	Niedzielin K, Kordecki H, Birkenfeld B. A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum 299V in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol. 2001 Oct;13(10):1143-7.
3.	Elective surgery pts	McNaught CE, Woodcock NP, MacFie J, Mitchell CJ. A prospective randomised study of the probiotic Lactobacillus plantarum 299V on indices of gut barrier function in elective surgical patients. Gut. 2002 Dec;51(6):827-31.
4.	Elective surgery pts	Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut. 2002 Sep;51(3):405-9.
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6.	Liver transplant pts	Rayes N, Seehofer D, Hansen S, Boucsein K, Müller AR, Serke S, Bengmark S, Neuhaus P. Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. Transplantation. 2002 Jul 15;74(1):123-7.
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11.	Elective surgery pts; No clinical outcomes	Woodcock NP, McNaught CE, Morgan DR, Gregg KL, MacFie J. An investigation into the effect of a probiotic on gut immune function in surgical patients. Clin Nutr. 2004 Oct;23(5):1069-73.
12.	Systematic review, Not ICU pts	Dendukuri N, Costa V, McGregor M, Brophy JM. Probiotic therapy for the prevention and treatment of Clostridium difficile-associated diarrhea: a systematic review. CMAJ. 2005 Jul 19;173(2):167-70.
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14.	Duplicate of Olah 2007	Oláh A, Belágyi T, Issekutz A, Olgyai G. [Combination of early nasojejunal feeding with modern synbiotic therapy in the treatment of severe acute pancreatitis (prospective, randomized, double-blind study)] [Article in Hungarian]. Magy Seb. 2005 Jun;58(3):173-8.
15.	Not critically ill	Olguin F, Araya M, Hirsch S, Brunser O, Ayala V, Rivera R, Gotteland M. Prebiotic ingestion does not improve gastrointestinal barrier function in burn patients. Burns. 2005 Jun;31(4):482-8. Epub 2005 Feb 16.
16.	Transplant pts	Rayes N, Seehofer D, Theruvath T, Schiller RA, Langrehr JM, Jonas S, Bengmark S, Neuhaus P. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation--a randomized, double-blind trial. Am J Transplant. 2005 Jan;5(1):125-30.

17.	Abstract only. Contacted authors, unable to retrieve data	Voudouris A, Kazamias P, Spyridaki E, Antonopoulou A, Giamarellos-Bourboulis E, Skourtis C, Kotzampassi K. Benefits of symbiotic 2000 forte in critically ill patients: a randomized controlled trial. Critical Care. 2005 March9(S1):S152
18.	Abstract only, unable to get data from authors	Dadak L, Stouracova M, Kuklinek P, Stetka P, Sramek V. Impact of synbiotics (Synbiotic 2000 Forte) on monocyte function in long-term ICU patients. Critical Care. 2006; 10(Suppl): P212
19.	Abstract only, unable to get data from authors	Gommersall et al. Does routine administration of probiotics improve outcome of critically ill patients? ANZCA 2006
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21.	Elective surgery pts	Sugawara G, Nagino M, Nishio H, Ebata T, Takagi K, Asahara T, Nomoto K, Nimura Y. Perioperative synbiotic treatment to prevent postoperative infectious complications in biliary cancer surgery: a randomized controlled trial. Ann Surg. 2006 Nov;244(5):706-14.
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23.	Not ICU pts	Hickson M, D'Souza AL, Muthu N, Rogers TR, Want S, Rajkumar C, Bulpitt CJ. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. BMJ. 2007 Jul 14;335(7610):80. Epub 2007 Jun 29.
24.	Prebiotics only	Karakan T, Ergun M, Dogan I, Cindoruk M, Unal S. Comparison of early enteral nutrition in severe acute pancreatitis with prebiotic fiber supplementation versus standard enteral solution: a prospective randomized double-blind study. World J Gastroenterol 2007;13(19):2733-7.
25.	Elective surgery patients	Nomura T, Tsuchiya Y, Nashimoto A, Yabusaki H, Takii Y, Nakagawa S, Sato N, Kanbayashi C, Tanaka O. Probiotics reduce infectious complications after pancreaticoduodenectomy. Hepatogastroenterology. 2007 Apr-May;54(75):661-3.
26.	Elective surgery pts	Rayes N, Seehofer D, Theruvath T, Mogl M, Langrehr JM, Nüssler NC, Bengmark S, Neuhaus P. Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: a randomized, double-blind trial. Ann Surg. 2007 Jul;246(1):36-41.
27.	Not ICU pts	Qin HL, Zheng JJ, Tong DN, Chen WX, Fan XB, Hang XM, Jiang YQ. Effect of Lactobacillus plantarum enteral feeding on the gut permeability and septic complications in the patients with acute pancreatitis. Eur J Clin Nutr. 2008 Jul;62(7):923-30. Epub 2007 Jun 20.
28.	Elective surgery pts, too many interventions	Reddy BS, Macfie J, Gatt M, Larsen CN, Jensen SS, Leser TD. Randomized clinical trial of effect of synbiotics, neomycin and mechanical bowel preparation on intestinal barrier function in patients undergoing colectomy. Br J Surg. 2007 May;94(5):546-54.
29.	Too many interventions [synbiotics, prebiotics, glutamine & peptide]	Spindler-Vesel A, Bengmark S, Vovk I, Cerovic O, Kompan L. Synbiotics, prebiotics, glutamine, or peptide in early enteral nutrition: a randomized study in trauma patients. JPEN J Parenter Enteral Nutr. 2007 Mar-Apr;31(2):119-26.

30.	Systematic review, Individual studies reviewed	Watkinson PJ, Barber VS, Dark P, Young JD. The use of pre- pro- and synbiotics in adult intensive care unit patients: systematic review. Clin Nutr. 2007 Apr;26(2):182-92.
31.	Duplicate of Besselink Lancet 2008	Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG; Acute Pancreatitis Werkgroep Nederland. [Probiotic prophylaxis in patients with predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial][Article in Dutch] Ned Tijdschr Geneeskd. 2008 Mar 22;152(12):685-96.
32.	Probiotics given as an oral swab, not ingested	Klarin B, Molin G, Jeppsson B, Larsson A. Use of the probiotic Lactobacillus plantarum 299 to reduce pathogenic bacteria in the oropharynx of intubated patients: a randomised controlled open pilot study. Crit Care. 2008 Nov 6;12(6):R136.
33.	Repeat data of Kotzampassi 2006	Giamarellos-Bourboulis EJ, Bengmark S, Kanellakopoulou K, Kotzampassi K. Pro- and synbiotics to control inflammation and infection in patients with multiple injuries. J Trauma. 2009 Oct;67(4):815-21.
34.	Systematic review, Individual studies reviewed	Koretz RL. Probiotics, critical illness, and methodologic bias. Nutr Clin Pract. 2009 Feb-Mar;24(1):45-9.
35.	Meta analysis, Individual studies reviewed	Sun S, Yang K, He X, Tian J, Ma B, Jiang L. Probiotics in patients with severe acute pancreatitis: a meta-analysis. Langenbecks Arch Surg. 2009 Jan;394(1):171-7. Epub 2008 Jul 17.
36.	Do not appear to have collected any clinical outcomes	Koutelidakis IM, Bezirtzoglou E, Giamarellos-Bourboulis EJ, Grosomanidis V, Kotzampassi K. Impact of synbiotics on the intestinal flora of critically ill patients with multiple injuries. Int J Antimicrob Agents. 2010 Jul;36(1):90-1.
37.	Meta-analysis, Individual studies reviewed	Siempos II, Ntaidou TK, Falagas ME. Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. Crit Care Med. 2010 Mar;38(3):954-62.
38.	Meta-analysis, Individual studies reviewed	Gu WJ, Wei CY, Yin RX. Lack of Efficacy of Probiotics in Preventing Ventilator-Associated Pneumonia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Chest 2012;142(4):859-868.
39.	Meta-analysis, Individual studies reviewed	Gu WJ, Deng T, Gong YZ, Jing R, Liu JC. The Effects of Probiotics in Early Enteral Nutrition on the Outcomes of Trauma: A Meta-Analysis of Randomized Controlled Trials. JPEN 2012.
40.	Systematic Review of patients on antibiotics, not ICU patients	Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B, Shekelle PG. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA. 2012 May 9;307(18):1959-69.
41.	meta-analyses, ICU studies are included	Liu KX, Zhu YG, Zhang J, Tao LL, Lee JW, Wang XD, et al. Probiotics' effects on the incidence of nosocomial pneumonia in critically ill patients: a systematic review and meta-analysis. Crit Care 2012;16(3):R109.
42.	meta-analyses, ICU studies are included	Petrof EO, Dhaliwal R, Manzanares W, Johnstone J, Cook C, Heyland DK. Probiotics in the critically ill: A systematic review of the randomized trial evidence. Crit Care Med 2012; 40(12).
43.	not ICU patients, only 15% ventilated	Plaudis H, Pupelis G, Zeiza K, Boka V. Early low volume oral synbiotic/prebiotic supplemented enteral stimulation of the gut in patients with severe acute pancreatitis: a prospective feasibility study. Acta Chir Belg. 2012 Mar-Apr;112(2):131-8.

44.	Elective surgery pts	Rayes N, Pilarski T, Stockmann M, Bengmark S, Neuhaus P, Seehofer D. Effect of pre- and probiotics on liver regeneration after resection: a randomised, double-blind pilot study. Benef Microbes. 2012 Sep;3(3):237-44. doi: 10.3920/BM2012.0006. PubMed PMID: 22968413.
45.	Meta analysis, Individual studies reviewed	Barraud D, Bollaert PE, Gibot S. Impact of the Administration of Probiotics on Mortality in Critically Ill Adult Patients: A Meta-analysis of Randomized Controlled Trials. Chest. 2013 Mar 1;143(3):646-55. doi: 10.1378/chest.12-1745.
46.	Meta-analyses, individual RCTs were reviewed	Gu WJ, Deng T, Gong YZ, Jing R, Liu JC. The effects of probiotics in early enteral nutrition on the outcomes of trauma: a meta-analysis of randomized controlled trials. JPEN J Parenter Enteral Nutr. 2013 May-Jun;37(3):310-7.
47.	No clinical outcomes, analysis of Sanaie 2014	Ebrahimi-Mameghani M, Sanaie S, Mahmoodpoor A, Hamishehkar H. Effect of a probiotic preparation (VSL#3) in critically ill patients: A randomized, double-blind, placebo-controlled trial (Pilot Study). Pak J Med Sci. 2013 Apr;29(2):490-4.
48.	No clinical outcomes, analysis of Sanaie 2014	Sanaie S, Ebrahimi-Mameghani M, Mahmoodpoor A, Shadvar K, Golzari SE. Effect of a Probiotic Preparation (VSL#3) on CardiovascularRisk Parameters in Critically-Ill Patients. J Cardiovasc Thorac Res. 2013;5(2):67-70.
49.	Same patient population as Tan 2011	Tan M, Lu X, Duan J et al. [Effects of probiotics on blood glucose levels and clinical outcomes in patients with severe cranocerebral trauma]. Chin Crit Care Med. 2013; 25(10): 627-630.
50.	Not RCT	Tahir SM, Makhdoom A, Awan S, Ali SA. Role of Probiotics in the Management of Burns Patients. World Journal of Medical Sciences. 2014;11(3):417-21.