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Eleni Pitsouni, Vangelis Alexiou, Vasilis Saridakis, George Peppas, Matthew E. Falagas

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PHARMACODYNAMICS

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Abstract
Background Advances in surgery have considerably lowered postoperative morbidity. However, infection remains a considerable morbidity factor. The aim of this review is to identify the potential benefit(s) of the perioperative administration of probiotics/synbiotics to patients undergoing abdominal surgery.
Methods We searched PubMed, Scopus, Web of Science, and Cochrane library to identify randomized controlled trials (RCTs) that studied the perioperative administration of probiotics/synbiotics to patients undergoing abdominal surgery.
Results Nine RCTs studying 733 patients were included in our review. The incidence of postoperative pneumonia, cholangitis, and any infections as well as the duration of postoperative hospital stay and length of antibiotic therapy were lower among patients receiving probiotics than in the control group [six RCTs, 355 patients, odds ratio (OR) 0.24, 95% confidence interval (CI) 0.09–0.68; three RCTs, 209 patients, OR 0.18, 95% CI 0.05–0.57; seven RCTs, 514 patients, OR 0.26, 95% CI 0.12–0.55; five RCTs, 313 patients, OR −2.70, 95% CI −5.15 to −0.25; four RCTs, 250 patients, OR −4.01, 95% CI −5.11 to −2.92, respectively], while the incidence of postoperative wound infection, urinary tract infection, intra-abdominal abscess, and mortality was not different between patients of the compared groups (six RCTs, 355 patients, OR 0.52, 95% CI 0.23–1.18; five RCTs, 313 patients, OR 0.44, 95% CI 0.04–5.54; four RCTs, 226 patients, OR 0.44, 95% CI 0.12–1.59; nine RCTs, 685 patients, OR 0.98, 95% CI 0.29–3.29, respectively).
Conclusion The use of probiotics/synbiotics may reduce postoperative infections after abdominal surgery. This is a promising infection-preventive measure that may decrease morbidity, length of antibiotic therapy, duration of hospital stay, and pressure for emergence of antimicrobial resistance. However, the results of this meta-analysis should be interpreted with caution due to the significant heterogeneity of the studies included.

Keywords Abdominal surgery · Infection-preventive measure · Postoperative infections · Probiotics/synbiotics · Randomized controlled trials

E. Pitsouni · V. Alexiou · V. Saridakis · G. Peppas · M. E. Falagas (✉)
Alfa Institute of Biomedical Sciences (AIBS),
9 Neapoleos Street,
151 23 Marousi, Greece
e-mail: m.falagas@aibs.gr

G. Peppas
Department of Surgery, Henry Dunant Hospital,
Athens, Greece

M. E. Falagas
Department of Medicine, Tufts University School of Medicine,
Boston, MA, USA

Background

Advanced surgical techniques and improved perioperative care have considerably lowered postoperative morbidity. However, infection following abdominal operation remains

a considerable morbidity factor for surgical patients. Urinary tract infections, pneumonia, wound infection, intra-abdominal abscess, and cholangitis are frequently observed among patients undergoing abdominal surgery for such medical conditions as biliary cancer surgery, pancreaticoduodenectomy, and liver transplantation [1–5].

The exact pathophysiological mechanism that predisposes patients undergoing major abdominal surgery to infection is yet to be identified. However, bacterial translocation from the gastrointestinal tract to the systemic circulation is considered to be of major importance for the pathogenesis of postoperative infections [6–9]. Physical injury of the intestinal mucosa leading to disruption of the gut barrier and increased intestinal permeability as well as microbial imbalance and decreased immunodeficiency of the surgical patient are considered to be the main causes of bacterial translocation [10–12].

Lilly and Stillwell [13] were the first to introduce probiotic therapy. It has been shown that probiotics are able to decrease and prevent, to a certain degree, bacterial translocation [14, 15]. Probiotics are food supplements containing live bacteria that, theoretically, have beneficial effects in the host, although a scientifically sound corroboration of these effects is not yet available for most, if not for all conditions. These bacteria inhibit the growth of pathogens and support microbial balance of the intestine towards a healthier flora [16]. Prebiotics are indigestible sugars that stimulate the growth or activity of certain bacteria of the gastrointestinal flora, to the benefit of the host [16]. The food supplements containing both probiotics and prebiotics are called synbiotics [16]. Several randomized controlled trials (RCTs) using probiotics/synbiotics preoperative and/or postoperative with a focus on the prevention of postoperative infections [17–26] have been performed, and a narrative review has been published [27].

We sought to review current literature and synthesize qualitatively the available data by performing a meta-analysis in order to identify the potential benefit(s) of the perioperative administration of probiotics/synbiotics to patients undergoing abdominal surgery. Specifically, we aimed to assess whether the administration of probiotics/synbiotics can prevent postoperative infectious complications, such as pneumonia, wound infection, urinary tract infections, intra-abdominal abscess, cholangitis, and/or any type of infections.

Methods

Sources

We searched PubMed, Scopus, Web of Science, and Cochrane library via Wiley Interscience to identify RCTs focusing on the use of probiotics/synbiotics for the prevention of postoperative infections. The keywords used were ‘probiotics and postoperative infections’. Additionally, in order to accomplish complete coverage of the literature, we performed a hand search of all references of the initially retrieved articles. The RCTs that were not available to us were requested from the authors.

Study selection

Articles eligible for inclusion were RCTs studying the perioperative administration of probiotics/synbiotics in patients undergoing abdominal surgery (i.e., biliary cancer surgery, liver transplantation, pancreaticoduodenectomy) published in the English language. Articles referring to animal studies, abstracts presented in conferences, and articles published only in an abstract form were excluded from our review.

Data extraction

Two reviewers (EP, VS) blinded to author(s), journal, and study institution, independently extracted data from all RCTs included in our meta-analysis. We focused on the year of publication, study design, patient population, number of patients [enrolled and clinically evaluable (CE)], study quality score, infectious complications [any infections, pneumonia, urinary tract infection, wound infection, bacteremia, intra abdominal abscess, and other (i.e., cholangitis)]. In particular, study quality was assessed using the Jadad score [28] in addition to allocation concealment. Thus, the maximum quality score that a study could achieve was 6.

Definitions

- Pneumonia: characteristic pulmonary infiltrate on a chest radiograph and leukocytosis.
- Urinary tract infection: dysuria, leukocyturia and a positive urine culture $>10^5$ colony forming units/mL with or without fever.
- Wound infection: spontaneous or surgically released purulent discharge with positive cultures.
- Intra-abdominal abscess: purulent discharge from abdominal drains placed at surgery, or as fluid collection requiring a drainage procedure with positive cultures.
- Cholangitis: fever, elevation of cholestatic enzymes and positive cultures from biliary drainage.
- Length of antibiotic therapy: the number of days that patients received antibiotic treatment.
- Length of hospital stay: the time from the day of surgery until hospital discharge.

- Probiotics/synbiotics group: patients that received any type of probiotics/synbiotics perioperative (preoperative and/or postoperative), despite the difference among the therapeutic protocols.
- Control group: patients that did not receive probiotics.

Statistical analysis

The outcomes extracted from the various RCTs were expressed as dichotomous variables or as continuous variables whenever a mean difference was present, pooled odds ratios (OR) and 95% confidence interval (CI) were estimated using a random effects model. The presence of statistical heterogeneity between the included trials was assessed by the χ^2-test; a p value <0.1 denoted the presence of significant heterogeneity. All statistical analyses were performed using the Review Manager (RevMan) v.5.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008).

Evidence from RCTs

Thirty articles were initially retrieved from our web search. Nineteen articles were not RCTs and thus were excluded from our study. From the remaining 11 RCTs, three were excluded: one article was a letter to the editor concerning an already published RCT, one focused on the combination of preoperative and postoperative use of probiotics versus postoperative use of probiotics [17], and one was an animal study. Thus, nine RCTs ultimately qualified for inclusion in our study [18–26].

In Table 1, we present the main characteristics of the nine RCTs included in our review. Six studies [18–23] used the combination of various bacterial species in the probiotic supplement, while three studies [24–26] used only one type of bacterial species. Four studies [18, 20, 23, 24] did not provide any data regarding the exact follow-up of patients following surgery, while four studies [19, 21, 22, 26] reported that patients were observed for 30 days after surgery and one study [25] observed patients for at least 3 months after surgery. In two studies [22, 23], patients did not receive antibiotics for at least 1 month before surgery, while in one study [26] the patients were not administered antibiotics for at least 1 week before surgery; six studies [18–21, 24, 25] did not provide any data regarding the administration of antibiotics in patients prior to surgery. Patients received intravenous antibiotic prophylaxis 30 min prior to surgery in all but three studies. Five studies [18, 19, 22, 24, 25] reported the type of the administered regimens, which was neomycin (3 g) in one study [18], cefuroxime (1.5 g) and metronidazole (500 mg) in two studies [19, 22], ceftriaxone (2 g) and metronidazole (500 mg) in one study [24], and cefotaxin (2 g) and metronidazole (500 mg) in one study [25]. One study [21] did not report any data on antibiotic prophylaxis. In one study [23] patients received intravenous antibiotics for 24 h after surgery, and in one study [25] patients received antibiotics postoperatively for 2 days. In addition, in one study [19], proton pump inhibitors (pantozole 40 mg) were supplied to all patients once daily, while in one study [22] H_2-blockers (ranitidine 150 mg) were administered to all patients once daily.

Overall, 733 patients undergoing abdominal surgery were enrolled, and 685 patients comprised the CE population. The baseline characteristics [i.e. age, gender, American Society of Anesthesiologists (ASA)-classification, the Child–Pugh classification, physiological and operative severity scores for enumeration of morbidity (POSSUM) scores, routine immunosuppression, body mass index, diabetes mellitus] of the compared groups of patients were well matched in all RCTs. The mean quality score of the included RCTs was 3.6 (range 2–6). Specifically, two RCTs [20, 21] scored 2 points, three RCTs [18, 24, 25] scored 3 points, two RCTs [22, 26] scored 4 points, one RCT [19] scored 5 points, and one RCT [23] scored 6 points. All articles used the words randomized or randomization in their title or abstract and described the exact number as well as specific reasons for withdrawal from the study.

The surgical outcomes extracted from nine RCTs included in our review are presented in Table 2. Six [19–22, 24, 25] of the nine reviewed studies showed that infectious complications are less frequent in patients receiving probiotics/synbiotics therapy than in controls. In addition, one study [19] reported that delayed gastric emptying (DGE) was less frequent in the group receiving probiotics than in the control group. Three studies [18, 23, 26] reported that septic morbidity did not differ significantly between the group of patients receiving synbiotic and the control group.

Laboratory outcomes, such as changes in intestinal permeability [assessed by lactulose-mannitol test (L/M ratio)], measurements of serum diamine oxidase (DAO) activity, natural killer (NK) cell activity, were provided by five studies [20, 22, 23, 24, 25], C-reactive protein (CRP) and interleukin-6 concentrations were presented in seven studies [18, 19, 21, 23–26], and changes in $CD3^+$, $CD4^+$, and $CD8^+$ cells and in the CD4:CD8 ratio were reported in two studies [24, 25]. Specifically, six studies [18, 19, 22–24, 26] reported that the above-mentioned parameters did not differ significantly between the compared groups at any time point, while one study [25] reported that cellular immune parameters were different between groups but within normal ranges; there was no difference regarding these parameters among patients with or without infections.

Table 1 Main characteristics of randomized controlled trials focusing on the use of probiotics/synbiotics for the prevention of postoperative infections

First author/ year of publication	Study design[a]	Population	Group A[b] (patients receiving prebiotics)	Group B (control population)	Primary end point	Number of enrolled patients	Number of clinically evaluable patients (CE)	Study quality score[c]
Reddy [18]/ 2007	RCT	Patients requiring elective colectomy [median age 68.5 years (range 62.5–74 years), 72.5 years (range 53–81 years)]	Preoperative treatment with 4×10^9 colony forming units of *L. acidophollus* La5, *L. bulgaricus, B. lactis* BB-12 and *S. thermophilus* plus 15 g oligofructose powder twice daily	Control group	Prevalence of Enterobacteriaceae in the gut microflora	42	20/22	2
Rayes [19] / 2007	MC DBRCT	Patients who were scheduled for pancreaticoduodenectomy (mean age 58±12 and 59±13 years)	One day preoperative treatment with 4 LAB: 10^{10} *P. pentosaceus 5–33:3*, *Leuconostoc mesenteroides 77:1*, *L. paracasei F19* and *L. plantarum 2362* plus 4 bioactive fibers: betaglucan, inulin, pectin, and resistant starch. Continued treatment the first 8 pod	Identical treatment as group A without the LAB	Occurrence of postoperative bacterial infection during the first 30 postoperative days	95	40/40	5
Nomura [20] /2007		Patients with pancreaticobiliary disease who were scheduled to undergo pancreaticoduodenectomy [median age 66 years (range 30–83 years) and 69 years (range 50–88 years)]	Preoperative treatment with 2mg of *E. faecalis* T-110, 10 mg of *C. butyricum* TO-A, and 10 mg of *Bacillus mesentericus* TO-A 3—15d before surgery and restarted 2 pod until hospital discharge	Control group	The potential beneficial effect of probiotics on patient outcome after pancreaticoduodenectomy	70	30/34	2
Kanazawa [21]/2005	RCT	Patients with biliary[d] cancer who were scheduled to undergo combined liver and extrahepatic bile duct resection with hepaticojejunostomy (mean age 62.5±9.9 and 64.9±9.4 years)	Postoperative enteral feeding with 10^8 *L. casei* and 10^8 *B. breve* and galactooligosaccharides for 14 pod	Postoperative enteral feeding without synbiotics	Several end points[f]	54	21/23	2
Rayes [22]/ 2005	DBRCT	Patients who were scheduled for liver transplantation (mean age 53±2 and 50±2 years)	Postoperative enteral feeding with four LAB: 10^{10} *P. pentosaceus*, *Leuconostoc mesenteroides*, *L. paracasei*, and *L. plantarum* 2362 plus four bioactive fibers: betaglucan, inulin, pectin and resistant starch started on the day of operation till 14 pod twice daily	Postoperative enteral feeding as Group A without the LAB	Occurrence of postoperative bacterial infection during the first 30 postoperative days	66	33/33	4
Anderson [23]/2004	RCT	Patients who were scheduled for elective laparatomy [median age 71 years (range 47–76 years) and 71 years (range 66–80 years)]	Preoperative treatment with probiotics (4×10^9 colony forming units of *L. acidophilus La5*, *L. Bulgaris*, *B. lactis Bb-12*, *S. thermofilus*) 1 caps t.i.d.	Preoperative and postoperative treatment with placebo caps and sucrose powder	Several end points[g]	144	72/65	6

			and prebiotics (oligofructose powder) b.i.d for 1–2 weeks before laparotomy and postoperative treatment with the same synbiotic until discharge from the hospital					
Rayes [24]/ 2002	RCT	Patients scheduled for major abdominal surgery (mean age 60± 15, 61±12 and 62±15, years)	Postoperative enteral formula for 5 pod, probiotics (10^9 *L. plantarum* 299) and oat fiber for the first 4 pod	Postoperative administration of standard crystalloid solution and parenteral nutrition for 8 pod	Incidence of early postoperative infections	60	30/30	3
Rayes [25]/ 2002	RCT	Patients scheduled for liver transplantation (mean age 50±2, 47±2 and 50±2 years)	Postoperative enteral formula 24 h after operation, probiotics (10^9 *L. plantarum* 299) and oat fiber for 12 pod	Postoperative enteral nutrition for 12pod	Development of postoperative bacterial infection	73	31/32	3
McNaught [26]/2002	RCT	Patients listed for major abdominal surgery[e] [median age 68 years (range 58–74 years) and 69 years (range 58–77 years)]	Preoperative treatment from the day of study entry to the day prior to surgery with 5×10^7 *L. plantarum* 299v and same postoperative treatment according to tolerance	Control group	Bacterial translocation and septic morbidity	129	64/65	4

[a] RCT, Randomized controlled study; MC, monocentric; DB, double blind

[b] pod, Postoperative days; t.i.d., three times daily; b.i.d., twice daily. All microorganisms are living. LAB, Lactic acid bacteria. *L.*, *Lactobacillus*; *B.*, *Bifidobacterium*; *P., Pediacoccus*; *S., Streptococcus*; *E., Enterococcus*; *C., Clostridium*

[c] Modified Jadad score [28] without description of withdrawals plus allocation concealment

[d] Biliary cancer: Perihilar cholangiocarcinoma or gallbladder cancer involving the hepatic hilus

[e] Small bowel resection, Hartmann's, AP resection, right hemicolectomy, anteriior resection, triple bypass, Whipples, laparotomy,

[f] Intestinal permeability, integrity, microflora, and surgical outcome in a clinical setting

[g] Bacterial translocation, gastric colonization, systemic inflammation, and postoperative sepsis

Table 2 Surgical outcomes among patients who received probiotics/synbiotics versus surgical outcomes among patients belonging to the control group

First author/year of publication	Infectious complications (%)							Mortality	Length of antibiotic therapy (days)	Postoperative hospital stay (days)
	Prebiotics group versus control group									
	Any infections	Pneumonia	Urinary tract infection	Wound infection	Cholangitis	Intra-abdominal abscess	Other			
Reddy [18]/2007	NR	1/20 (5) vs 2/22 (9)	NR	2/20 (10) vs 3/22 (14)	NR	1/20 (5) vs 0/22 (0)	NR	0/20 (0) vs 0/22 (0)	NR	NR
Rayes [19]/2007	5/40 (13) vs 16/40 (40)	0/40 (0) vs 4/40 (10)	1/40 (3) vs 1/40 (3)	4/40 (10) vs 6/40 (15)	0/40 (0) vs 1/40 (3)	0/40 (0) vs 5/40 (13)	0/40 (0) vs 2/40 (5)[a,b]	1/40 (3) vs 1/40 (3)	2±5 vs 10±14	17±8 vs 22±16
Nomura [20]/2007	7/30 (23) vs 18/34 (53)	NR	NR	NR	NR	NR	NR	0/30 (0) vs 1/34 (3)	NR	median 19 (range 11–40) vs median 24 (range 11–91)
Kanazawa [21]/2005	4/21 (19) vs 12/23 (52)	0/21(0) vs 1/23 (4)	0/21 (0) vs 0/23 (0)	3/21 (14) vs 6/23 (26)	NR	2/21 (10) vs 4/23 (17)	1/21 (5) vs 4/23 (17)[b]	0/21 (0) vs 0/23 (0)	10.4±7.4 vs 15.7±13.9	36.9±16.4 vs 47.0±19.2
Rayes [22]/2005	1/33 (3) vs 16/33 (48)	0/33 (0) vs 1/33 (3)	1/33 (3) vs 12/33 (36)	0/33 (0) vs 1/33 (3)	0/33 (0) vs 2/33 (6)	NR	NR	0/33 (0) vs 0/33 (0)	0.1±0.1 vs 3.8±0.9	27.8±2.4 vs 27.9±2.1
Anderson [23]/2004	23/72 (32) vs 20/65 (31)	NR	NR	NR	NR	NR	NR	5/72 (7) vs 9/65 (14)	NR	median 8 vs median 8
Rayes [24]/2002	3/30 (10) vs 3/30 (10) vs. 9/30 (30)	2/30 (7) vs 1/30 (3) vs. 6/30 (20)	1/30 (3) vs 0/30 (0) vs 0/30 (0)	0/30 (0) vs 0/30 (0) vs 1/30 (3)	NR	0/30 (0) vs 0/30 (0) vs 1/30 (3)	0/30 (0) vs 1/30 (3) vs 0/30 (0)[c]	0/30 (0) vs 0/30 (0) vs 0/30 (0)	4±3.7 vs 7±5.2 vs 8±6.5	14±4 vs 15±7.4 vs 16±5.5
Rayes [25]/2002	4/31 (13) vs 11/32 (34) vs 15/32 (48)	1/31 (3) vs 4/32 (13) vs 6/32 (19)	0/31 (0) vs 3/32 (9) vs 0/32 (0)	0/31 (0) vs 0/32 (0) vs 1/32 (3)	3/31 (10) vs 10/32(31)vs 13/32(41)	NR	0/31 (0) vs 0/32 (0) vs 3/32 (9)[a]	0/31 (0) vs 0/32 (0) vs 0/32 (0)	NR	35±2.4 vs 36±2.7 vs 39±5
McNaught [26]/2002	NR	NR	NR	NR	NR	NR	NR	7/64 (11) vs 2/65 (3)	NR	NR

NR, Not reported

[a] Sepsis

[b] 0/40 (0) vs 1/40 (3) had empyema

[c] Bacteremia

Three studies [18, 23, 26] reported that changes in fecal microflora were not significant between the compared groups, while one study [21] reported that live bacteria administered as probiotics, colonized patients' intestine.

Outcomes of the meta-analysis

Infectious complications in CE patients

Any infections that did occurr did so less frequently in patients receiving probiotics/synbiotics than in patients in the control group (seven RCTs, 514 patients, OR 0.26, 95% CI0.12–0.55; Fig. 1). There were fewer patients with pneumonia in the probiotics/synbiotics group (six RCTs, 355 patients, OR0.24, 95% CI 0.09–0.68). The incidence of urinary tract infections was the same between the compared groups (five RCTs, 313 patients, OR0.44, 95% CI0.04–0.54), and wound infection occurred in the same proportion of patients of the two groups (six RCTs, 355 patients, OR0.52, 95% CI0.23–1.18). Cholangitis was rarer in patients receiving probiotics/synbiotics (three RCTs, 209 patients, OR0.18, 95% CI0.05–0.57). The incidence of intra-abdominal abscess was not different between the compared groups (four RCTs, 226 patients, OR0.44, 95% CI0.12–1.59). Other infectious complications were more common in patients in the control group (four RCTs, 147 patients, 0R0.19, 95% CI0.04–0.92).

Mortality, length of antibiotic therapy, and postoperative hospital stay

Mortality occurred in the same proportion of patients of the compared groups (nine RCTs, 685 patients, OR0.98, 95% CI0.29–3.29). The length of antibiotic therapy was shorter in patients receiving probiotics/synbiotics than patients in the control group (four RCTs, 250 patients, OR −4.01, 95% CI −5.11 to −2.92; Fig. 2).The incidence of postoperative hospital stay was briefer in the probiotics/synbiotics group (five RCTs, 313 patients, OR –2.70, 95% CI −5.15 to −0.25; Fig. 3).

Side effects of enteral nutrition

Five RCTs [19, 20, 22, 23, 25] provided details on the side effects of enteral nutrition, consisting of diarrhea and abdominal cramps. Specifically, diarrhea noted in nine patients out of 196 patients (4.6%) receiving probiotics/synbiotics, while abdominal cramps were noted in 12 out of 196 patients (6.1%) receiving probiotics/synbiotics. In addition, the incidence of diarrhea or abdominal cramps was the same between the probiotics/synbiotics group and the control group (five RCTs, 388 patients, OR1.22, 95% CI 0.35–4.26; five RCTs, 388 patients, OR 0.76, 95% CI 0.34–1.72, respectively).

Discussion

The main finding of this review is that the use of probiotics/synbiotics in patients undergoing abdominal surgery is a very promising clinical measure for the prevention of postoperative infectious complications. However, there is as yet an inadequate amount of evidence to derive any specific conclusions; we noted significant heterogeneity among the identified RCTs in terms of the type of probiotic/synbiotic, administration strategies (i.e., combination of perioperative or postoperative use vs. no use), dosage, and type of surgery.

It should be noted that the rates of infectious complication were rather high in both the case and control groups,

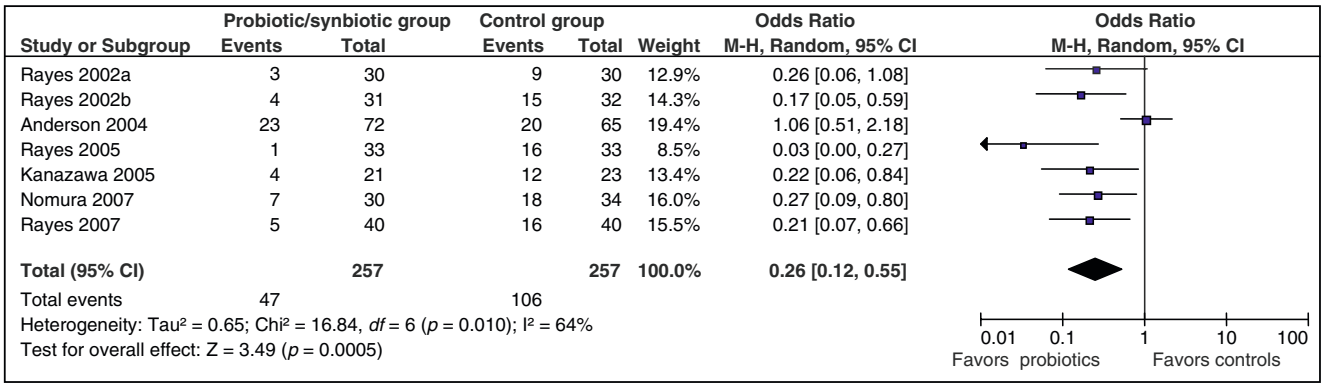

Fig. 1 Any infections noted in patients receiving probiotics/synbiotics versus patients who did not receive probiotics/synbiotics (control group). The statistical method used was Mantel-Haenszel (M-H). *Vertical line* indicates no difference between the compared treatment groups, *diamond* indicate pooled odds ratios [with 95% confidence intervals (*CI*) in *square parenthesis*], *horizontal lines* indicate 95% CIs, *squares* indicate point estimates, with the *size of the squares* indicating the weight that each individual study has in the meta-analysis

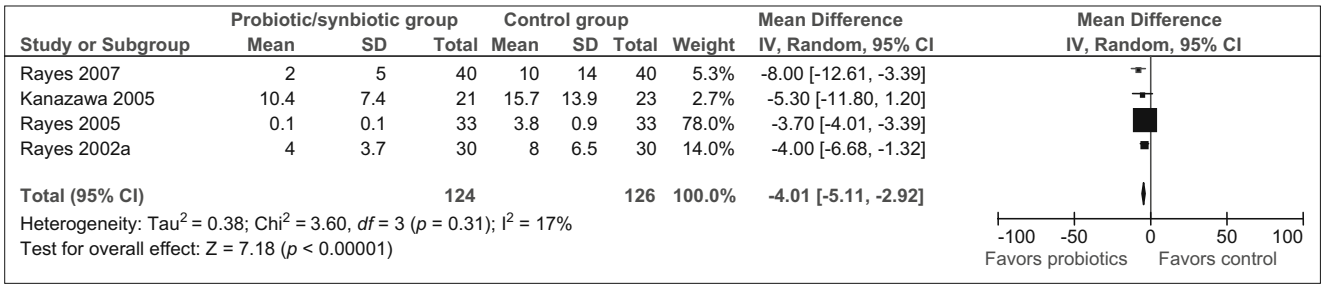

Fig. 2 Length of antibiotic therapy in patients receiving probiotics/synbiotics versus patients who did not receive probiotics/synbiotics (control group). The statistical method used was inverse variance (IV). *Vertical line* indicates no difference between the compared treatment groups, *diamond shapes* indicate pooled odds ratios (with 95% CI in *square parenthesis*), *horizontal lines* indicate 95% CIs, *squares* indicate point estimates, with the *size of the squares* indicating the weight that each individual study has in the meta-analysis. *SD* Standard deviation

ranging from 3 to 32% for the groups of patients that received probiotics/synbiotics and from 30 to 53% for the control groups. This may be due to the severity and extension of the surgery (i.e., liver transplantation). Of interest, the most common infectious complications that occurred in both the case and control groups were wound infections and intra-abdominal abscesses; the incidence of urinary and respiratory tract infections was considerably fewer. Rayes et al. [22] reported a significant reduction of urinary tract infections of from 36 to 3%; it should be noted that the duration of urinary catheterization as well as baseline characteristics did not differ significantly between the compared groups and that patients belonging to the control group developed infections mainly caused by gut-derived bacteria. On the other hand, gut-derived bacteria are not directly associated with pneumonia and other respiratory tract infections; thus, the preventive role of probiotics/synbiotics for respiratory tract infections may be based on the reduction of bacterial translocation.

Another interesting finding is that the length of hospital stay and antibiotic therapy among patients receiving probiotics/synbiotics was significantly shorter. This is of great importance since shorter antibiotic regimens may decrease the risk of emerging antimicrobial resistance. In addition, a shortened hospital stay may further reduce the risk of hospital infections and result in financial benefit. None of the identified RCTs provided a cost-effectiveness analysis; this may be an interesting focus for future studies. Intensive care unit stay among patients receiving probiotics/synbiotics, where data was available, tended to be shorter without reaching statistical significance. This finding may be attributed to the specific policy of the hospital; liver transplant patients are hospitalized for at least 25 days regardless of the presence of infectious complications [22]. Patients undergoing major abdominal surgery, especially liver transplantation, are in need of prolonged care and a cautious approach to avoid postsurgical complications of various types (i.e., rejection of graft).

Most of the reviewed RCTs reported that probiotics/synbiotics were well tolerated by all patients and that minor side effects, such as diarrhea and/or abdominal cramps, were resolved after the amount of probiotics administered was reduced or after synbiotics discontinuation, and/or administration of the probiotic supplement without the oligofructose. This finding is in accordance with those of other studies performed in various medical fields [29–31]. However, it should be noted that *Lactobacillus* bacteremia has been associated with probiotic therapy [32–36], and it is possible that patients undergoing major abdominal surgery, such as liver transplantation, may be susceptible to

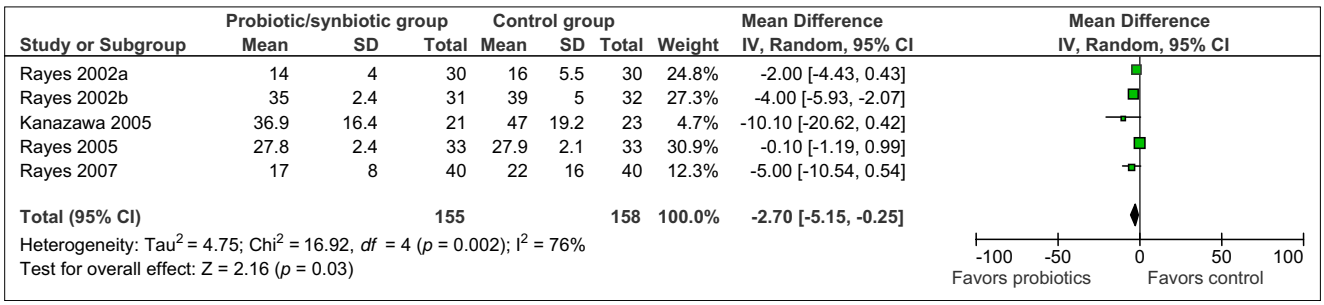

Fig. 3 Postoperative stay in hospital in patients receiving probiotics/synbiotics versus patients who did not receive probiotics/synbiotics (control group). The statistical method used was inverse variance (IV). *Vertical line* indicates no difference between the compared treatment groups, *diamonds* indicate pooled odds ratios (with 95% CI in square parenthesis), *horizontal lines* indicate 95% CIs, *squares* indicate point estimates, with the *size of the squares* indicating the weight that each individual study has in the meta-analysis. *SD* Standard deviation

Lactobacillus bacteremia. This may be attributed to the fact that such patients are often immunosuppressed, suffer from malnutrition, and have a protein deficit. Besselink et al. [37] reported that patients with severe acute pancreatitis who received probiotics had more infectious complications as well as an increased risk of mortality compared to patients who did not receive probiotics but placebo; most of the deaths were due to multiorgan failure, respiratory failure, cerebral infarction/bleeding and bowel ischemia. Specifically, bowel ischemia did not occur in any patients receiving placebo.

The first two studies in the field involving patients undergoing elective surgery who were administered probiotics/synbiotics containing only one type of bacteria failed to provide statistically significant results [24, 26]. Conversely, recent RCTs that have used probiotics containing more than one type of bacterial species [19–23] have reported statistically significant outcomes. The combination of different bacteria may act synergistically to more effectively inhibit the growth of pathogens and stimulate the immune response of the host. In addition, these two studies involved patients that underwent a less invasive surgery compared to studies that noted a significant reduction of postoperative infections and involved patients undergoing pancreaticoduodenectomy [19, 20], liver transplantation [22], and hepatectomy [21]. The possibility of a wrong selection of probiotics or therapeutic route or dose was unlikely although the median duration of postoperative therapy was rather short [24].

The appropriate therapeutic route, length of therapy, time of administration, and dosage of the probiotics and/or synbiotics, as derived from this review, remain controversial issues. A review of the current literature does not reveal a uniform preventive strategy. Two of the four RCTs [19, 20, 23, 24] that compared perioperative use to non-use of probiotics/synbiotics showed a significant decrease in postoperative infections with probiotics/synbiotics. On the other hand, all articles [21, 22, 24, 25] that compared postoperative use to non-use of probiotics/synbiotics report an actual lessening of postoperative infections. Furthermore, the length of the selected regimens varies considerably—from 4 to 15 days—even among studies that report a positive preventive result. Sugawara et al. [17] focused on the comparison of perioperative to postoperative use of synbiotics in biliary cancer surgery. Overall, synbiotics were administered for 29 and 14 days, respectively. Infectious complications (bacteremia, intra-abdominal abscess, wound infection, and pneumonia) were significantly fewer in patients receiving perioperative synbiotic therapy; the infections observed were bacteremia, intra-abdominal abscess, wound infection, and pneumonia. In addition, the length of the hospital stay and antibiotic therapy was shorter among patients receiving synbiotics perioperatively. Future RCTs focusing on the correct preventive use of probiotics/synbiotics, including dosage, length, route, and time of administration, may help in the development of a strategy leading to a more appropriate use of probiotics/synbiotics in abdominal surgery.

Limitations

The RCTs retrieved from the current literature present significant incongruities, and the type of probiotic administered, the therapeutic route (i.e., combination of perioperative or postoperative use vs. no use), and the type of abdominal surgery vary considerably among the reviewed studies. Furthermore, in order to evaluate the methodological quality of RCTs, we used the Jadad score [28], which is not perfect due to its lack of coverage of financial conflicts of interest and the handling of dropouts, but it is the most widely used indicator. Finally, taking into account that a proportion of patients had a urinary catheter in place, the definition of urinary tract infection used by the authors of the RCTs is rather weak.

Conclusion

In conclusion, despite its various limitations, we believe that this review provides evidence that the use of probiotics/synbiotics may prevent postoperative infections following abdominal surgery. Randomized controlled studies focusing on specific abdominal surgery and using the same synbiotic supplement and the same therapeutic route are warranted to further evaluate this promising infection-preventive measure that may decrease morbidity, length of antibiotic therapy, duration of the hospital stay, and pressure for emergence of antimicrobial resistance.

Conflict of interest The authors state that they have no conflict of interest.

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