The efficacy and safety of probiotics in people with cancer: a systematic review

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Background: Probiotics are living microorganisms that are generally thought of as being beneficial to the recipient. They have been shown to be effective in people with acute infectious diarrhoea, and cost-effective in antibiotic-associated diarrhoea. Probiotics may have a role in people with cancer, as various cancer treatments often lead to diarrhoea. However, as people with cancer are often immunocompromised, it is important to assess for adverse events (AEs) such as infection, which could potentially be a consequence of deliberate ingestion of living microorganisms.

Design: A systematic review was carried out to collect, analyse and synthesise all available data on the efficacy and safety of probiotics in people with cancer (PROSPERO registration: CRD42012003454). Randomised, controlled trials, identified through screening multiple databases and grey literature, were included for analysing efficacy, while all studies were included for the analysis of safety of probiotics. Primary outcomes were the reduction in duration, severity and incidence of antibiotic-associated diarrhoea and chemotherapy-associated diarrhoea, and AEs, especially probiotic-associated infection. Where possible, data were combined for meta-analysis by a random-effects model, assessing causes of heterogeneity, including differences in strains, dosage and patient characteristics.

Results: Eleven studies ($N = 1557$ participants) were included for assessing efficacy. Results show that probiotics may reduce the severity and frequency of diarrhoea in patients with cancer and may reduce the requirement for anti-diarrhoeal medication, but more studies are needed to assess the true effect. For example comparing probiotic use to control 25 groups on effect on Common Toxicity Criteria ≥ 2 grade diarrhoea, odds ratio (OR) = 0.32 [95% confidence interval (CI) of 0.13–0.79; $P = 0.01$]. Seventeen studies ($N = 1530$) were included in the safety analysis. Five case reports showed probiotic-related bacteraemia/fungaemia/positive blood cultures.

Conclusion(s): Probiotics may be a rare cause of sepsis. Further evidence needs to be collated to determine whether probiotics provide a significant overall benefit for people with cancer.

Key words: probiotics, systematic review, cancer, diarrhoea, health care-associated infection

introduction

Probiotics are defined by the World Health Organisation and Food and Agricultural Organization of the United Nations as: 'Live microorganisms which when administered in adequate amounts confer a health benefit on the host' [1]. *Lactobacillus* and *Bifidobacterium* are commonly used strains, though *Saccharomyces cerevisiae*—a yeast—is also used as a probiotic [2].

A previous Cochrane Review [3] in immunocompetent patients demonstrated probiotics reduce episodes and duration of presumed/proven acute infectious diarrhoea. Diarrhoea related to cancer therapy incurs additional costs largely due to more admissions to hospital and time spent there [4]. Probiotics

have been argued to be cost-effective in the context of antibiotic-associated diarrhoea [5]. Therefore, it is worth considering if probiotics are effective in people with cancer from both a patient's perspective and a financial perspective.

Diarrhoea induced by chemotherapy use is the most common associated toxicity which leads to the chemotherapy regime being stopped or reduced; one factor contributing to this is that chemotherapeutic agents can alter the recipient's normal protective gut microflora [6]. Diarrhoea is unpleasant for the patient and may reduce their tolerance for undergoing radiotherapy and chemotherapy; they may also require further treatment to prevent associated morbidity and mortality [7]. As infections are common and the gut microflora plays a role in immunity [6], probiotics should be evaluated both for efficacy in preventing infection and for safety, particularly to investigate whether probiotics cause infection themselves. There is currently uncertainty as to the occurrence of adverse events (AEs) after

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probiotic consumption. In generally healthy people, no AE of a serious nature have been reported [3]. However, it is essential to investigate the safety of probiotic use in immunocompromised cancer patients, as case reports have identified a *Lactobacillus* strain used in probiotic therapy to be involved with sepsis [8]. Current UK dietary advice is for neutropenic cancer patients to avoid products containing probiotics [9]; however, Gibson et al. recommend that in patients with pelvic malignancies, consumption of probiotics containing *Lactobacillus* species may help prevent diarrhoea secondary to chemotherapy or radiotherapy [10].

A systematic review and meta-analyses were carried out to assess the safety of probiotics in patients with malignancy and to determine whether probiotics are beneficial through assessing quantitative markers such as grade of diarrhoea.

methods

A protocol was registered on PROSPERO (the international register of systematic reviews, registration: CRD42012003454) [11].

eligibility

Randomised, controlled trials (RCTs) were considered for assessing the efficacy of probiotics. Both RCT and non-RCTs were also considered for assessing the safety of probiotics.

Studies were deemed eligible if they:

- Included people with a diagnosis of cancer who have received probiotics.
- Reported health outcomes such as antibiotic-associated diarrhoea, gastrointestinal infection, mucositis, AEs.

For efficacy assessment, probiotics had to be randomised in comparison to not receiving probiotics.

The primary outcomes to assess were:

- The proportion of people who suffered any AEs, especially probiotic-associated infection.
- The duration, severity and incidence of antibiotic-associated diarrhoea and chemotherapy-associated diarrhoea.

Secondary outcomes were:

- Faecal organic acid concentration.
- Faecal bacteriological examination.
- NK cell number.

search strategy

Databases and sources searched included: the Cochrane Central Register of Controlled Trials, Medline®, EMBASE, Literatura Latino-Americana e do Caribe em Ciências da Saúde, Allied and Complementary Medicine (AMED), Database of Abstracts of Reviews of Effects, American Society of Clinical Oncology, International Society of Paediatric Oncology, Multinational Association of Supportive Care in Cancer, International Cancer Research Portfolio, National Cancer Institute Clinical Trials, National Cancer Research Institute, Current Controlled Trials and Centerwatch.

A 40-step search strategy was produced and used for Medline®, EMBASE and AMED (see protocol) without language limitation. For the other databases, a simpler strategy was used. The search strategies were run from database inception until December 2012. Both published and unpublished studies were included. 'Grey literature' was sought, including on-going

clinical trials, conference proceedings and abstracts. Authors and experts in the field were contacted to request additional unpublished trials and data, where possible. Reference lists of each included study were screened, and forward citations searched using Google Scholar.

selection of studies

For studies found through Medline®, EMBASE and AMED, titles and abstracts were screened by two independent assessors. Non-English studies were screened by fluent medical academics. For other databases, a second reviewer double-checked a narrowed down list of potential studies and a final list of studies to include was agreed upon. Where there was uncertainty about the relevance of the studies, the full text was obtained to further evaluate.

data collection

Data about the efficacy of probiotic treatment were extracted using a tailored form and checked by the second reviewer. The form included study demographics, trial design, probiotic regimens and outcomes (see supplementary File S1, available at *Annals of Oncology* online). A similar form was used for the safety of probiotic treatment (see supplementary File S2, available at *Annals of Oncology* online).

Where data were unclear, the primary author was contacted requesting further information. Further information was successfully obtained regarding three studies [12–14].

Each RCT was scrutinised for quality using the Cochrane Collaboration's 'Risk of bias' tool [15] and non-RCTs reviewed using guidance from Loke et al. [16].

Data were input into RevMan 5.2 [17] software for analysis.

statistical analysis

Where outcome measures were comparable, datasets were pooled in meta-analyses. I^2 was used to evaluate between-study heterogeneity. $I^2 \geq 50\%$ was deemed to represent significant heterogeneity [15, 18] warranting further investigation.

Data were pooled using random-effects models; the Mantel–Haenszel method for analysis of dichotomous data and inverse variance models for continuous data, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* [15] and *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care* [18].

Random effects meta-analyses provide confidence intervals for their average estimates of effect, and prediction intervals (PIs), indicating the 'potential effect of treatment when it is applied within an individual study setting, as this may be different from the average effect' [19]. These were calculated according to the method described by Higgins et al. [20] (as cited by Riley et al. [19]), when datasets contained at least three studies. Sensitivity analyses were carried out.

results

included studies

Adapted PRISMA flow diagrams [21] display the process (see Figure 1A and B) for including studies, resulting in 11 RCTs assessing the efficacy of probiotics and 17 studies assessing safety. Further details about the eligible studies are provided in Tables 1 and 2. Ten ongoing studies were also found (see Supplementary File S3, available at *Annals of Oncology* online). Three studies in Chinese could not be translated due to resource limitations. Other included studies were all in English.
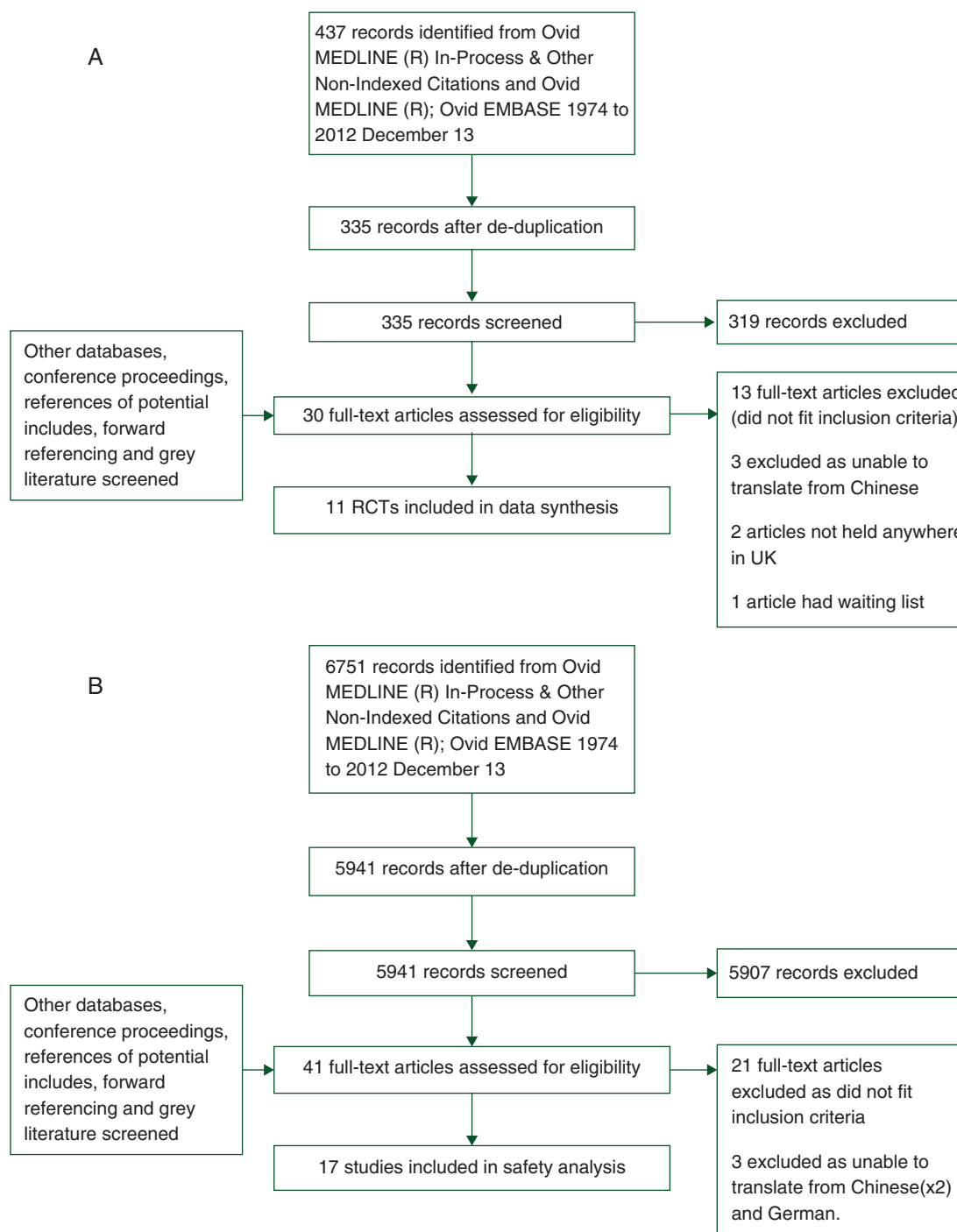
A

437 records identified from Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R); Ovid EMBASE 1974 to 2012 December 13

↓

335 records after de-duplication

↓

335 records screened → 319 records excluded

Other databases, conference proceedings, references of potential includes, forward referencing and grey literature screened → 30 full-text articles assessed for eligibility → 13 full-text articles excluded (did not fit inclusion criteria)

3 excluded as unable to translate from Chinese

2 articles not held anywhere in UK

1 article had waiting list

↓

11 RCTs included in data synthesis

B

6751 records identified from Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R); Ovid EMBASE 1974 to 2012 December 13

↓

5941 records after de-duplication

↓

5941 records screened → 5907 records excluded

Other databases, conference proceedings, references of potential includes, forward referencing and grey literature screened → 41 full-text articles assessed for eligibility → 21 full-text articles excluded as did not fit inclusion criteria

3 excluded as unable to translate from Chinese(x2) and German.

↓

17 studies included in safety analysis

Figure 1. (A) An adapted PRISMA flow diagram [21] showing the implementation of the search strategy for the efficacy of probiotics in people with cancer. (B) An adapted PRISMA flow diagram [21] showing the implementation of the search strategy for the safety of probiotics in people with cancer.

quality assessment

The individual breakdown of risk of bias for each RCT is displayed in Figure 2, while Figure 3 displays risk of bias across all RCTs. These show that performance and detection bias were the items that scored the overall highest risk of bias. The quality assessment of studies for the safety analysis (using the Loke method [16]) highlighted that many studies had an unclear definition of AEs and specifically raised concerns about reporting bias, given the lack of clarity about how AEs were measured.

efficacy of probiotics

Four RCTs looked at the frequency of grade ≥3 diarrhoea, according to the National Cancer Institute Common Toxicity Criteria (now called the Common Terminology Criteria for Adverse Events) [39] (CTC) (see Table 3). As displayed in Figure 4, meta-analysis comparing probiotic to control group showed an OR of 0.72 with a 95% CI of 0.42–1.25, a 95% PI of 0.41–1.27.

Four RCTs looked at the frequency of CTC grade ≥2 diarrhoea. Figure 5 shows the meta-analysis, which, comparing

Table 1. Characteristics of included RCTs for efficacy analysis

Study first author	Country of study	Therapy (RT, CHT, surgery)	Probiotic administered
Castro [14]	Brazil	RT	*Lactobacillus casei* Shirota and *Bifidobacterium breve*
Chitapanarux [22]	Thailand	RT	*Lactobacillus acidophilus*, *Bifidobacterium bifidum* (Infloran®)
Delia [23]	Italy	RT	VSL#3 (*Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *Bulgaricus*, *Bidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Streptococcus salivarius* subsp. *thermophilus*)
Germain [13]	Canada	RT ± CHT ± surgery	Bifilact (*Lactobacillus acidophilus* LAC-361 and *Bifidobacterium longum* BB-536)
Gianotti [24]	Italy	Surgery	*Lactobacillus johnsonii*, *Bifidobacterium longum* (with maltodextrin)
Giralt [12]	Spain	RT ± CHT	*Lactobacillus casei* DN-114 001, *Streptococcus thermophilus*, *Lactobacillus delbrueckii* subsp. *Bulgaricus*
Liu [25]	China	Surgery	*Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Bifidobacterium longum*
Osterlund [26]	Finland	Adjuvant CHT following surgery	*Lactobacillus rhamnosus*
Sharma [27]	India	RT + CHT	*Lactobacillus brevis*
Urbancsek [28]	Hungary	RT	*Lactobacillus rhamnosus*
Wada [29]	Japan	CHT	*Bifidobacterium breve* strain Yakult (BBG-01)

RT, radiotherapy; CHT, chemotherapy.

probiotic to control group, results in OR = 0.32 (95% CI 0.13–0.79; PI 0.11–0.97; P = 0.01) suggesting probiotics are beneficial in reducing the frequency of CTC grade ≥2 diarrhoea.

Stool consistency was comparable across three RCTs, as shown in Figure 6. Urbancsek et al. [28] only clearly defined formed stools, which they labelled as 'normal'. Giralt et al. [12] used the Bristol Stool Chart to compare stool consistencies. A rating of 7 on the Bristol Stool Chart was equated to 'liquid' stools, whereas a rating of either 5 or 6 was equated to 'soft/semi-solid stools'. When comparing probiotic groups to control groups, for liquid stools OR = 0.46 (95% CI 0.04–5.64; P = 0.55), whereas for soft/semi-solid stools OR = 1.91 (95% CI 0.18–20.78; P = 0.60). For formed/solid stools, OR = 1.18 (95% CI 0.69–2.04; P = 0.54).

Two RCTs looked at average daily bowel movements, but insufficient data were provided for meta-analysis. The mean difference between probiotics and control in the single study was −9.60 stools per day (95% CI −10.45 to −8.75; P < 0.00001).

The use of anti-diarrhoeal (rescue) medication can be considered a surrogate marker for severity of diarrhoea. Three studies evaluated the use of anti-diarrhoeal medication with an OR = 0.63 (95% CI 0.27–1.45; PI 0.20–1.99; P = 0.28) of taking anti-diarrhoeal medication in the probiotics group (Figure 7).

A secondary outcome measure was faecal bacteriological comparison. Three RCTs [24, 25, 29] looked at faecal bacteriological components; the change in bacteriological counts were combined where possible. The evidence was very limited and uncertain with regards to total anaerobe, bacillus and enterococci counts, but showed a significant mean reduction in enterobacteriaceae count of −1.98 [log10 colony-forming units (CFU)/g] of faeces (95% CI −2.56 to −1.39; P < 0.00001) (Figure 8).

The two remaining secondary outcomes were NK cell number and faecal organic acid concentration. Both of these outcomes were only investigated by Wada et al. [29], who did not find an increase in the amount of NK cells in the blood of those consuming probiotics. They found that faecal organic acid concentrations remained normal until week 5, from which point pH became constantly <7.0 in those consuming probiotics [29].

safety of probiotics

Seventeen studies were found that met the inclusion criteria. Three other studies [40–42] were unable to be evaluated. The 17 studies found included 1530 people (756 consuming probiotics, 774 not consuming probiotics).

It is unclear how many individuals suffered AEs, as, in some studies, individual events rather than people suffering from events were reported. There were 105 AE in those consuming probiotics, and 145 AE in those not consuming probiotics. There were no deaths attributed by the authors to probiotic-associated infection in the probiotic group. However, there was one death in a person consuming probiotics [38], as discussed later, which was attributed to progression of malignancy. There was also one death in the placebo group due to neutropenia and sepsis [27]. One patient was withdrawn from probiotic treatment due to sicchasia, while three paused then recommenced their probiotic treatment due to a rise in blood pressure [35].

In the report by Cesaro et al. [32], an 8-month-old baby with acute myeloid leukaemia had been receiving *Saccharomyces boulardii* capsules (and fluconazole prophylaxis), developed a fever after a completing a course of chemotherapy, and *S. cerevisiae* was isolated from the blood culture. The baby was treated with Amphotericin B until they recovered from neutropenia, had

Table 2. Characteristics of included studies for safety analysis

Study first author	Type of study	Total people (subgroups)	Probiotic administered	Summary of potential adverse events (AEs)
Abd El-Atti [30]	Case report	1	Multispecies	0 AE
Bellette [31]	Case report	1	Colotium (ADVITEC)—Culture showed growth of *Candida pelliculosa, Candida krusei, A. corymbifera* and *Aspergillus flavus.*	Appendicitis and liver abscesses
Cesaro [32]	Case report	1	*Saccharomyces boulardii*	*Saccharomyces cerevisiae* fungaemia
Chitapanarux [22]	Randomised control trial (RCT)	63 (placebo = 31; probiotics = 32)	*Lactobacillus acidophilus* and *Bifidobacterium bifidum* (Infloran®)	0 AE
Delia [23]	RCT	482 analysed (placebo = 239; probiotics = 243)	VSL#3 (multispecies)	0 AE
Giralt [12]	RCT	85 (placebo = 41; probiotics = 44)	*Lactobacillus casei* DN-114 001, *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus*	0 AE
Henry [33]	Case report	1	*Saccharomyces boulardii* (Perenterol)	*Saccharomyces cerevisiae* found on blood cultures
LeDoux [34]	Case report	1	Lactobacillus acidophilus but not clear if additional organisms	Persistent *Lactobacillus acidophilus* bacteraemia on serial blood cultures for 3 days
Liu [25]	RCT	100 analysed (placebo = 50; probiotics = 50)	*Lactobacillus plantarum, Lactobacillus* and *Bifido-bacterium longum*	0 AE
Malkov [35]	Case series	10	Bacillus oligonitrophilus KU-1	5 potential AE- Sicchasia (patient withdrew), blood pressure rise ×3 (patients' probiotics paused), ICP gain
Mehta [36]	Case report	1	Unclear but did contain *Lactobacillus acidophilus*	*Lactobacillus acidophilus* on blood cultures—though not clear to tell if symptomatic
Naito [37]	RCT	202 analysed (group without probiotics = 102; group with probiotics = 100)	*Lactobacillus casei*	126 AE in group without probiotics; 80 AE in group with probiotics – unclear how many individuals these were distributed over. Wide range of gastrointestinal and urinary symptoms - unable to differentiate from malignancy (transitional cell carcinomas) or chemotherapy
Oggioni [38]	Case report	1	*Bacillus subtilis* spores (Enterogermina)	Blood cultures positive for *B. subtilis*
Osterlund [26]	RCT	148 (group without probiotics = 97, group with probiotics = 51)	*Lactobacillus rhamnosus* GG	No probiotic = 2 of 51; probiotic = 9 of 97—all cases of neutropenic infection (but no growth of Lactobacillus in blood cultures)
Sharma [27]	RCT	188 analysed (placebo = 95, probiotic = 93)	*Lactobacillus brevis* CD2	Placebo group = (7 × grade II dysphagia, 6 × grade II nausea and vomiting) + 1 died after developing grade IV neutropenia and sepsis; probiotic group = 1 × grade II dysphagia; 1 × developed acute myocardial infarction after 4 weeks of anticancer therapy - all attributed to chemotherapy by authors
Urbancsek [28]	RCT	205 (placebo = 103, probiotic = 102)	Antibiophilus sachets (containing *Lactobacillus rhamnosus*)	Placebo = 2 × GI problems (mild to moderate), 1 × labial oedema; probiotic = 3 × GI problems (mild to moderate)
Wada [29]	RCT	40 (placebo = 22; probiotic = 18)	*Bifidobacterium breve* strain Yakult (BBG-01)	0 AE

Figure 2. Risk of bias for each included randomised, controlled trial for efficacy analysis, judged according to Cochrane 'Risk of bias' assessment tool. Data from [15].

their occluded central venous catheter removed and no other cause of infection was found [32]. The authors noted that routine laboratory methods lead to difficulties distinguishing *S. boulardii* and *S. cerevisiae* [32].

Saccharomyces cerevisiae was reportedly found on blood cultures by Henry et al. [33]. A 65-year-old male was treated with *S. boulardii* for 2 days, then developed a fever, inflammatory syndrome and neutrophilic leucocytosis [33]. Results from six consecutive blood cultures showed *S. cerevisiae* (no other infection was identified) [33]. The patient was treated with Amphotericin B and improved [33].

LeDoux et al. [34] reported *Lactobacillus acidophilus* bacteraemia during 3 days of blood cultures in a 38-year-old male with AIDS and stage IV Hodgkin's disease being treated with probiotics containing *L. acidophilus*. He had finished chemotherapy 3 weeks prior and had had methicillin-susceptible *Staphylococcus aureus* and *Prevotella loescheii* Hickman catheter bacteraemia [34], treated with ceftriaxone. After 4 days of antibiotics, his Hickman line was removed, and after 6 days of antibiotics, his cultures from blood and previous catheter site showed *L. acidophilus* bacteraemia [34]. He was hospitalised on day 10 of antibiotics. By day 3 of hospitalisation, his blood cultures were sterile [34].
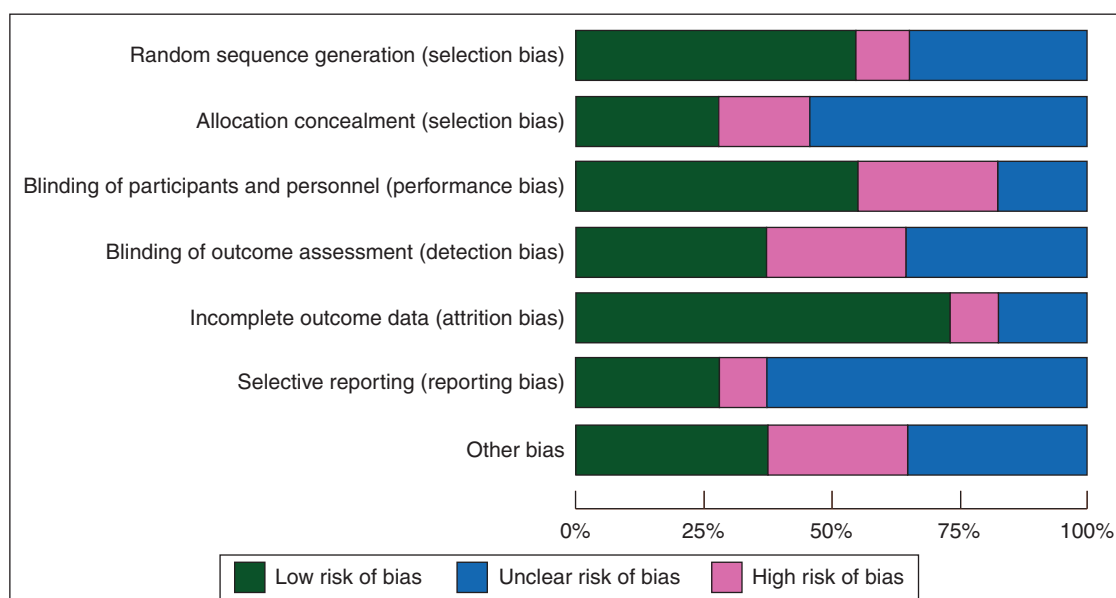
Figure 3. Bar chart comparing percentage risk of bias for each item as judged according to Cochrane 'Risk of bias' assessment tool. Data from [15].

Table 3. National Cancer Institute Common Terminology Criteria for adverse events. Data from [39]

Toxicity grade	Criteria
1	Stools: Increase of <4 per day; mild increase colostomy output
	Ostomy output: Mild increase
2	Stools: Increase of 4–6 per day
	Ostomy output: Moderate increase
3	Stools: Increase of 7 or more per day
	Ostomy output: Severe increase
	Other: loss of continence, hospitalization, limiting activities of daily living
4	Life-threatening consequences
5	Death

Mehta et al. [36] reported a 69-year-old gentleman with mantle cell lymphoma who had been consuming probiotics for severe mucositis developed during conditioning before an autologous haematopoietic stem cell transplant. *Lactobacillus acidophilus* was grown on his blood cultures after the transplant, and the report describes the resolution of his fever, symptoms and blood count after the yogurt was stopped [36].

A 73-year-old male with chronic lymphocytic leukaemia (CLL) was reported by Oggioni et al. [38] as consuming *Bacillus subtilis* spores (Enterogermina). *Bacillus subtilis* was then found on blood cultures, and remained despite multiple antibiotic treatment [38]. The patient died within a few days, which was attributed to CLL with central nervous system involvement, rather than the *B. subtilis* positive blood cultures [38].

Bellette et al. [31] reported a 10-year-old girl with an isolated medullary relapse of acute lymphatic leukaemia, who had been consuming a probiotic mixture containing *Absidia corymbifera* [31]. The girl developed appendicitis followed by sub-hepatic abscesses, which were found to contain *A. corymbifera* [31]. She was treated with Amphotericin B and developed no further abscesses [31].

The other potential AEs, as shown in Table 2, are of similar frequencies between groups consuming probiotics and groups not consuming probiotics.

discussion

This review found 11 RCTs of probiotics in cancer and identified 17 studies reporting on AEs. The studies were heterogeneous in treatments used; strain, dose and duration of probiotic (s); the patients' ages, comorbidities, cancers and therapies received; and in outcomes assessed, potentially explaining some of the between-study heterogeneity of the results.

The risk of bias in the efficacy RCTs mainly concerned detection bias and performance bias. However, the impact of this may not be substantial given the objective nature of most outcome measures, such as number of stools per day and use of anti-diarrhoeal medication.

As a qualitative measurement tool, the Loke method [16] for quality assessing the safety of probiotics (Supplementary File S4, available at *Annals of Oncology* online) highlighted that many studies were unclear on their definition of an AE, and how they were measured.

Sensitivity analyses showed no qualitative change in conclusions where meta-analyses were still possible when changes between studies were assessed. Subgroup analysis could not be carried out due to the small number of heterogeneous studies.

efficacy

CTC grade ≥2 and ≥3 diarrhoea were useful indicators for frequency and severity of diarrhoea. Meta-analysis found that those in the probiotic group had a significantly reduced incidence of CTC grade ≥2 diarrhoea, (OR = 0.32; 95% CI 0.13–0.79; PI 0.11–0.97; P = 0.01), but was unclear if CTC grade ≥3
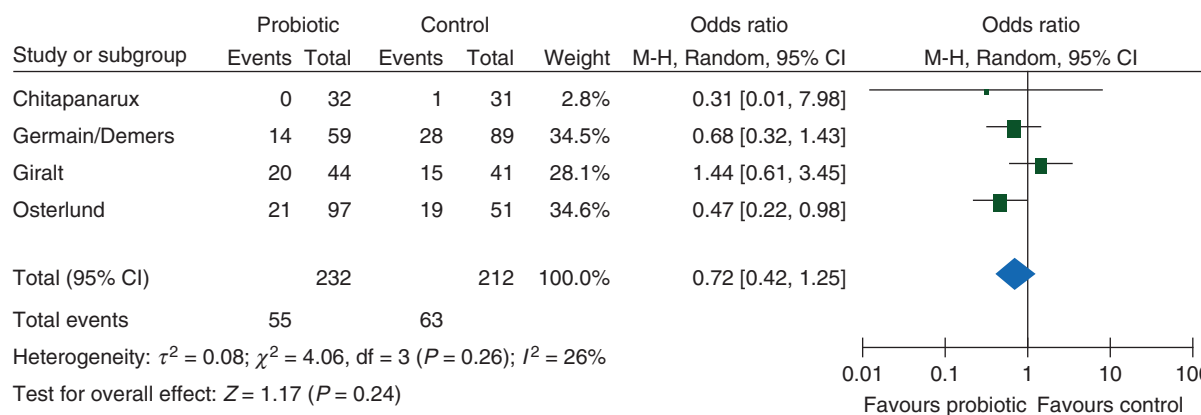
Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Chitapanarux	0	32	1	31	2.8%	0.31 [0.01, 7.98]
Germain/Demers	14	59	28	89	34.5%	0.68 [0.32, 1.43]
Giralt	20	44	15	41	28.1%	1.44 [0.61, 3.45]
Osterlund	21	97	19	51	34.6%	0.47 [0.22, 0.98]
Total (95% CI)		232		212	100.0%	0.72 [0.42, 1.25]
Total events	55		63			

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 4.06$, df = 3 ($P = 0.26$); $I^2 = 26\%$
Test for overall effect: $Z = 1.17$ ($P = 0.24$)

Figure 4. Forest plot of grade ≥3 diarrhoea (Common Toxicity Criteria). Prediction interval (PI) was calculated as 0.41–1.27. M-H, Mantel–Haenszel meta-analysis method; random, random-effects model; CI, confidence interval, upper and lower ends are displayed within the bracketed region; I^2 represents heterogeneity; the 'P' value in overall effect represents the probability of the overall effect being due to chance; the diamond on the plot represents the pooled odds ratio with its width representing the CIs; the odds ratio of each study, as labelled by its main author, is represented by a square, with a horizontal line demarcating the 95% CIs.
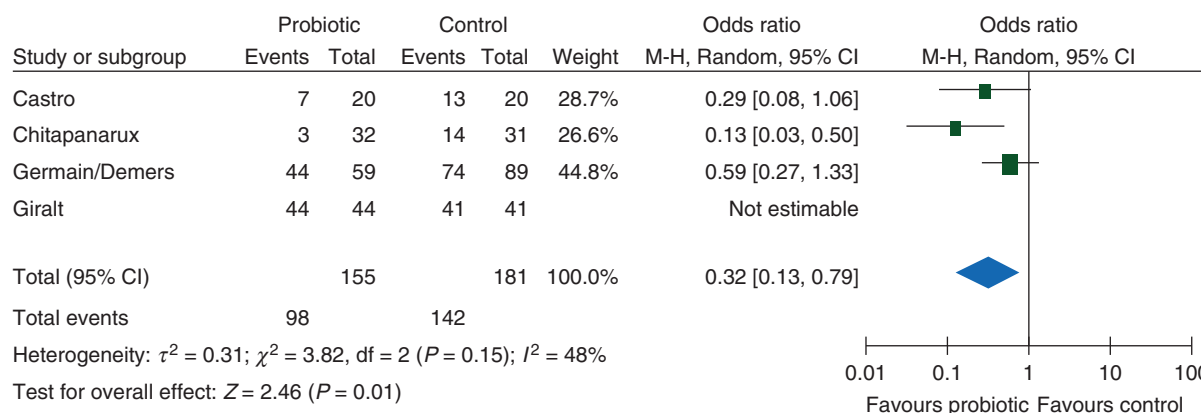
Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Castro	7	20	13	20	28.7%	0.29 [0.08, 1.06]
Chitapanarux	3	32	14	31	26.6%	0.13 [0.03, 0.50]
Germain/Demers	44	59	74	89	44.8%	0.59 [0.27, 1.33]
Giralt	44	44	41	41		Not estimable
Total (95% CI)		155		181	100.0%	0.32 [0.13, 0.79]
Total events	98		142			

Heterogeneity: $\tau^2 = 0.31$; $\chi^2 = 3.82$, df = 2 ($P = 0.15$); $I^2 = 48\%$
Test for overall effect: $Z = 2.46$ ($P = 0.01$)

Figure 5. Forest plot of grade ≥2 diarrhoea (CTC). PI was calculated as 0.11–0.97.

diarrhoea was also reduced (OR = 0.72; 95% CI 0.42–1.25; PI 0.41–1.27; P = 0.24).

Probiotics were also not clearly associated with a decreased use of rescue (anti-diarrhoeal) medication (OR = 0.63; 95% CI 0.27–1.45; PI 0.20–1.99; P = 0.28), but the CI are wide, so firm conclusions cannot be drawn.

Stool consistency reflects the severity/incidence of diarrhoea. This pattern of results suggests that there may be a shift from liquid stools to soft/semi-solid stools when trial participants consumed probiotics. However, the results of these analyses were all statistically non-significant, so while point estimates suggest liquid stools tended to be less common in the probiotic group (OR = 0.46; 95% CI 0.04–5.64; P = 0.55), and soft/semi-solid stools possibly occurred more commonly (OR = 1.91; 95% CI 0.18–20.78; P = 0.60), such assertions are speculative.

In the one study reporting mean number of average daily bowel movements, it showed a reduction with probiotics of −9.60 stools per day (95% CI −10.45 to −8.75; P < 0000.1). Given the lack of studies contributing to these data, it would be unwise to draw firm conclusions based on this result.

The final quantitative result is with regards to a secondary outcome of faecal bacteriological count, which was not studied extensively. Considering the faecal bacteriological composition is important in understanding a scientific basis for any effects of probiotics. Alongside faecal organic acid concentration, it can be used as a surrogate measure to compare changes to the gut flora, which is an important mucosal barrier to infection. These are still important aspects to pursue as they may give some indication into the viability of probiotics and their effectiveness at altering the gut's flora. There is scope for further investigation into this area.

safety

A previous systematic review [3], which included 43 trials on the use of probiotics in acute infectious diarrhoea, reported no AEs attributable to probiotics, but one trial reporting a potentially related mild hypersensitivity reaction. However, people with cancer are more likely to be immunocompromised, so it may be that probiotic-associated infections are more likely in this group.
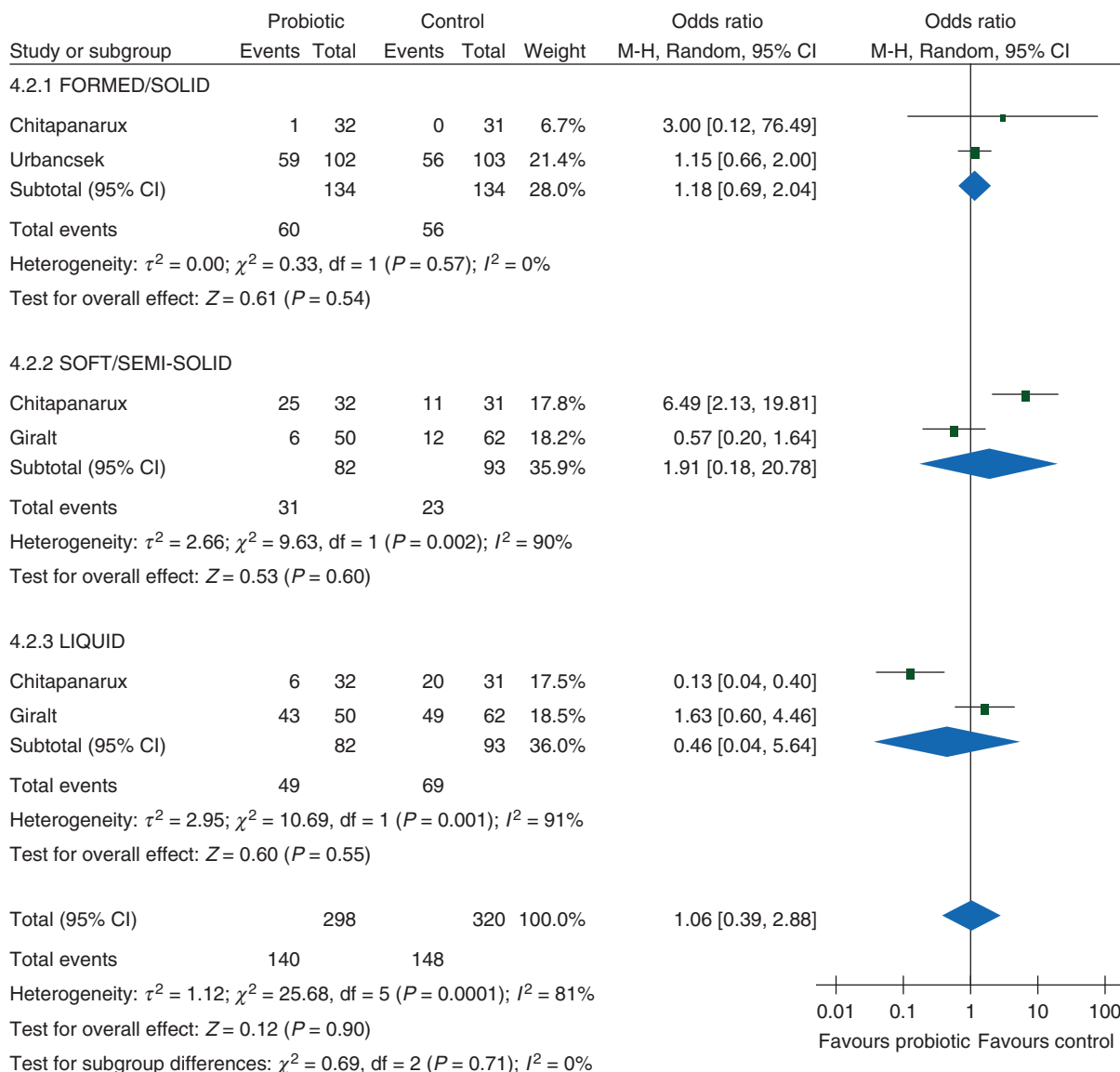
Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI	Odds ratio M-H, Random, 95% CI
4.2.1 FORMED/SOLID							
Chitapanarux	1	32	0	31	6.7%	3.00 [0.12, 76.49]	
Urbancsek	59	102	56	103	21.4%	1.15 [0.66, 2.00]	
Subtotal (95% CI)		134		134	28.0%	1.18 [0.69, 2.04]	
Total events	60		56				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.33$, df = 1 ($P = 0.57$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.61$ ($P = 0.54$)							
4.2.2 SOFT/SEMI-SOLID							
Chitapanarux	25	32	11	31	17.8%	6.49 [2.13, 19.81]	
Giralt	6	50	12	62	18.2%	0.57 [0.20, 1.64]	
Subtotal (95% CI)		82		93	35.9%	1.91 [0.18, 20.78]	
Total events	31		23				
Heterogeneity: $\tau^2 = 2.66$; $\chi^2 = 9.63$, df = 1 ($P = 0.002$); $I^2 = 90\%$							
Test for overall effect: $Z = 0.53$ ($P = 0.60$)							
4.2.3 LIQUID							
Chitapanarux	6	32	20	31	17.5%	0.13 [0.04, 0.40]	
Giralt	43	50	49	62	18.5%	1.63 [0.60, 4.46]	
Subtotal (95% CI)		82		93	36.0%	0.46 [0.04, 5.64]	
Total events	49		69				
Heterogeneity: $\tau^2 = 2.95$; $\chi^2 = 10.69$, df = 1 ($P = 0.001$); $I^2 = 91\%$							
Test for overall effect: $Z = 0.60$ ($P = 0.55$)							
Total (95% CI)		298		320	100.0%	1.06 [0.39, 2.88]	
Total events	140		148				
Heterogeneity: $\tau^2 = 1.12$; $\chi^2 = 25.68$, df = 5 ($P = 0.0001$); $I^2 = 81\%$							
Test for overall effect: $Z = 0.12$ ($P = 0.90$)							
Test for subgroup differences: $\chi^2 = 0.69$, df = 2 ($P = 0.71$); $I^2 = 0\%$							

0.01 0.1 1 10 100
Favours probiotic Favours control

Figure 6. Forest plot of stool consistency.

Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight	Odds ratio M-H, Random, 95% CI	Odds ratio M-H, Random, 95% CI
Chitapanarux	3	32	10	31	21.7%	0.22 [0.05, 0.89]	
Giralt	16	44	12	41	33.6%	1.38 [0.56, 3.43]	
Urbancsek	36	102	50	103	44.6%	0.58 [0.33, 1.01]	
Total (95% CI)		178		175	100.0%	0.63 [0.27, 1.45]	
Total events	55		72				
Heterogeneity: $\tau^2 = 0.33$; $\chi^2 = 5.13$, df = 2 ($P = 0.08$); $I^2 = 61\%$							
Test for overall effect: $Z = 1.09$ ($P = 0.28$)							

0.05 0.2 1 5 20
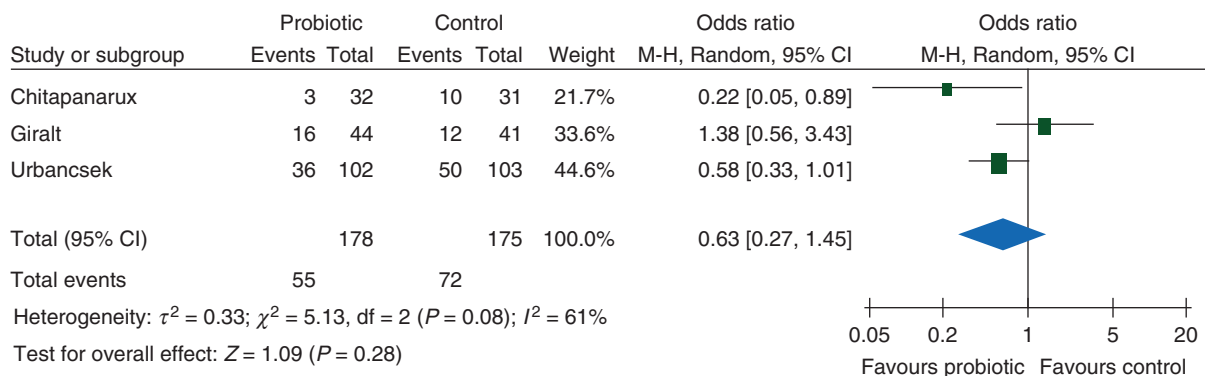Favours probiotic Favours control

Figure 7. Forest plot for use of anti-diarrhoeal (rescue) medication PI was calculated as 0.20–1.99.

Current dietary advice for neutropenic cancer patients is to avoid products containing probiotics, which is based upon bacteraemia case reports and manufacturers' recommendations [9], rather than robust scientific evidence.

The 17 studies assessed in our review included 1530 people (756 people consuming probiotics, 774 people not consuming probiotics). There were 105 AE in those consuming probiotics, and 145 AE in those not consuming probiotics. A wide range of
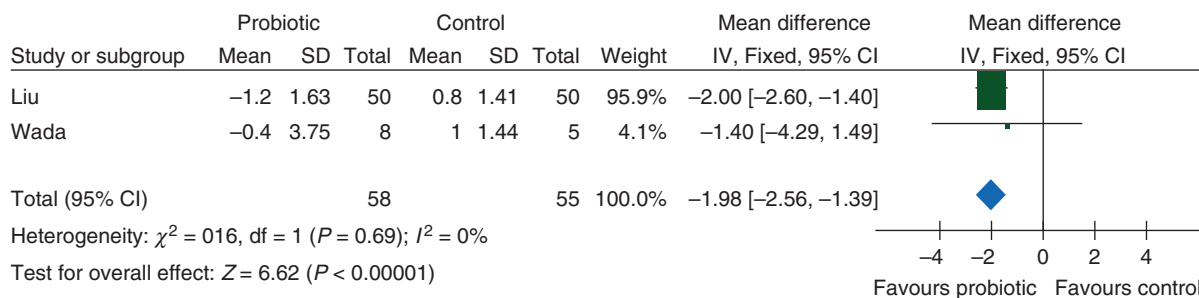
Study or subgroup	Probiotic			Control			Weight	Mean difference IV, Fixed, 95% CI	Mean difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Liu	−1.2	1.63	50	0.8	1.41	50	95.9%	−2.00 [−2.60, −1.40]	
Wada	−0.4	3.75	8	1	1.44	5	4.1%	−1.40 [−4.29, 1.49]	
Total (95% CI)			58			55	100.0%	−1.98 [−2.56, −1.39]	

Heterogeneity: $\chi^2 = 016$, df = 1 ($P = 0.69$); $I^2 = 0\%$

Test for overall effect: $Z = 6.62$ ($P < 0.00001$)

Figure 8. Forest plot for change in enterobacteriaceae count (log10 CFU/g of faeces).

AEs were noted, including: bacteraemia/fungaemia, infection, gastrointestinal symptoms (diarrhoea, constipation, dysphagia, nausea and vomiting), urinary symptoms (only present in patients with transitional cell carcinomas), sicchasia, raised blood pressure and raised intra-cranial pressure. The heterogeneity of the different treatment regimes and malignancies mean we cannot judge which AEs are related to probiotic consumption. A gentleman with CLL and persistent *B. subtilis* on blood cultures died, though his death was attributed to CNS malignant involvement [38]. The concerns around bacteraemia/fungaemia/blood culture growth are significant; although only noted in five case reports [32–34, 36, 38] of the 756 cases described consuming probiotics, this risk needs to be considered alongside any potential benefit.

Streptococcus lactis septicaemia has also been diagnosed in a person with CLL who consumed a non-probiotic yogurt drink [43]. Also, *S. cerevisiae* fungaemia was found in a 48-year-old cancer patient after bone marrow transplantation [44] with no known record of probiotic consumption. Therefore, similar organisms may lead to bacteraemia/fungaemia in patients not known to be consuming probiotics.

further work

The search strategy for the review was robust and broad and included grey literature.

As previously mentioned, 10 ongoing trials were found (Supplementary File 3, available at *Annals of Oncology* online), which should be incorporated into future iterations of this review. No firm conclusions can be drawn from the review currently, but as further studies are completed and become available, they could be incorporated and may give more clinically convincing results. A highly relevant unanswered question is if probiotic use could reduce rates of *Clostridium difficile* infection in people with cancer.

conclusion

This systematic review demonstrates that there is currently insufficient evidence to claim that probiotics are effective and safe in people with cancer. Meta-analyses found that probiotics significantly reduced the incidence of CTC grade ≥2 diarrhoea, may reduce the incidence of CTC grade ≥3 diarrhoea, may reduce the average frequency of daily bowel movements and may reduce the need for anti-diarrhoeal medication, but most of the evidence is not clinically convincing, and they may be a rare cause of sepsis. An effect on faecal bacteriological composition may be found, but this needs to be examined in further trials. Further studies, which are ongoing, need to be evaluated before there can be sufficient confidence regarding these outcomes.

acknowledgements

disclosure

The authors have declared no conflicts of interests.

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