



Meta-analyses

A systematic review and meta-analysis of probiotics for the management of radiation induced bowel disease[☆]Adeel Hamad^{a,b}, Konstantinos C. Fragkos^{a,b}, Alastair Forbes^{a,b,*}^a Centre for Gastroenterology & Clinical Nutrition, University College London, London, United Kingdom^b GI Services, University College London Hospitals, London, United Kingdom

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SUMMARY

Background & aims: A meta-analysis to estimate the efficacy of probiotics in prevention of radiation-induced bowel disease after pelvic radiotherapy has been performed. Previous attempts have arguably failed to provide a comprehensive analysis of clinical trials and their outcomes.

Methods: We searched for studies indexed in Medline, EMBASE, Cochrane Library, and on-line clinical trials registers. There was no language or time limit. Each study was evaluated for methodological quality and outcomes. We identified four outcomes on which to perform meta-analysis: incidence of diarrhoea, loperamide use, watery, and soft stools (Bristol Stool Chart). Odds ratio (OR) was used to compare efficacy, and the pooled OR was estimated using a random effects model; heterogeneity was assessed with Cochran's Q and Higgins I^2 test. Analyses were performed using Review Manager 5.2.

Results: Ten studies were included in our systematic review, of which six were subjected to meta-analysis to compare probiotics against placebo. Quality assessment showed an unclear risk due to incomplete outcome data and lack of performance of intention-to-treat analysis, while blinding and randomization issues were present in certain studies. Pooled results showed heterogeneity (Cochran's Q: $p < 0.05$; I^2 : high). However the pooled OR for the incidence of diarrhoea, synthesized from 6 studies, significantly favoured the use of probiotics over control (OR = 0.44, 95% CI 0.21–0.92). Numerically, but not statistically, probiotics seem to decrease loperamide use (OR = 0.29, 95% CI 0.01–6.80) and the incidence of watery stools (OR = 0.36, 95% CI 0.05–2.81).

Conclusions: In conclusion, probiotic supplementation shows a probable beneficial effect in the prevention, and possible benefit in the treatment, of radiation-induced diarrhoea.

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1. Introduction

Radiation-induced bowel damage was first described in 1897, only a few years after the discovery of radium, in a paper published in the British Medical Journal by David Walsh.¹ The bowel is susceptible to damage during therapeutic irradiation of abdomino-pelvic malignancies as it is located within or very near to the intended radiotherapy field.² Lower gastrointestinal side effects of radiotherapy present as acute toxicity (mainly diarrhoea and bleeding), which is experienced by many patients during or near to the completion of radiotherapy. A recent paper estimates moreover

that 90% of patients develop a permanent, if usually minor, change in their bowel habit.³ Formal chronic radiation bowel disease presents months or years after exposure, and has been reported in up to 20% of patients receiving pelvic radiotherapy.⁴

Historically however, the condition largely failed to attract the attention of either gastroenterologists or oncologists, who often seemed to overlook the impact of post-radiotherapy symptoms on the lives of patients. Fortunately this is changing and oncologists increasingly recognize the need to minimize the risk of radiation injury without compromising the possibility of cure.⁵ This is timely as the number of survivors of pelvic radiotherapy rises (12,000 per annum in the UK),⁶ and increasing numbers of patients with gastrointestinal sequelae of radiotherapy are seen in specialist clinics.^{7–10} Radiation bowel disease is a demanding condition for both the doctor and the patient, remains difficult to manage, and may severely affect quality of life.⁶

Traditional oncology practice incorporates advice on following a low fibre or fibre-free diet during the course of radiotherapy.¹¹ This

Abbreviations: CI, confidence interval; df, degrees of freedom; OR, odds ratio.

[☆] Conference presentation: Some initial results of this study were presented at the 34th ESPEN Congress, Barcelona, Spain, 8–11 September 2012.

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Table 1
Study characteristics.

Study	Year	Design	Participants	Interventions	Outcomes
Probiotics vs placebo or no treatment					
Germain et al. ³⁴	2011	Randomized parallel-group, trial (3 groups), placebo-controlled	Patients with rectal, cervical, endometrial or prostatic cancer were treated between 2006 and 2010 at L'Hotel-Dieu de Quebec (n = 246)	Standard dose probiotics (Biflact 2 caps of 1.3 milliards of <i>Lactobacillus acidophilus</i> and <i>Bifidobacterium longum</i>) vs High dose probiotics (3 caps of 10 milliards) vs placebo	Time of appearance and grade of diarrhoea; other digestive symptoms. No significant difference was found between standard dose and placebo groups for the incidence of grade 3 diarrhoea
Chitapanarux et al. ²⁸	2010	Randomized, double-blind, placebo-controlled study	Patients undergoing pelvic radiotherapy concurrent with weekly cisplatin (n = 63); Age: 18–65 years old, FIGO stage IIB–IIIB squamous cell carcinoma of cervix	Placebo and <i>Lactobacillus acidophilus</i> plus <i>Bifidobacterium bifidum</i> (n = 32) (Infloran®) vs placebo (n = 31)	Incidence of diarrhoea, anti diarrhoea drug used, stool, WCC in stools, red blood cells in stools, median overall time, median weight change
Castro et al. ³³	2009	Double blind placebo controlled trials	Radiation-induced bowel damage patients with gynaecologic cancer (n = 40)	<i>Lactobacillus casei</i> Shirota e o <i>Bifidobacterium breve</i> (n = 20) vs placebo (n = 20)	1) Daily stool consistency (Bristol scale); 2) Diarrhoea: graded weekly according to the common toxicity criteria CTC system Primary endpoint: incidence of diarrhoea, defined by a CTC of 2 or greater, or the need for loperamide
Giralt et al. ²⁷	2008	Double-blind, placebo-controlled, randomized clinical trial in two parallel groups	Female patients (age >18 years) with a diagnosis of endometrial adenocarcinoma requiring post-operative pelvic radiotherapy or advanced cervical squamous cell carcinoma treated with pelvic radiotherapy and concomitant weekly cisplatin (n = 85)	96 mL three times daily of a fermented liquid yogurt containing approximately 108 CFU/g of <i>L. casei</i> DN-114 001, in addition to the standard starters <i>Streptococcus thermophilus</i> and <i>Lactobacillus delbrueckii</i> , subsp. <i>Bulgaricus</i> vs placebo	Incidence of diarrhoea; Incidence of loperamide use; mean time to diarrhoea symptoms; Stool consistency; Median time before loose stools
Delia et al. ²⁶ Note: Two are subpopulations ^{36,37}	2007	Double-blind, randomized, parallel-group, placebo-controlled trial	Patients who underwent adjuvant post-operative radiation therapy after surgery for sigmoid, rectal, or cervical cancer (n = 490)	High-potency probiotic preparation VSL#3 (one sachet t.i.d.) vs placebo starting from first day of radiation therapy	Incidence of diarrhoea; daily bowel movements; mean time to the use of loperamide
Urbancsek et al. ²⁵	2001	Randomized, double-blind, placebo-controlled, parallel-group trial	Cancer patients (19–75 years) developing diarrhoea within 4 weeks after receiving radiotherapy in the abdominal region (n = 205)	Antibiophilus (n = 102) vs placebo (n = 103)	Number of bowel movements; faeces consistency ratings by investigators; patients' self-ratings with regard to diarrhoea grade and faeces consistency
Okawa et al. ³¹	1993	Randomized, parallel-group, controlled trial	Patients with FIGO Stage IIIB squamous cell carcinoma of the uterine cervix who were newly treated with radiation therapy were studied (n = 213)	Radiotherapy + LC9018 (Yakult, prepared from <i>Lactobacillus casei</i>) (n = 102) vs radiotherapy (n = 111) LC9018 was administered intradermally at a dose of 0.1 mg twice a week or 0.2 mg once a week during radiation therapy, and afterwards at 0.1 mg/2 weeks or 0.2 mg/month for 2 years or until tumour recurrence	Incidence of diarrhoea; incidence of abdominal pain
Salminen et al. ³⁰	1988	Randomized parallel group study (with no treatment group)	Patients with diagnosis of cervix or uterus carcinoma (age: 40–75 years) (n = 24)	Dietary counselling (n = 10) vs dietary counselling + daily dose of at least 2 × 10 ⁹ live <i>Lactobacillus acidophilus</i> bacteria in yoghurt-type product (n = 11) (6.5% lactulose was added to yoghurt to support <i>Lactobacillus acidophilus</i> growth in large intestine)	Incidence of diarrhoea, flatulence and loss of appetite
Probiotic vs probiotic					
Henriksson et al. ³²	1995	Randomized, double-blind, parallel-group trial	Patients with chronic bowel discomfort persisting at least 1 year following last session of irradiation. Eligibility criteria: primary diagnosis of carcinoma of the prostate or urinary bladder with a performance status above 90% on the Karnofsky scale	Verum h�alsofil (<i>Lactococcus lactis</i> , <i>Lactococcus cremoris</i>) (n = 20) vs Norriandsfil (<i>L. lactis</i> , <i>L. diacetylactis</i> , <i>Leuconostock</i> , <i>L. cremoris</i>) (n = 40)	Details of bowel action (frequency, stool consistency, pain, occurrence of blood or mucus) and medication other than the test drugs
Timko ²⁹	2010	Randomized, double-blind, parallel-group trial	Radio-oncology patients who had undergone adjuvant post-operative radiation therapy after abdominal and pelvic cancer (n = 42)	"5" Strain Dophilus (twice per day; n = 22) vs Hylak Tropfen Forte (40 drops, three times per day; n = 20). Supplementation started on the first day and lasted until the end of radiation therapy	Incidence and the severity of the radiation-induced diarrhoea

Note: VSL#3: 450 billions/g viable lyophilized bacteria, including four strains of lactobacilli (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*), three strains of bifidobacteria (*B. longum*, *B. breve*, and *B. infantis*), one strain of *Streptococcus salivarius* subsp. *thermophilus*.

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