Bijlage Evidence tabellen en GRADE profielen

VRAAG 1: WAT IS DE BIJDRAGE VAN AANVULLEND ONDERZOEK BIJ PATIËNTEN IN DE PALLIATIEVE FASE MET (VERDENKING OP) DIARREE BIJ HERKENNING VAN BELANGRIJKE OORZAKEN VAN DIARREE?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Khan 2020	• Design: systematic review • Funding: Ipsen; CoI: several authors received sponsorship • Search date: Sep 2018 • Databases: MEDLINE, Embase and the Cochrane Library • Study designs: all • N included studies: N=44 studies	• Eligibility criteria: adults with GEP-NETs who were experiencing diarrhoea	Interventions to diagnose the cause of diarrhoea	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: no comparative evidence • Quality of life: no comparative evidence • Patient satisfaction: no comparative evidence	• Review process by two independent reviewers • Unclear if search restrictions were used • Included relevant studies: no

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; GEP-NET: gastroenteropancreatic neuroendocrine tumours; RCT: randomised controlled trial.

References

Khan MS, Walter T, Buchanan-Hughes A, Worthington E, Keeber L, Feuilly M, et al. Differential diagnosis of diarrhoea in patients with neuroendocrine tumours: A systematic review. World J Gastroenterol. 2020;26(30):4537-56.

VRAAG 2: WELKE VOCHT- EN VOEDINGSINTERVENTIES ZIJN GESCHIKT BIJ HET SYMPTOMATISCH BEHANDELEN VAN DIARREE?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Amiri Khosroshahi 2023	• Design: systematic review of review and meta-analyses • Funding: Students' Scientific Research Center (SSRC) of Tehran University of Medical Sciences (code: IR.TUMS.MEDICINE.REC.1401.163); CoI: none • Search date: Feb 2022 • Databases: PubMed, Scopus, ISI Web of Science • Study designs: SR and MA of RCTs • N included studies: N=13 (with 18 RCTs)	• Eligibility criteria: adults with cancer who were receiving chemotherapy and/or radiotherapy	Probiotic supplementation for the prevention or treatment of chemotherapy and/or radiotherapy-related diarrhoea	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: not reported separately for Urbancsek 2001 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported separately for Urbancsek 2001	• Review process by two independent reviewers • No search restrictions • Included relevant studies: Urbancsek 2001
Andreou 2021	• Design: systematic review • Funding: not reported; CoI: none • Search date: 2020 • Databases: MEDLINE, EMBASE, CINAHL, CENTRAL and Scopus • Study designs: RCTs • N included studies: N=11	• Eligibility criteria: adults ≥18 years, undergoing curative pelvic radiotherapy, receiving a nutritional intervention involving dietary counselling with or without supplements • Exclusion: <18 years, receiving palliative treatment, medically diagnosed gastrointestinal conditions that may impact toxicities (e.g. inflammatory bowel disease, coeliac and stoma), tube-feeding, gastrostomy feeding and parenteral nutrition	Nutritional interventions involving dietary counselling on gastrointestinal toxicities	• No relevant studies identified	• Selection by two independent reviewers • Unclear if data extraction was done by two independent reviewers • Included relevant studies: none
Deleemans 2021	• Design: systematic review • Funding: Enbridge Psychosocial Oncology Research Chair awarded to Dr. Linda Carlson, and by the	• Eligibility criteria: adult cancer patients and survivors; gastrointestinal and/or psychosocial outcomes measured	Prebiotic or probiotic interventions	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: "Occurrence rate of abdominal pain, flatulence and diarrhea on 7 and 14 days post-treatment was significantly lower in treatment group vs controls (p<0 .05)"	• Review process by two independent reviewers • Restricted to English language • Included relevant studies: Shao 2014

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Killam Foundation in the form of a scholarship awarded to Ms. Deleemans; CoI: none • Search date: Sep 2021 • Databases: PubMed, MEDLINE (Ovid), CINHAL, PsychINFO, Web of Science • Study designs: all • N included studies: N=12 (10 RCTs)			• Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	
Fuccio 2009	• Design: systematic review and meta-analysis • Funding: none; CoI: none • Search date: Jan 2009 • Databases: PubMed, EMBASE, Cochrane Library, Google Scholar • Study designs: RCTs • N included studies: N=4	• Eligibility criteria: RCTs with at least 2 parallel groups that evaluated the efficacy of probiotic supplementation in the prevention or treatment of radiation-induced diarrhea	Probiotics	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: ○ Diarrhoea grade: small but statistically significant difference in patients' rating of diarrhoea and feces consistency in favor of probiotic supplementation; however, this difference was not confirmed when the parameter was rated by the investigators ○ Proportion of participants requiring rescue medication for diarrhoea: after 1-week supplementation with probiotics or placebo, less frequently patients in the active group needed antidiarrhoeal drugs; however, the difference between the 2 groups was not statistically significant • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: probiotic supplementation was well-tolerated and only mild-to-moderate, transient, unspecified gastrointestinal problems were reported	• Review process by two independent reviewers • No search restrictions • Included relevant studies: Urbancsek 2001
Hamad 2013	• Design: systematic review • Funding: funding from the Department of Health's NIHR as a Biomedical Research Centre; CoI: none • Search date: June 2012 • Databases: Medline, EMBASE, Cochrane Library • Study designs: RCTs	• Eligibility criteria: humans with radiation-induced diarrhoea	Probiotics	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: not reported separately for Urbancsek 2001 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	• Unclear if selection was done by two independent reviewers • Data extraction by two independent reviewers • No search restrictions • Included relevant studies: Urbancsek 2001

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• N included studies: N=10				
Hassan 2018	• Design: systematic review and meta-analysis • Funding: not reported; CoI: not reported • Search date: Oct 2016 • Databases: Medline, Embase and Allied and Complementary Medicine (AMED) • Study designs: RCTs (for efficacy) • N included studies: N=21	• Eligibility criteria: people diagnosed with cancer who received probiotics as an intervention	Probiotics	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: not reported separately for Urbancsek 2001 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported separately for Urbancsek 2001	• Review process by two independent reviewers • No search restrictions • Included relevant studies: Urbancsek 2001
Henson 2013	• Design: systematic review and meta-analysis • Funding: none; CoI: none • Search date: May 2012 • Databases: Medline, Embase, Central • Study designs: all • N included studies: N=10	• Eligibility criteria: adults aged 18 years or over undergoing radical pelvic radiotherapy (external beam radiotherapy, brachytherapy, or both) as part of anticancer treatment for a primary pelvic malignancy, including gynaecological (cervix or uterus), lower gastrointestinal (rectal or anal) and urological (prostate or bladder) malignancies • Exclusion: patients with stomas and a previous history of inflammatory bowel disease	Nutritional interventions	• No relevant studies identified	• Review process by two independent reviewers • No search restrictions • Included relevant studies: none
Holm 2023	• Design: systematic review • Funding: Faculty of Medicine, Aalborg University, Center for Nutrition and Bowel Failure, Aalborg University Hospital, Aalborg and Research Foundation, The North Denmark Region, Denmark; CoI: none • Search date: Oct 2022 • Databases:	• Eligibility criteria: patients diagnosed with cancer in the pelvic region, who had received EBRT, brachytherapy, with or without chemotherapy, and nutritional intervention aimed at prophylaxis for or improvement of acute radiation-induced diarrhoea • Exclusion: animal studies, studies with fewer than 20 patients, and medical antidiarrheal treatment as the only intervention	Nutritional interventions	• No relevant studies identified	• Review process by independent reviewers • Restriction to English studies • Included relevant studies: none

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• PubMed, Embase, CINAHL, Cochrane Library • Study designs: RCTs and prospective observational studies • N included studies: N=21				
Jolfaie 2015	• Design: systematic review • Funding: Isfahan University of Medical Sciences, Isfahan, Iran; CoI: none • Search date: July 2015 • Databases: PubMed, Google Scholar, Cochrane Library, and SID databases • Study designs: RCTs • N included studies: N=9	• Eligibility criteria: RCTs to investigate the effects of Glutamine intake on several complications of chemotherapy, radiochemotherapy, and postoperation including, diarrhoea, vomiting and T-cell dysfunction in patients with colon and colorectal cancer • Exclusion: animal or in vitro studies	Glutamine	• No relevant studies identified	• Selection by two independent reviewers • Unclear if data extraction was done by two independent reviewers • No search restrictions • Quality assessment with Jadad-scale • Included relevant studies: none
Redman 2014	• Design: systematic review and meta-analysis • Funding: not reported; CoI: none • Search date: Dec 2012 • Databases: Central, Medline, Embase, AMED, DARE • Study designs: RCTs (for efficacy) • N included studies: N=11 RCTs	• Eligibility criteria: people with a diagnosis of cancer who have received probiotics	Probiotics	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: not reported separately for Urbancsek 2001 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported separately for Urbancsek 2001	• Review process by two independent reviewers • No search restrictions • Included relevant studies: Urbancsek 2001
Sun 2012	• Design: systematic review and meta-analysis • Funding: not reported; CoI: none • Search date: not reported • Databases: Embase, MEDLINE, Cochrane Library, BIOSIS • Study designs: RCTs • N included studies: N=8	• Eligibility criteria: patients with chemotherapy-induced diarrhoea	Glutamine	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: ○ Diarrhoea score (vs. placebo): 1.31 vs. 2.82 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	• Unclear if review process was done by two independent reviewers • Restriction to English and Chinese articles • Quality assessment with Jadad-scale • Included relevant studies: Li 2009

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Wei 2018	• Design: systematic review and meta-analysis • Funding: Belgian Health Care Knowledge Centre (KCE); CoI: none • Search date: July 2017 • Databases: Medline, Embase, Central, trial registers • Study designs: RCTs • N included studies: N=12	• Eligibility criteria: adults aged 18 years and over with histologically diagnosed cancer at any stage of disease and receiving chemotherapy or radiotherapy	Probiotics	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: ○ Diarrhoea grade: ▪ Mean: 0.7 for the Antibiophilus group and 1.0 for the placebo group at the end of the study (no significant differences between the two groups) ▪ Patients' self-ratings with regard to diarrhoea grade and faeces consistency showed a difference in treatment-by-time interaction (p<0.001) ○ Time to rescue medication for diarrhoea: MD 13 hours, 95%CI -0.86 to 26.86; 205 participants ○ Proportion of participants requiring rescue medication for diarrhoea: RR 0.74, 95%CI 0.53 to 1.03; 205 participants • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: study authors reported that they observed no serious adverse events and "In the Antibiophilus group, three participants reported mild to moderate gastrointestinal problems; in the placebo group, two participants reported moderate to severe gastrointestinal events, and one patient observed a mild labial oedema; all documented events were of a transient nature; in three patients, symptomatic treatment of adverse events was prescribed"	• Review process by two independent reviewers • No search restrictions • Included relevant studies: Urbancsek 2001

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; MD: mean difference; RCT: randomised controlled trial; RR: relative risk.

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Vraag 3: Wat is het effect van symptomatische medicamenteuze behandeling op het verminderen van diarreeklachten bij patiënten met diarree in de palliatieve fase?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
van de Wetering 2016	• Design: systematic review • Funding: none; CoI: none • Search date: Nov 2015 • Databases: Central, Medline Embase, CancerCD, Science Citation Index, Cinahl • Study designs: RCTs • N included studies: N=16	• Eligibility criteria: people diagnosed with a pelvic malignancy, who had undergone pelvic radiotherapy as part of their treatment schedule (primary radiotherapy, pre- or postoperative radiotherapy, with or without chemotherapy, or as a palliative treatment) and subsequently developed late radiation proctopathy, defined as radiation proctopathy of any grade, continuing from completion of radiotherapy for more than three months, or occurring more than three months after completion of radiotherapy	Non-surgical interventions	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: ○ Cavcic 2000: ▪ Diarrhoea score <2 after 1y: RR 1.44 (95%CI 0.96-2.16) • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	• Review process by two independent reviewers • Included relevant studies: Cavcic 2000 (metronidazole vs. no metronidazole)

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; RCT: randomised controlled trial; RR: relative risk.

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Vraag 4: Wat is het effect van medicamenteuze en niet-medicamenteuze behandeling op tenesmi, loze aandrang of proctalgia fugax bij patiënten in de palliatieve fase?

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Cao 2017	• Design: systematic review + meta-analysis • Funding: not reported; CoI: none • Search date: Apr 2016 • Databases: Embase, Pubmed, The Cochrane Library, CNKI (China National Knowledge Infrastructure) • Study designs: RCTs • N included studies: N=13, of which 2 reporting on tenesmus	• Eligibility criteria: RCTs reporting protective efficacy of glutamine versus placebo in preventing occurrence of radiation enteritis or curative efficacy of glutamine versus placebo in cancer patients with radiation enteritis after receiving pelvic and/or abdominal radiotherapy • Exclusion: animal studies	Glutamine	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: ○ Tenesmus: ▪ Grade 0: OR 1.14, 95%CI 0.34-3.77 ▪ Grade 1: OR 0.92, 95%CI 0.49-1.74 ▪ Grade 2: OR 1.38, 95%CI 0.24-8.03 ▪ Grade 3: OR 1.02, 95%CI 0.14-7.44 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	• Review process by two independent reviewers • Restriction to English and Chinese • Included relevant studies: Kozelsky 2003, Yang 2004
Mueller 2020	• Design: systematic review • Funding: none; CoI: none • Search date: Jan 2017 • Databases: PubMed, Embase • Study designs: all • N included studies: N=20, of which 0 comparative studies	• Eligibility criteria: studies involving patients with rectal or tenesmoid pain secondary to a pelvic malignancy in which the primary outcome was pain management • Exclusion: patients with acute surgery related pain, patients with pain secondary to treatment with chemotherapy or radiation (e.g., radiation proctitis), patients with bony metastasis as the cause of pain, management strategies that aim to reduce tumor burden (chemotherapy, radiation, surgical, and ablation procedures), pain management not a primary outcome of study	Management of malignant rectal pain and tenesmus	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: no comparative data • Quality of life: no comparative data • Patient satisfaction: no comparative data • Adverse events: no comparative data	• Selection process by one reviewer • Restriction to English • No comparative studies included
Ni Laoire 2017	• Design: systematic review • Funding: none; CoI: none • Search date: Apr 2016 • Databases: Medline, Embase, Cochrane Library	• Eligibility criteria: adult patients with tenesmus caused by cancer • Exclusion: disease-modifying interventions (surgery, chemotherapy and radiotherapy)	Palliative interventions for rectal tenesmus	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: no comparative data • Quality of life: no comparative data • Patient satisfaction: no comparative data • Adverse events: no comparative data	• Selection process by one reviewer • No language or time restriction • No comparative studies included

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: all • N included studies: N=9, of which 0 comparative studies				
van de Wetering 2016	• Design: systematic review • Funding: none; CoI: none • Search date: Nov 2015 • Databases: Central, Medline Embase, CancerCD, Science Citation Index, Cinahl • Study designs: RCTs • N included studies: N=16	• Eligibility criteria: people diagnosed with a pelvic malignancy, who had undergone pelvic radiotherapy as part of their treatment schedule (primary radiotherapy, pre- or postoperative radiotherapy, with or without chemotherapy, or as a palliative treatment) and subsequently developed late radiation proctopathy, defined as radiation proctopathy of any grade, continuing from completion of radiotherapy for more than three months, or occurring more than three months after completion of radiotherapy	Non-surgical interventions	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: ○ Nelamangala 2012: symptom score (RPSAS) after treatment 9 (6 to 24) vs. 13 (8 to 27) (p<0.001) ○ Sahakitrungruang 2012: ▪ median decrease in frequency of tenesmus: -2 vs. 0 days/week, p=0.07 ▪ median decrease in frequency of diarrhoea: -2 vs. 0 days/week, p=0.007 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: ○ Nelamangala 2012: mild pain occurred in 33.3% patients in Group 1 during the application of formalin but this subsided within 1 day; there were no complications in Group 2 ○ Sahakitrungruang 2012: anorectal discomfort with gauzes 80%, nausea due to antibiotics 24%	• Review process by two independent reviewers • Included relevant studies: Nelamangala 2012 (enema with sucralfate and steroids vs. formalin 4% gauzes), Sahakitrungruang 2012 (rectal irrigation vs. formalin 4% gauzes)

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Pui 2020	• Design: RCT • Funding: research grant of Universiti Kebangsaan Malaysia (UKM); CoI: none • Setting: single centre, Malaysia • Sample size: N=34 • Duration: Sep 2015 – May 2016	• Eligibility criteria: patients who previously underwent external beam pelvic radiation more than 3 months ago and had hemorrhagic radiation proctitis with at least one rectal bleeding per week • Exclusion criteria: patients with chronic radiation proctitis with major complications like stricture, fistula, deep ulcer and sepsis, patients with hemorrhagic radiation proctitis but need for further surgery,	Rectal irrigation with 1l of clean water, oral ciprofloxacin 2x500 mg/d and oral metronidazole 3x400 mg/d for the first week (N=17) vs. Formalin 4% gauzes dabbed onto affected rectum for 3 minutes using proctoscopy;	CRITICAL OUTCOMES • Diarrhoea, symptom improvement: ○ Diarrhoea: median difference in days/week, 0 vs. 0 days/week, p=0.278 ○ Tenesmus: median difference in days/week, 0 vs. 0 days/week, p=0.043 • Quality of life: not reported • Patient satisfaction: not reported • Adverse events: not reported	Level of evidence: unclear risk of bias • Unclear randomization method and allocation concealment • Blinding not reported, but unlikely

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		chemotherapy or radiotherapy for their primary disease, patients allergic to ciprofloxacin and metronidazole, patients who are given any form of treatment like formalin, APC or steroid therapy within the period of less than 1 month, patients on antigoagulants • *A priori* patient characteristics: ○ M/F: 0/100 ○ Mean age: 56 vs. 62y ○ % Tenesmus: unclear	repeated after 4 weeks (N=17)		

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; OR: odds ratio; RCT: randomised controlled trial; RPSAS: Radiation Proctopathy System Assessments Scale.

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