

ORIGINAL ARTICLE

Nutritional problems and their non-pharmacological treatment in adults undergoing haematopoietic stem cell transplantation—A systematic review

Doris Eglseer¹  | Carola Seymann² | Christa Lohrmann¹ | Manuela Hoedl¹

¹Institute of Nursing Science, Medical University of Graz, Graz, Austria

²Department of Internal Medicine, Haematology University Hospital of Graz, Graz, Austria

Correspondence

Doris Eglseer, Institute of Nursing Science, Medical University of Graz, Universitätsplatz 4, 8010 Graz, Austria.
Email: doris.eglseer@medunigraz.at

Abstract

Objective: This systematic review aimed to identify the most relevant problems related to malnutrition in adult patients undergoing haematopoietic stem cell transplantation (HSCT) and to identify non-pharmacological interventions to treat these problems.

Methods: A systematic search for each research question was performed in MEDLINE, CINAHL, Embase, the Cochrane Library, Google Scholar and reference lists in the period 2009–2019.

Results: Six and nine studies were included respectively. Quantitative pooling of data was not possible due to the heterogeneity of the studies. Oral mucositis (OM), nausea/vomiting, diarrhoea and dysgeusia were the most frequently reported nutritional problems. Cryotherapy and laser therapy seem to be effective in the prevention and treatment of OM. Recommendations for or against the use of mouth rinses and light therapy in the treatment of OM cannot be made, as too few studies have been conducted in this area. The evidence for non-pharmacological treatment options in the case of nausea/vomiting and diarrhoea is rather limited. No study was identified with regard to treatment of dysgeusia.

Conclusion: Nutrition in HSCT patients has not yet been studied to a satisfactory extent. There is an urgent need for high-quality studies to be conducted in this area to optimise the care of patients undergoing haematopoietic stem cell transplantation.

KEYWORDS

cryotherapy, haematopoietic stem cell transplantation, laser therapy, malnutrition, mucositis

1 | INTRODUCTION

Malnutrition is common in patients undergoing haematopoietic stem cell transplantation (HSCT) (Arends et al., 2017; Bassim et al., 2014). Studies have shown that prior to undergoing HSCT, between 10% and 50% of all patients with haematological malignancies are already malnourished, mostly defined by low body mass index (BMI) (Brotelle

et al., 2018; Fuji et al., 2015; Liu, Zhang, Cai, Wang, & Yan, 2012; Rieger, Wischumerski, Rust, & Fiegl, 2015). In addition, around a quarter of the patients experience significant weight loss prior to HSCT (Urbain et al., 2012). During and after the HSCT period, most patients continue to lose weight and their nutritional status deteriorates even further (Rieger et al., 2015; Urbain et al., 2012). Urbain et al. (2012) monitored 105 patients during the post-transplant period

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. *European Journal of Cancer Care* published by John Wiley & Sons Ltd

and found that the BMI of these patients decreased significantly by 11% within the first 100 days after HSCT. Authors of another study reported that more than 55% of the patients who underwent allogeneic HSCT experienced significant weight loss (>5%) and a decrease in BMI of 9.2% until hospital discharge (Rieger et al., 2015).

The causes of weight loss and malnutrition are multifactorial. Side effects of therapies such as chemotherapy (e.g. high-dose melphalan) and radiotherapy administered before HSCT increase the risk of HSCT patients suffering from nutritional problems and malnutrition (Arends et al., 2017; Lalla et al., 2014). Side effects of chemotherapy and radiotherapy include loss of appetite, dry mouth, oral mucositis (OM), nausea, vomiting, altered sense of taste and smell, and gastrointestinal problems (Malihi et al., 2013). In their clinical practice guideline, the American Society for Parenteral and Enteral Nutrition (ASPEN) states that all patients undergoing HSCT with myeloablative conditioning regimens are thus at risk of malnutrition (August & Huhmann, 2009).

In the later stages of treatment, the occurrence of graft-versus-host disease (GvHD) in the gastrointestinal tract, for example, can lead to nutritional problems such as swallowing difficulties, nausea, vomiting, severe diarrhoea, mucositis, loss of appetite or early satiety. These symptoms negatively impact the patients' food and fluid intake (Roberts & Thompson, 2005). Several studies have demonstrated that GvHD is an independent determinant of malnutrition in adults undergoing HSCT (Fuji et al., 2015; Mattsson, Westin, Edlund, & Remberger, 2006; Urbain et al., 2012).

Malnutrition has serious negative consequences in HSCT patients and is associated with a higher susceptibility to bacterial and fungal infections, a greater number of fever days and longer hospital stays (Baumgartner et al., 2016), and with higher mortality and lower overall survival rates (Baumgartner et al., 2017).

Healthcare professionals who work in HSCT units should address patients' nutritional problems early in the process and re-evaluate the patients' nutritional status on a regular basis. To optimise patients' nutrition and nutritional status, multidisciplinary cooperation between staff in different professions, such as dietitians, physicians and nurses, is required (Arends et al., 2017; August & Huhmann, 2009). Therefore, all healthcare professionals need to be aware of the most common nutritional problems affecting adult patients undergoing HSCT and their non-pharmacological therapeutic options.

There are pharmacological and non-pharmacological treatment options for nutritional problems. Non-pharmacological interventions are a major part of nursing, since nursing is a holistic profession that aims to help patients learn to cope with their situation, including their nutritional problems. Non-pharmacological interventions have less side effects and are less costly. Furthermore, some interventions can be performed by the patients themselves even after hospital discharge. Therefore, non-pharmacological interventions are of high relevance for patients.

This systematic review aimed to identify the most relevant problems related to malnutrition in adult patients undergoing HSCT and to identify non-pharmacological interventions that could be used to treat these problems.

Based on the aims of this systematic review, we focused on two research questions:

1. What are the most frequently reported problems relating to malnutrition in adult patients undergoing HSCT?
2. Which non-pharmacological interventions can be conducted in adult patients undergoing HSCT who experience the identified nutritional problems?

2 | METHODS

A systematic review was conducted to systematically collate and summarise the available evidence regarding nutritional problems and their non-pharmacological treatment in adults undergoing HSCT. We carried out a standardised and structured process, following the recommendations stated in the evidence-based Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for transparent reporting of systematic reviews (Moher et al., 2015). There is no protocol available for this systematic review, and it was not registered in a prospective register of systematic reviews.

2.1 | Search strategy

Two systematic literature searches were conducted in April and June 2019 to address each of the research questions. Specific Medical Subject Heading (MeSH) terms and keywords were used to search the MEDLINE database (accessed via the PubMed search engine), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database, the Embase biomedical literature database and the Cochrane Library (accessed via the Ovid research platform). In addition, we used the Google Scholar search engine to identify additional literature and screened the reference lists of relevant identified articles. For the first research question, the following MeSH terms were combined during the search using the Boolean operators "AND" and "OR": "stem cell transplantation", "bone marrow transplantation", "diet, food and nutrition". For the second research question, the MeSH terms "stem cell transplantation", "bone marrow transplantation" and "dysgeusia" were combined with the keywords "management", "treatment", "intervention", "mucositis", "vomiting", "nausea" and "diarrhoea". The conducted searches were restricted to articles written in the English and German languages and published in the period 2009–2019. Regarding the first research question, no restrictions were placed on the study design. Regarding the second research question, the search was restricted to randomised controlled trials (RCTs).

2.2 | Eligibility criteria

To address the first research question, studies were included if they met the following criteria: (a) the study population consisted of adults (≥ 18) and patients undergoing HSCT (either allogeneic or autologous), (b) nutritional problems were covered, and (d) the study

was conducted in a hospital setting. Studies that referred to mesenchymal stem cell transplantation were excluded; haematopoietic stem cells differ from mesenchymal stem cells, as the latter are not significantly involved in the formation of blood cells.

To address the second research question, studies were included if they met the following inclusion criteria: (a) the study covered one of the nutritional problems identified while conducting the literature review to address the first research question (i.e. mucositis, nausea/vomiting, diarrhoea, dysgeusia), (b) the study population consisted of adults (≥ 18) undergoing stem cell transplantation (either allogeneic or autologous), (c) non-pharmacological interventions were covered, and (d) the study was conducted in a hospital setting. Pilot studies and studies including pharmacological interventions were excluded. Studies covering nutritional supplements were also excluded, as these must be prescribed by a physician in most countries.

2.3 | Study selection

After removing duplicate records, the titles and abstracts of the identified relevant articles were screened. The articles were selected for further analysis if they met the eligibility criteria as described above. After screening the full texts of the remaining studies, two researchers (C.S. and D.E.) independently appraised the quality of the studies and the risk of bias. Therefore, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (von Elm

et al., 2014) and the internationally recognised appraisal tool from the Oxford Centre for Evidence-based Medicine (Oxford, 2019) for randomised, controlled studies were used. Discrepancies were discussed until a consensus was reached between the researchers. The flow chart shows the process used to select studies relevant to the second research question (Figure 1).

2.4 | Data extraction

Data were independently extracted by two authors (C.S. and D.E.) using a template that included the categories: first author, year of publication, country of publication, sample size, interventions in the two groups (intervention/control), main outcomes, instrument(s) used to measure the outcome(s) and main results. Tables 1 and 2 show detailed information extracted from the individual studies.

3 | RESULTS

3.1 | Description of the identified studies

To address the first research question, namely what are the most frequently reported problems relating to malnutrition in adult patients undergoing HSCT, six studies were identified as relevant.

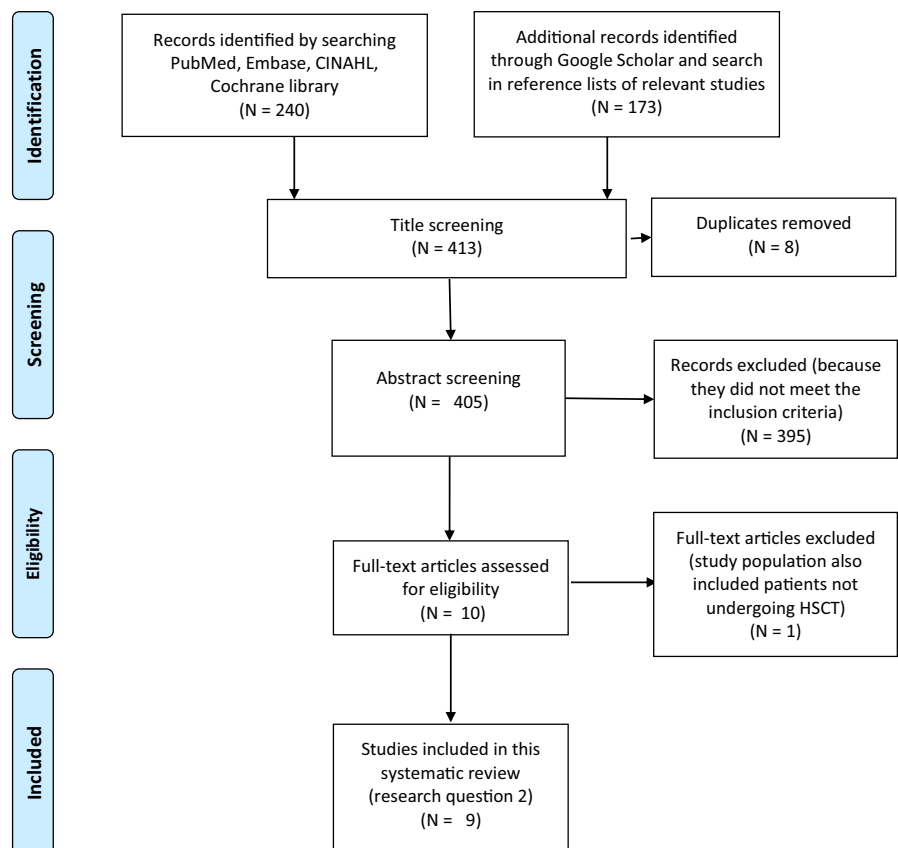


FIGURE 1 Flow diagram showing the process used to select included randomised controlled trials (RCTs) on the basis of the PRISMA scheme (Moher et al., 2015)

TABLE 1 RCTs on the effectiveness of different non-pharmacological interventions for oral mucositis (OM)

Author (year)	Country	N	Nutritional problem addressed	Intervention	Control	Outcomes	Treatment duration	Instrument to measure the outcome(s)	Results
Askarifar et al. (2016)	Iran	29	Mucositis	Cryotherapy (ice cubes) before, during and after chemotherapy	Saline mouth rinses	OM severity	2 times a day, 30 min	WHO Scale	<p>p-values and effect sizes (IG vs. CG)</p> <p>Significant effect in OM severity after 7 days ($p = 0.04$) and after 14 days ($p < 0.01$) but not after 3 days ($p = 0.112$)</p> <p>Mean score WHO scale for OM severity after 7 days 1.81 (SD 0.83) vs. 2.54 (SD 0.87) and after 14 days 0.13 (SD 0.08) vs. 0.92 (SD 0.08)</p>
Johansson et al. (2019)	Sweden	94	Mucositis	Cryotherapy (7 hr) (crushed ice) before and during chemotherapy	Cryotherapy (2 hr)	OM incidence	2 hr or 7 hr	WHO Scale	<p>No significant difference in 7-hr cryotherapy vs. 2-hr cryotherapy in incidence of grade 3 and grade 4 OM ($p = 0.98$)</p> <p>Incidence of OM grade 3 and 4 was 2% vs. 4%</p>
Braga et al. (2015)	Brazil	40	Mucositis	Herbal mouth rinse (<i>Matricaria chamomilla</i>) (3 different dosages: 0.5%, 1%, 2%)	Standard care	OM incidence, OM severity, OM duration	2 times a day, 1 hr before meals for 1 min	WHO Scale	<p>Significant effect in OM incidence, severity and duration for dosage 1% <i>Matricaria chamomilla</i> ($p = 0.01$) but not for dosages 0.5% and 2%</p> <p>Incidence of OM was 30% vs. 90%; mean score WHO scale for OM severity 0.7 (SD 1.1) vs. 2.1 (SD 1.1); mean duration of OM 1.9 (SD 3.4) vs. 5.7 (SD 4.0)</p>
Tavakoli Ardakani et al. (2016)	Iran	60	Mucositis	Herbal mouth rinse (<i>Mentha piperita</i> and <i>Matricaria chamomilla</i>)	Placebo	OM incidence, OM severity, OM duration	3 times a day, 30 s, for 1 week	NCICTC Scale	<p>Significant effect in OM severity (maximum grade of OM: $p = 0.006$; average daily grade of OM: $p = 0.04$) and duration of OM ($p < 0.0001$) but not in mucositis incidence</p> <p>Incidence of OM 20% vs. 30%; mean score NCICTC scale for the average daily OM grade 1.54 (SD 0.44) vs. 1.83 (SD 0.49); mean duration of OM 5.6 (SD 5.0) days vs. 11.3 (SD 6.7)</p>
Elad et al. (2011)	Israel	20	Mucositis	Visible light therapy	Placebo	OM severity, OM incidence	5 times a week	WHO Scale	<p>Significant effect in OM severity ($p = 0.01$) and incidence ($p = 0.02$) one week after HSCT but not at other time points</p> <p>Mean score WHO scale for OM severity 0.5 (SD 0.9) vs. 2.0 (SD 1.1); incidence of OM 40% vs. 80%</p>
Silva et al. (2011)	Brazil	42	Mucositis	Laser therapy	Standard care	OM incidence, OM severity	Once a day, 3 s. per laser point	WHO Scale	<p>Significant effect in OM incidence and OM severity ($p < 0.001$). Incidence of OM 33% vs. 95%. No exact data for OM severity reported</p>
Silva et al. (2015)	Brazil	30	Mucositis	Laser therapy	Standard care	OM incidence, OM severity, duration	Once a day	WHO Scale	<p>Significant effect in OM incidence and severity 4 days ($p = 0.01$), 7 days ($p = 0.04$) and 8 days ($p = 0.04$) after HSCT (not at other time points) and mucositis duration ($p = 0.0001$)</p> <p>Incidence of OM 27% vs. 97%; mean duration of OM 1.1 vs. 5.4 days. No exact data for OM severity reported</p>

Abbreviations: HSCT, haematopoietic stem cell transplantation; NCICTC Scale, National Cancer Institute Common Toxicity Criteria mucositis scale; OM, oral mucositis; WHO scale, WHO oral mucositis grading scale.

TABLE 2 RCTs on the effectiveness of different non-pharmacological interventions for nausea/diarrhoea

Author (year)	Country	N	Nutritional problem addressed	Intervention	Control	Outcome Measurement	Treatment duration	Results
Jarden et al. (2009)	Denmark	42	Diarrhoea/ Nausea	Multimodal programme (exercise, relaxation, psychoeducation), 4–6 weeks	Standard care	Items of the EORTC QLQ-C30	5 times a week, for 1 hr	Significant effect in diarrhoea ($p = 0.014$), but only directly after treatment and not after 3 and 6 months. No significant effect in nausea and incidence of diarrhoea directly after treatment: 20% vs. 41%; Incidence of nausea directly after treatment: 15% vs. 25%
Bates et al. (2017)	USA	82	Nausea	Music therapy	Standard care	VAS	2 sessions, each lasting 30 min	Significant effect in nausea in favour of the control group after 7 days ($p = 0.035$) but not at other time points (after 1 and 5 days) Mean VAS score after 7 days: 2.1 vs. 1.1

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; HSCT, haematopoietic stem cell transplantation; VAS, Visual Analogue Scale.

These were observational studies with sample sizes ranging from 28 patients to 822 patients (Aoyama et al. $n = 28$, Ferreira et al. $n = 64$, Krawczyk et al. $n = 100$, Okada et al. $n = 48$ patients, Trifilio et al. $n = 822$, Urbain et al. $n = 105$). The most frequently reported nutritional problems described in these studies for patients undergoing HSCT were mucositis (4%–93%), nausea/vomiting (11%–100%), diarrhoea (70%–83%) and dysgeusia (taste disorder, 14%–22%) (Aoyama et al., 2018; Ferreira, Guerra, Baluz, de Resende Furtado, & da Silva Bouzas, 2014; Krawczyk, Kraj, Korta, & Wiktor-Jedrzejczak, 2017; Okada et al., 2016; Trifilio, Pi, & Mehta, 2013; Urbain et al., 2012).

Nine RCTs were included to address the second research question, namely which non-pharmacological interventions can be conducted in patients undergoing HSCT who experience the identified problems. The largest number of studies was found for the non-pharmacological treatment of mucositis ($n = 7$). Interventions examined in the studies were cryotherapy ($n = 2$), mouthwash with herbs ($n = 2$), laser therapy ($n = 2$) and light therapy ($n = 1$). Music therapy ($n = 1$) was examined with regard to impact on nausea and vomiting. One study assessed the effectiveness of a multimodal intervention (exercise, relaxation, psychoeducation) on the quality of life of patients undergoing HSCT with the EORTC QLQ-C30 questionnaire, in which nausea/vomiting and diarrhoea were cited as symptoms ($n = 1$). No study was identified that dealt with non-pharmacological interventions used in overcoming dysgeusia.

Due to the heterogeneity of the identified studies in terms of the variable types of interventions used, outcomes and follow-up times, it was not possible to pool the data in a meta-analysis. At most, two studies were identified in which the same intervention was examined, a finding that implied that it would be better not to summarise these results statistically (Borenstein, Hedges, Higgins, & Rothstein, 2011).

3.2 | Study quality

The risk of bias in the included studies was high in the observational studies, which is mainly attributable to the cross-sectional and, in half of the studies, the retrospective study design. The authors described hardly any efforts to address potential sources of bias and the sample sizes varied widely (from 28 to 822). The risk of bias for most of the RCTs was rather low. Table 3 provides an overview of the risk of bias in the included RCTs.

3.3 | Oral mucositis (OM)

Of the six RCTs that included OM treatment, two investigated the effects of cryotherapy during chemotherapy in patients undergoing HSCT (Askarifar, Lakdzaji, Ramzi, Rahmani, & Jabbarzadeh, 2016; Johansson et al., 2019). Askarifar et al. compared cryotherapy treatment with a standard saline mouthwash treatment. They found that OM severity decreased in the case of both treatments, but cryotherapy was significantly more effective. The results of the cryotherapy and the saline mouthwash groups differed significantly after 7 ($p = 0.03$) and 14 days ($p < 0.01$) but not after 3 days (Askarifar

Author	Randomisation	Similar groups	Equal treatment	Equal analysis	Blinding
Tavakoli Ardakani et al. (2016)	Yes	Yes	Yes	No	No
Askarifar et al. (2016)	Yes	Yes	Yes	Yes	Unclear
Bates et al. (2017)	Yes	Yes	Yes	No	No
Braga et al. (2015)	Yes	Yes	Yes	Yes	Unclear
Elad et al. (2011)	Yes	Yes	Yes	Yes	Yes
Jarden et al. (2009)	Yes	Yes	Yes	Yes	No
Johansson et al. (2019)	Yes	Yes	Yes	Yes	Unclear
Silva et al. (2011)	Yes	Yes	Unclear	Yes	Patients: no Investigators: yes
Silva et al. (2015)	Yes	Yes	Yes	No	Patients: no Investigators: yes

TABLE 3 Risk of bias of the included studies based on the critical appraisal sheet from the Centre for Evidence-Based Medicine at the University of Oxford (University of Oxford, 2019)

et al., 2016). Johansson et al. (2019) compared two different durations of cryotherapy and demonstrated that two hours of treatment were as effective as seven hours to prevent severe OM in patients undergoing chemotherapy before autologous HSCT.

Two studies assessed the effectiveness of herbal mouth rinses. Treatment with herbal mouth rinses containing 1% *Matricaria chamomilla* (chamomile) extract leads to significantly lower OM incidence ($p = 0.01$), lower OM severity ($p = 0.01$) and lower OM duration (1.9 days vs. 5.7 days, $p = 0.01$), as compared to treatment with standard care products (Braga et al., 2015). Treatment with herbal mouth rinses containing 0.5% or 2% *Matricaria chamomilla* extract did not show significant effects (Braga et al., 2015). Treatment with herbal mouth rinses containing *Matricaria chamomilla* and *Mentha piperita* (peppermint) extracts had significant effects with regard to OM severity ($p = 0.04$) and OM duration ($p < 0.01$) but had no significant impact on OM incidence.

Visible light therapy uses wavelengths of light in the spectra of 300–800 nm. This therapy option is associated with lower costs than, that is the use of laser therapy. The effectiveness of visible light therapy was investigated in one study and compared to the effectiveness of placebo therapy. Significant improvements were found with regard to OM severity ($p = 0.01$) and incidence ($p = 0.02$) for visible light therapy one week after HSCT but not at other time points. Laser therapy was found to be effective in significantly reducing OM incidence and severity in two studies (Silva, Mendonca, Bariani, Antunes, & Silva, 2011; Silva et al., 2015) and OM duration in one study (Silva et al., 2015).

3.4 | Nausea/Diarrhoea

Three studies were identified that addressed interventions used to treat nausea or diarrhoea in HSCT patients. Jarden et al. tested

a multimodal programme (exercise, relaxation, psychoeducation) to improve quality of life. To measure this outcome, the European Organisation for Research and Treatment of Cancer Quality-Of-Life Questionnaire Core 30 (EORTC QLQ-C30) was used, which includes diarrhoea and nausea. The programme had a positive short-term effect on diarrhoea ($p = 0.014$) but no effect at all on nausea (Jarden, Baadsgaard, Hovgaard, Boesen, & Adamsen, 2009). One study investigated the impact of music therapy on nausea and found a significant difference with regard to the nausea score in favour of the control group after 7 days ($p = 0.035$), but no differences were observed at other time points (after 1 and 5 days) (Bates et al., 2017).

3.5 | Dysgeusia

No study was identified that dealt with non-pharmacological interventions used to overcome dysgeusia.

4 | DISCUSSION

The most frequently reported problems with consequences for nutritional intake faced by patients undergoing HSCT were oral mucositis, nausea/vomiting, diarrhoea and dysgeusia. In general, we identified only few studies that specifically addressed patients undergoing haematological stem cell transplantation (HSCT), although these belong to a high-risk group of patients who experience nutritional problems before, during and after the transplantation period (Arends et al., 2017).

Another systematic review confirmed the hypothesis that OM is a troublesome problem that has a major impact on HSCT patients' eating and drinking habits. The incidence rates of OM among these

patients can be up to 80% (Chaudhry et al., 2016). Despite this high prevalence and the serious consequences of OM (e.g. severe pain, interruptions in therapies and malnutrition), we only identified six studies that addressed the non-pharmacological treatment of oral mucositis in this patient group. Four different non-pharmacological interventions were mentioned in these studies, namely cryotherapy implemented with ice cubes, two different herbal mouth rinses, and laser and light therapies. The results of these studies indicate that it is possible to reduce OM incidence, severity and duration by applying relatively simple treatments. The use of cryotherapy during chemotherapy and of herbal mouth rinses and light and laser therapies had statistically significant positive effects on the incidence and severity of OM in this patient group. These positive effects are not only statistically significant but also clinically relevant. For example, the studies focusing on interventions such as the use of herbal mouth rinses and laser therapy showed that OM duration was reduced by 4–5 days compared to the controls (Braga et al., 2015; Silva et al., 2015; Tavakoli Ardakani et al., 2016). Insufficient nutritional intake for a further 4–5 days due to OM contributes significantly to the deterioration of nutritional status in this vulnerable patient group and increases the risk of malnutrition. These findings correlate with those of another systematic review on the prevention and treatment of OM in adult patients undergoing chemotherapy or radiotherapy (Daugelaite, Uzkuiraityte, Jagelaviciene, & Filipauskas, 2019). The authors concluded that besides pharmacological interventions, laser therapy, cryotherapy and professional oral hygiene are successful interventions that may be used in OM prevention and treatment (Daugelaite et al., 2019).

The authors of a Cochrane review published in 2015 also suggested that cryotherapy reduces OM in patients undergoing HSCT who receive high-dose melphalan-based chemotherapy, although the effect size may not be as large as it is in patients with solid cancers (Riley et al., 2015). Johansson et al. showed that a two-hour cryotherapy session has the same effect as a session lasting seven hours (Johansson et al., 2019). Furthermore, clinical practice guidelines for the management of OM in cancer patients also suggest that cryotherapy treatment should be used to prevent OM in patients who are receiving chemotherapy, with or without total body irradiation, as conditioning for HSCT (Lalla et al., 2014).

The clinical practice guidelines for oral mucositis from the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) do not include a recommendation for or against the use of herbal mouth rinses (Lalla et al., 2014). We identified two studies, published after publication of the MASCC/ISOO guidelines, that cited positive effects when chamomile and peppermint/chamomile mouth rinses were used (Braga et al., 2015; Tavakoli Ardakani et al., 2016). However, Braga et al. found significant effects in terms of OM incidence, severity and duration, but only at extract dosages of 1% and not for extract dosages of 0.5% or 2% (Braga et al., 2015). This leaves room for discussion regarding adequate dosages of these extracts. However, as this study was a phase II RCT, the sample size was rather small and the results must be interpreted with care. At this time, far too few

studies have been conducted on the basis of which specific recommendations for or against the use of particular herbal mouth rinses can be made.

Low-level laser therapy seems to be an effective treatment option for oral mucositis. The two studies included in our systematic review that addressed the effectiveness of laser therapy found convincing results with regard to improvements in OM incidence, severity and duration in HSCT patients (Silva et al., 2011; Silva et al., 2015). These findings are supported by those of a recently published systematic review and meta-analysis. The authors of this review found that low-level laser treatment effectively reduced the duration of mucositis in general cancer patients; the time required to completely resolve mucositis in these patients was reduced by an average of 4.2 days as compared to the time required in a control group (Anschau, Webster, Capra, de Azeredo da Silva, & Stein, 2019). The MASCC/ISOO clinical practice guidelines also recommend the use of low-level laser therapy to *prevent* OM in HSCT patients (Lalla et al., 2014), but they only include studies published up until 2013.

The number of studies in which the management of nausea/vomiting or diarrhoea in HSCT patients has been investigated is unsatisfactory and unfortunately does not allow us to derive recommendations for treatment options. A recently published article summarised the results of several systematic reviews related to nausea and vomiting in advanced cancer patients (Walsh et al., 2017). This article mainly included information about pharmacological treatment (antiemetics) and cited few non-pharmacological intervention studies, although the authors stated that such interventions play an important role and should therefore also be addressed in future studies. Taste and smell disorders are troublesome conditions for cancer patients (Belqaid, Tishelman, Orrevall, Mansson-Brahme, & Bernhardson, 2018). No RCT addressing this important topic in HSCT patients was identified, although the prevalence of these disorders can reach up to nearly 80% in cancer patients undergoing chemotherapy and such disorders increase the risk of malnutrition (Amezaga et al., 2018; Cohen, Wakefield, & Laing, 2016; Okada et al., 2016).

This systematic review provides an overview of current evidence about nutritional problems suffered by patients undergoing haematopoietic stem cell transplantation and their non-pharmacological treatment options. However, the results of this systematic review must be interpreted with care. Most of the studies included low numbers of patients and had therefore limited power to detect possible effects. The comparability of the extracted data included in this study is limited due to differences regarding the type of intervention, follow-up times and outcomes. Because the results of the individual studies were provided in heterogeneous ways, the comparison and summary of these results had to be performed carefully. Quantitative pooling of the data was impossible. None of the studies investigated showed actual changes in nutritional status. The outcomes in the selected papers are potential mediators of malnutrition and may be associated with improved nutritional status. However, within the included studies, there were no reported adverse effects, which speaks for the application of the interventions. Within the single studies, it

was possible to identify performance and/or detection bias due to the fact that most of the included studies were not blinded. On review level, it is possible that we might not have identified all relevant studies as we, for example, did not search for grey literature.

In general, only a limited number of studies addressing nutritional status, nutritional problems and non-pharmacological treatment options of these problems in HSCT patients were identified. Malnutrition is a major problem experienced by all cancer patients, and especially by patients undergoing HSCT and preconditioning regimes such as chemotherapy and/or radiotherapy (Baumgartner et al., 2017). Since malnutrition is a prognostic indicator and is strongly associated with mortality and worse clinical outcomes, it is of the utmost importance that nutritional problems be addressed at an early stage (Baumgartner et al., 2016). The studies included in this systematic review did not reveal any significant side effects of the non-pharmacological therapies, which implies that the interventions are safe and probably have less side effects than pharmacological interventions. Therefore, non-pharmacological treatment options for nutritional problems are of great interest to both practitioners in this field and patients, and we thus strongly recommend conducting more high-quality studies in this field.

For clinical practice, the results of this systematic review revealed several non-pharmacological treatment options for nutritional problems. Especially, the results about cryotherapy, herbal mouth rinses (with *Matricaria chamomilla* or *Mentha piperita* and *Matricaria chamomilla*) and laser or light therapy reported significant improvements in the incidence, severity and duration of oral mucositis. Therefore, it can be recommended that these interventions be integrated into daily nursing practice, since these interventions have a low risk for adverse events compared to pharmacological interventions.

5 | CONCLUSIONS

In conclusion, patients undergoing HSCT face several nutritional problems, such as mucositis, nausea, vomiting, diarrhoea or dysgeusia. Subsequently, these problems have a major impact on their food and fluid intake, leading in turn to a significant risk of malnutrition. Evidence that supports the use of cryotherapy and laser therapy in the prevention and treatment of oral mucositis in HSCT patients seems to be convincing. In general, nutritional status and non-pharmacological interventions to reduce nutritional problems in HSCT patients have not yet been studied to a satisfactory extent. High-quality studies urgently need to be conducted to explore new non-pharmacological treatment options and optimise the care of patients undergoing haematopoietic stem cell transplantation.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. All authors meet the criteria for authorship and have approved the final article, and all those entitled to authorship are listed as authors. The material has not been submitted for publication elsewhere while under consideration.

ORCID

Doris Eglseer  <https://orcid.org/0000-0002-9739-7555>

REFERENCES

- Amezaga, J., Alfaro, B., Rios, Y., Larraioz, A., Ugartemendia, G., Urruticoechea, A., & Tueros, I. (2018). Assessing taste and smell alterations in cancer patients undergoing chemotherapy according to treatment. *Supportive Care in Cancer*, 26(12), 4077–4086. <https://doi.org/10.1007/s00520-018-4277-z>
- Anschau, F., Webster, J., Capra, M. E. Z., de Azeredo da Silva, A. L. F., & Stein, A. T. (2019). Efficacy of low-level laser for treatment of cancer oral mucositis: A systematic review and meta-analysis. *Lasers in Medical Science*, 34(6), 1053–1062. <https://doi.org/10.1007/s10103-019-02722-7>
- Aoyama, T., Imataki, O., Arai, H., Kume, T., Shiozaki, H., Katsumata, N., ... Ikeda, T. (2018). Comparison of nutrition-related adverse events and clinical outcomes between ICE (Ifosfamide, Carboplatin, and Etoposide) and MCEC (Ranimustine, Carboplatin, Etoposide, and Cyclophosphamide) therapies as pretreatment for autologous peripheral blood stem cell transplantation in patients with malignant lymphoma. *Medical Science Monitor Basic Research*, 24, 31–39. <https://doi.org/10.12659/msmbr.908113>
- Arends, J., Baracos, V., Bertz, H., Bozzetti, F., Calder, P. C., Deutz, N., ... Weimann, A. (2017). ESPEN expert group recommendations for action against cancer-related malnutrition. *Clinical Nutrition*, 36(5), 1187–1196. <https://doi.org/10.1016/j.clnu.2017.06.017>
- Askarifar, M., Lakdizaji, S., Ramzi, M., Rahmani, A., & Jabbarzadeh, F. (2016). The effects of oral cryotherapy on chemotherapy-induced oral mucositis in patients undergoing autologous transplantation of blood stem cells: A clinical trial. *Iranian Red Crescent Medical Journal*, 18(4), e24775. <https://doi.org/10.5812/ircmj.24775>
- August, D. A., & Huhmann, M. B. (2009). A.S.P.E.N. clinical guidelines: Nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *Journal of Parenteral and Enteral Nutrition*, 33(5), 472–500. <https://doi.org/10.1177/0148607109341804>
- Bassim, C. W., Fassil, H., Dobbin, M., Steinberg, S. M., Baird, K., Cole, K., ... Pavletic, S. Z. (2014). Malnutrition in patients with chronic GVHD. *Bone Marrow Transplantation*, 49(10), 1300–1306. <https://doi.org/10.1038/bmt.2014.145>
- Bates, D., Bolwell, B., Majhail, N. S., Rybicki, L., Yurch, M., Abounader, D., ... Liu, H. D. (2017). Music therapy for symptom management after autologous stem cell transplantation: Results from a randomized study. *Biology of Blood and Marrow Transplantation*, 23(9), 1567–1572. <https://doi.org/10.1016/j.bbmt.2017.05.015>
- Baumgartner, A., Bargetzi, A., Zueger, N., Bargetzi, M., Medinger, M., Bounoure, L., ... Schuetz, P. (2017). Revisiting nutritional support for allogeneic hematologic stem cell transplantation—a systematic review. *Bone Marrow Transplantation*, 52(4), 506–513. <https://doi.org/10.1038/bmt.2016.310>
- Baumgartner, A., Zueger, N., Bargetzi, A., Medinger, M., Passweg, J. R., Stanga, Z., ... Schuetz, P. (2016). Association of nutritional parameters with clinical outcomes in patients with acute myeloid leukemia undergoing haematopoietic stem cell transplantation. *Annals of Nutrition & Metabolism*, 69(2), 89–98. <https://doi.org/10.1159/000449451>
- Belqaid, K., Tishelman, C., Orreval, Y., Mansson-Brahme, E., & Bernhardson, B. M. (2018). Dealing with taste and smell alterations—A qualitative interview study of people treated for lung cancer. *PLoS One*, 13(1), e0191117. <https://doi.org/10.1371/journal.pone.0191117>
- Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2011). *Introduction to meta-analysis*. Chichester, GB: John Wiley & Sons.

- Braga, F. T., Santos, A. C., Bueno, P. C., Silveira, R. C., Santos, C. B., Bastos, J. K., & Carvalho, E. C. (2015). Use of *Chamomilla recutita* in the prevention and treatment of oral mucositis in patients undergoing hematopoietic stem cell transplantation: A randomized, controlled. Phase II clinical trial. *Cancer Nursing*, 38(4), 322–329. <https://doi.org/10.1097/ncc.000000000000194>
- Brotelle, T., Lemal, R., Cabrespine, A., Combal, C., Hermet, E., Ravinet, A., ... Bouteloup, C. (2018). Prevalence of malnutrition in adult patients previously treated with allogeneic hematopoietic stem cell transplantation. *Clinical Nutrition*, 37(2), 739–745. <https://doi.org/10.1016/j.clnu.2017.03.016>
- Chaudhry, H. M., Bruce, A. J., Wolf, R. C., Litzow, M. R., Hogan, W. J., Patnaik, M. S., ... Hashmi, S. K. (2016). The incidence and severity of oral mucositis among allogeneic hematopoietic stem cell transplantation patients: A systematic review. *Biology of Blood and Marrow Transplantation*, 22(4), 605–616. <https://doi.org/10.1016/j.bbmt.2015.09.014>
- Cohen, J., Wakefield, C. E., & Laing, D. G. (2016). Smell and taste disorders resulting from cancer and chemotherapy. *Current Pharmaceutical Design*, 22(15), 2253–2263. <https://doi.org/10.2174/1381612822666160216150812>
- Daugelaite, G., Uzkuraityte, K., Jagelaviciene, E., & Filipauskas, A. (2019). Prevention and treatment of chemotherapy and radiotherapy induced oral mucositis. *Medicina (Kaunas)*, 55(2), 1–14. <https://doi.org/10.3390/medicina55020025>
- Elad, S., Luboshitz-Shon, N., Cohen, T., Wainchwaig, E., Shapira, M. Y., Resnick, I. B., et al. (2011). A randomized controlled trial of visible-light therapy for the prevention of oral mucositis. *Oral Oncol*, 47(2), 125–130. <https://doi.org/10.1016/j.oraloncology.2010.11.013>. [Epub ahead of print].
- Ferreira, E. E., Guerra, D. C., Baluz, K., de Resende Furtado, W., & da Silva Bouzas, L. F. (2014). Nutritional status of patients submitted to transplantation of allogeneic hematopoietic stem cells: A retrospective study. *Revista Brasileira De Hematologia E Hemoterapia*, 36(6), 414–419. <https://doi.org/10.1016/j.bjhh.2014.07.014>
- Fuji, S., Mori, T., Khattry, N., Cheng, J., Do, Y. R., Yakushijin, K., ... Kim, S.-W. (2015). Severe weight loss in 3 months after allogeneic hematopoietic SCT was associated with an increased risk of subsequent non-relapse mortality. *Bone Marrow Transplantation*, 50(1), 100–105. <https://doi.org/10.1038/bmt.2014.228>
- Jarden, M., Baadsgaard, M. T., Hovgaard, D. J., Boesen, E., & Adamsen, L. (2009). A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. *Bone Marrow Transplantation*, 43(9), 725–737. <https://doi.org/10.1038/bmt.2009.27>
- Johansson, J. E., Bratel, J., Hardling, M., Heikki, L., Mellqvist, U. H., & Haseus, B. (2019). Cryotherapy as prophylaxis against oral mucositis after high-dose melphalan and autologous stem cell transplantation for myeloma: A randomised, open-label, phase 3, non-inferiority trial. *Bone Marrow Transplantation*, 54(9), 1482–1488. <https://doi.org/10.1038/s41409-019-0468-6>
- Krawczyk, J., Kraj, L., Korta, T., & Wiktor-Jedrzejczak, W. (2017). Nutritional status of hematological patients before hematopoietic stem cell transplantation and in early posttransplantation period. *Nutrition and Cancer*, 69(8), 1205–1210. <https://doi.org/10.1080/01635581.2017.1367937>
- Lalla, R. V., Bowen, J., Barasch, A., Elting, L., Epstein, J., Keefe, D. M., ... International Society of Oral, O (2014). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*, 120(10), 1453–1461. <https://doi.org/10.1002/cncr.28592>
- Liu, P., Zhang, Z.-F., Cai, J.-J., Wang, B.-S., & Yan, X. (2012). NRS2002 assesses nutritional status of leukemia patients undergoing hematopoietic stem cell transplantation. *Chinese Journal of Cancer Research = Chung-kuo Yen Cheng Yen Chiu*, 24(4), 299–303. <https://doi.org/10.3978/j.issn.1000-9604.2012.09.01>
- Malihi, Z., Kandiah, M., Chan, Y. M., Hosseinzadeh, M., Sohanaki Azad, M., & Zarif Yeganeh, M. (2013). Nutritional status and quality of life in patients with acute leukaemia prior to and after induction chemotherapy in three hospitals in Tehran, Iran: A prospective study. *Journal of Human Nutrition & Dietetics*, 26(Suppl 1), 123–131. <https://doi.org/10.1111/jhn.12043>
- Mattsson, J., Westin, S., Edlund, S., & Remberger, M. (2006). Poor oral nutrition after allogeneic stem cell transplantation correlates significantly with severe graft-versus-host disease. *Bone Marrow Transplantation*, 38(9), 629–633. <https://doi.org/10.1038/sj.bmt.1705493>
- Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., ... Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*, 4, 1. <https://doi.org/10.1186/2046-4053-4-1>
- Okada, N., Hanafusa, T., Abe, S., Sato, C., Nakamura, T., Teraoka, K., ... Ishizawa, K. (2016). Evaluation of the risk factors associated with high-dose chemotherapy-induced dysgeusia in patients undergoing autologous hematopoietic stem cell transplantation: Possible usefulness of cryotherapy in dysgeusia prevention. *Supportive Care in Cancer*, 24(9), 3979–3985. <https://doi.org/10.1007/s00520-016-3244-9>
- Oxford, U. o. (2019). *Critical appraisal sheet for randomized controlled trials*. Retrieved from <https://www.cebm.net/wp-content/uploads/2018/11/RCT.pdf>
- Rieger, C. T., Wischumerski, I., Rust, C., & Fiegl, M. (2015). Weight loss and decrease of body mass index during allogeneic stem cell transplantation are common events with limited clinical impact. *PLoS One*, 10(12), e0145445. <https://doi.org/10.1371/journal.pone.0145445>
- Riley, P., Glenny, A. M., Worthington, H. V., Littlewood, A., Clarkson, J. E., & McCabe, M. G. (2015). Interventions for preventing oral mucositis in patients with cancer receiving treatment: Oral cryotherapy. *Cochrane Database of Systematic Reviews*, (12), Cd011552. <https://doi.org/10.1002/14651858.CD011552.pub2>
- Roberts, S., & Thompson, J. (2005). Graft-vs-host disease: Nutrition therapy in a challenging condition. *Nutrition in Clinical Practice*, 20(4), 440–450. <https://doi.org/10.1177/0115426505020004440>
- Silva, G. B., Mendonca, E. F., Bariani, C., Antunes, H. S., & Silva, M. A. (2011). The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: A randomized clinical trial. *Photomedicine and Laser Surgery*, 29(1), 27–31. <https://doi.org/10.1089/pho.2009.2699>
- Silva, G. B. L., Sacono, N. T., Othon-Leite, A. F., Mendonça, E. F., Arantes, A. M., Bariani, C., ... Batista, A. C. (2015). Effect of low-level laser therapy on inflammatory mediator release during chemotherapy-induced oral mucositis: A randomized preliminary study. *Lasers in Medical Science*, 30(1), 117–126. <https://doi.org/10.1007/s10103-014-1624-2>
- Tavakoli Ardakani, M., Ghassemi, S., Mehdizadeh, M., Mojab, F., Salamzadeh, J., Ghassemi, S., & Hajifathali, A. (2016). Evaluating the effect of *Matricaria recutita* and *Mentha piperita* herbal mouthwash on management of oral mucositis in patients undergoing hematopoietic stem cell transplantation: A randomized, double blind, placebo controlled clinical trial. *Complementary Therapies in Medicine*, 29, 29–34. <https://doi.org/10.1016/j.ctim.2016.08.001>. [Epub ahead of print].
- Trifilio, S. M., Pi, J., & Mehta, J. (2013). Changing epidemiology of Clostridium difficile-associated disease during stem cell transplantation. *Biology of Blood and Marrow Transplantation*, 19(3), 405–409. <https://doi.org/10.1016/j.bbmt.2012.10.030>
- University of Oxford, C. f. E.-B. M. C. (2019). *Critical appraisal sheet – Randomised controlled trials (RCT)*. Retrieved from <https://www.cebm.net/wp-content/uploads/2018/11/RCT.pdf>
- Urbain, P., Birlinger, J., Lambert, C., Finke, J., Bertz, H., & Biesalski, H. K. (2012). Longitudinal follow-up of nutritional status and its

- influencing factors in adults undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplantation*, 48, 446. <https://doi.org/10.1038/bmt.2012.158>
- von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gotsche, P. C., & Vandenbroucke, J. P. (2014). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. *International Journal of Surgery*, 12(12), 1495–1499. <https://doi.org/10.1016/j.ijsu.2014.07.013>
- Walsh, D., Davis, M., Ripamonti, C., Bruera, E., Davies, A., & Molassiotis, A. (2017). 2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer. *Supportive Care in Cancer*, 25(1), 333–340. <https://doi.org/10.1007/s00520-016-3371-3>

How to cite this article: Eglseer D, Seymann C, Lohrmann C, Hoedl M. Nutritional problems and their non-pharmacological treatment in adults undergoing haematopoietic stem cell transplantation—A systematic review. *Eur J Cancer Care*. 2020;29:e13298. <https://doi.org/10.1111/ecc.13298>