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Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation

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ABSTRACT

Purpose To develop an evidence-based clinical practice guideline for the prevention of oral mucositis in children (0–18 years) receiving treatment for cancer or undergoing haematopoietic stem cell transplantation (HSCT).

Methods The Mucositis Prevention Guideline Development Group was interdisciplinary and included internationally recognised experts in paediatric mucositis. For the evidence review, we included randomised controlled trials (RCTs) conducted in either children or adults evaluating the following interventions selected according to prespecified criteria: cryotherapy, low level light therapy (LLLT) and keratinocyte growth factor (KGF). We also examined RCTs of any intervention conducted in children. For all systematic reviews, we synthesised the occurrence of severe oral mucositis. The Grades of Recommendation, Assessment, Development and Evaluation approach was used to describe quality of evidence and strength of recommendations.

Results We suggest cryotherapy or LLLT may be offered to cooperative children receiving chemotherapy or HSCT conditioning with regimens associated with a high rate of mucositis. We also suggest KGF may be offered to children receiving HSCT conditioning with regimens associated with a high rate of severe mucositis. However, KGF use merits caution as there is a lack of efficacy and toxicity data in children, and a lack of long-term follow-up data in paediatric cancers. No other interventions were recommended for oral mucositis prevention in children.

Conclusions All three specific interventions evaluated in this clinical practice guideline were associated with a weak recommendation for use. There may be important organisational and cost barriers to the adoption of LLLT and KGF. Considerations for implementation and key research gaps are highlighted.

INTRODUCTION

Oral and oropharyngeal mucositis are important and common consequences of cytotoxic cancer treatment and haematopoietic stem cell transplantation (HSCT) conditioning in adults and children.[1] This guideline for the prevention of oral and oropharyngeal mucositis was developed in order to prevent or reduce the severity of mucositis in children 0–18 years of age receiving cytotoxic chemotherapy or radiotherapy for cancer or undergoing HSCT. For the purpose of this guideline, oesophageal mucositis is encompassed by the terms oral and oropharyngeal mucositis; these conditions will be referred to as oral mucositis for the remainder of this guideline for the sake of brevity.

Oral mucositis is a complex phenomenon that involves a wide variety of cells and tissues of the oral mucosa.[2] It may cause severe mouth and throat pain, and lead to the inability to eat and drink, sometimes resulting in hospitalisation for hydration or parenteral nutrition. Mucositis also provides a portal of entry for bacteria residing within the oral cavity, leading to bacteraemia with mouth flora such as viridans group streptococci.[3] In addition, oral mucositis has become a major dose-limiting toxicity and, consequently, may limit the ability to deliver

anticancer therapy.[4] Finally, there is growing recognition of the impact of oral mucositis on quality of life and of its economic burden.[5]

We have explicitly excluded lower gastrointestinal mucositis from the scope of this guideline. While oral hygiene is an important component of clinical care, we have not addressed its role in the prevention or reduction of oral mucositis, as good oral care should be encouraged in all children, including children with cancer.[6] Reduction or modification of subsequent chemotherapy as an option for secondary oral mucositis prevention is outside the scope of this guideline.

The target users of this guideline are healthcare providers who care for children (0–18 years) who are receiving chemotherapy and/or radiotherapy for cancer or undergoing HSCT, and who are at risk of experiencing oral mucositis. This guideline is aimed particularly at physicians, nurse practitioners, nurses, pharmacists and dentists treating paediatric oncology, and HSCT patients. The overall objective was to develop an evidence-based clinical practice guideline for the prevention of oral mucositis in children (0–18 years) receiving treatment for cancer or undergoing HSCT.

METHODS

Guideline development panel

The Pediatric Oncology Group of Ontario (POGO) Mucositis Prevention Guideline Development Group was formed in March 2014 (see online supplementary appendix 1). Members were selected with a view to obtain interdisciplinary representation from internationally recognised experts in paediatric mucositis and POGO institutions. Panel members completed conflict of interest forms; no members had important conflicts. The guideline was editorially independent from the funding body.

Evidence identification and synthesis

There is a large literature base of studies that evaluate oral mucositis prevention in single arm and randomised controlled trials (RCTs) among adult and paediatric populations. Biologically, interventions that are effective in adult populations are likely to have a similar effect in children. However, differences in efficacy may arise related to changing pharmacokinetics and pharmacodynamics, age-related variance in the distribution of receptors for targeted interventions and lack of patient cooperation for some interventions. Specific interventions may have less utility in children if there is limited use of an antineoplastic agent in children when the mechanism of protective activity is agent specific. Toxicities of therapy may also be different and interference with anticancer activity may differ by underlying tumour type. Paediatric studies are also critical to determine dosing recommendations. Consequently, we decided to evaluate the adult and paediatric literature with an emphasis on the appraisal of paediatric studies.

In order to limit the scope of the adult and paediatric review, we took a pragmatic approach that builds on work conducted by a recent Cochrane Collaboration systematic review,[7] and The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO).[8–17] More specifically, because our health question was to identify prophylactic interventions that are effective at preventing or reducing the severity of oral mucositis, we chose to systematically review interventions that were recommended or suggested in any population by MASCC/ISOO for the prevention of oral mucositis and that showed evidence of benefit in the Cochrane Collaboration systematic review. These interventions were cryotherapy, low level light therapy (LLLT) and keratinocyte growth factor (KGF). Since the best way to evaluate the efficacy of an intervention is through conduct of RCTs, we evaluated RCTs of these agents in any age group and assessed if the effect appeared to differ by adult or paediatric population. We did not conduct systematic reviews of agents that the MASCC/ISOO guideline recommended against using.

We also conducted additional reviews restricted to paediatric patients. Because of the potential risk of harm with KGF in children, we undertook a systematic review of any primary study type of KGF use in paediatric cancer or HSCT. Finally, in order to better understand the full scope of the evidence base for mucositis prevention in children, we conducted a systematic review of all RCTs of any intervention to prevent oral mucositis in paediatric patients. If an agent other than cryotherapy, LLLT or KGF appeared promising in children, we had planned to conduct a combined adult and paediatric review of that agent. The search strategies, selection criteria, approach to appraisal and specific search details can be found in online supplementary appendix 2.

For all systematic reviews, we synthesised the occurrence of severe oral mucositis when at least three studies reported on this outcome for a specific intervention. Severe oral mucositis was defined as WHO, National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) V.2.0 or Radiation Therapy Oncology Group (RTOG) scale score of 3 or 4. All these scores use a five-point scale ranging from 0 to 4 in which scores of 3 and 4 represent the worst mucositis. The NCI-CTCAE V.3.0 scale ranges from 1 to 5 in which 5 is fatal mucositis. NCI-CTCAE V.3.0 scores of 3–5 were considered severe. All syntheses used the risk ratio (RR) as the effect measure where ratios less than 1 suggest that the intervention is better than placebo or no therapy. The 95% CI was also described. As we anticipated heterogeneity across studies, a random effects model

was used for all analyses. Analyses were conducted using Review Manager (RevMan, V.5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

Decision-making process for formulation of the recommendations

We identified outcomes most important for this guideline. Outcomes of critical importance were severe oral mucositis, mucositis of any severity, pain and adverse events associated with the intervention. Outcomes of lower importance included receipt of opioid analgesia, enteral or parenteral nutrition, infection outcomes and fever, since these outcomes are subject to confounding and institutional variation.

We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to describe quality of evidence and strength of recommendations.[18 19] Quality of evidence was evaluated in terms of risk of bias (methodological limitations), imprecision of estimates, inconsistency of results between studies and indirectness (lack of applicability to the target population). In this guideline, indirectness primarily occurred when the data were not paediatric specific. A strong recommendation was made when benefits clearly outweighed the risks and burdens or vice versa. In contrast, a weak recommendation was made when benefits and risks or burdens were closely matched, or when there was considerable uncertainty about the magnitude of the benefits and risks. Each recommendation was carefully deliberated by the panel. Decisions were taken through panel discussions and any differences in opinion were resolved by consensus.

External review, consultative process and plans for updates

The draft guideline was distributed to 12 external experts in adult and paediatric mucositis. Specific recommendations were reviewed by the panel and the guideline was revised accordingly. The guideline development process took 6 months from constitution of the panel to guideline completion. This guideline will be reviewed every 5 years or earlier if important new information becomes available.

RESULTS

Online supplementary appendix 3 outlines the results of the search strategies and flow charts of study identification, selection and reasons for exclusion. Table 1 presents the summary of recommendations, strength of recommendations, level of evidence and remarks.

Health question

What prophylactic interventions are effective at preventing or reducing the severity of oral mucositis in children (0–18 years) receiving treatment for cancer or undergoing HSCT

Recommendation 1.1: We suggest that cryotherapy may be offered to cooperative children receiving chemotherapy or HSCT conditioning with regimens associated with a high rate of mucositis.

Remarks: This recommendation places high value on the possible reduction in mucositis with an intervention with a low risk of harm. It is a weak recommendation because of the lack of paediatric-specific evidence, because the majority of studies that demonstrated the benefit of cryotherapy were conducted

Table 1 Summary of recommendations for the prevention of oral mucositis in paediatric patients receiving treatment for cancer or undergoing haematopoietic stem cell transplantation

Health question and recommendations	Strength of recommendation Level of evidence
What prophylactic interventions are effective at preventing or reducing the severity of oral and oropharyngeal mucositis in children (0–18 years) receiving treatment for cancer or undergoing haematopoietic stem cell transplantation (HSCT)?	
Recommendation 1.1: We suggest that cryotherapy may be offered to cooperative children receiving chemotherapy or HSCT conditioning with regimens associated with a high rate of mucositis *Remarks*: This recommendation places high value on the possible reduction in mucositis with an intervention with a low risk of harm. It is a weak recommendation because of the lack of paediatric-specific evidence, because the majority of studies that demonstrated the benefit of cryotherapy were conducted using chemotherapy regimens not commonly given to children and because of the methodological limitations of the conducted trials. Regimens appropriate for cryotherapy are restricted to agents with a short infusion time and a short half-life	Weak recommendation Moderate-quality evidence
Recommendation 1.2: We suggest that low-level light therapy may be offered to cooperative children receiving chemotherapy or HSCT conditioning with regimens associated with a high rate of mucositis *Remarks*: This recommendation places high value on the possible reduction in mucositis with an intervention with a low risk of harm. It is a weak recommendation because this strategy requires specialised equipment and expertise and it is unknown whether it is feasible to deliver this therapy modality in routine clinical practice, particularly in a paediatric population. The ideal treatment parameters and cost-effectiveness of this approach are unknown	Weak recommendation High-quality evidence
Recommendation 1.3: We suggest that keratinocyte growth factor (KGF) may be offered to children receiving HSCT conditioning with regimens associated with a high rate of severe mucositis *Remarks*: This recommendation places high value on the evidence of efficacy of KGF in adult populations. It is a weak recommendation because of the lack of efficacy and toxicity data in children, a theoretical concern that young children may be at increased risk of adverse effects related to mucosal thickening and the lack of long-term follow-up data in paediatric cancers	Weak recommendation High-quality evidence

using chemotherapy regimens not commonly given to children and because of the methodological limitations of the conducted trials. Regimens appropriate for cryotherapy are restricted to agents with a short infusion time and short half-life.

Oral cryotherapy involves placing ice cubes or ice chips in the mouth and continually replenishing fresh ice during the period of cytotoxic treatment (typically 30–60 min). It is an attractive intervention because of its low cost and universal access. In reviewing the evidence tables (see online supplementary appendices 4–6), there have been 14 RCTs conducted of cryotherapy in which 1301 patients have been randomised. In 13 studies, cryotherapy was given during chemotherapy administration and in 1 study, it was given before and after localised radiotherapy to the head and neck. Of the 14 studies, 12 reported a benefit of cryotherapy. Figure 1 illustrates that cryotherapy significantly reduced severe oral mucositis (RR 0.46, 95% CI 0.30 to 0.71; p=0.0005) among the eight studies reporting this outcome.

In spite of the many RCTs available, the quality of evidence supporting this recommendation was only moderate due to indirectness and limitations in study design. Only one study included children, and the youngest child was 8 years of age.[20] This study included adults and children undergoing allogeneic HSCT, and cryotherapy was administered with low-dose methotrexate for graft-versus-host disease (GVHD) prophylaxis. Notably, this study was one of only two studies that failed to show a benefit of cryotherapy. Likely, the conditioning regimen contributed much more to the risk of mucositis than did low-dose methotrexate given for GVHD prophylaxis; thus, this study is difficult to interpret. In addition, the most common regimen used in the studies of cryotherapy was 5-fluorouracil (8/14 studies); this agent is rarely used in children. Indirectness is also a concern as there is likely to be an age at which children cannot or will not comply with cryotherapy during chemotherapy administration.

Limitations in study design are also a concern. Online supplementary appendix 5 illustrates that three of the studies were quasi-RCTs. Adequate sequence generation was only present for two studies and it was inadequate in three. None of the 14 RCTs adequately concealed allocation, a major methodological limitation, as lack of allocation concealment has been associated with exaggerated treatment effects.[21] Finally, only two studies used blinded outcome assessors. The low quality of the RCTs evaluating the efficacy of cryotherapy for mucositis prevention raises concerns about the possibility of bias.

Cryotherapy is only feasible if chemotherapy is administered as a short infusion and has a short half-life. The chemotherapeutic agents used in the studies of cryotherapy were 5-fluorouracil (8 studies), melphalan as conditioning for HSCT (2 studies), a variety of conditioning regimens for autologous and allogeneic HSCT (1 study), and etoposide, cisplatin, mitomycin-C and vinblastine (1 study). It would be reasonable to use cryotherapy for paediatric patients receiving short infusions of these chemotherapeutic agents. In addition, since the biological mechanism underlying the effect of cryotherapy is likely related to reduced distribution of the cytotoxic agent to the oral mucosa due to vasoconstriction, it may also be reasonable to use cryotherapy for other regimens associated with a higher risk of mucositis as long as the regimen is given over a short period of time such as 30 min, and the agent has a short half-life. Flavoured ice popsicles, ice slushy drinks or 'freezies' are likely to be more acceptable to children than plain ice.

There are two safety considerations with cryotherapy. First, if ice chips are to be used, they may be a choking hazard in very young children, although children who are old enough to comply with cryotherapy are unlikely to be at risk for choking. Second,

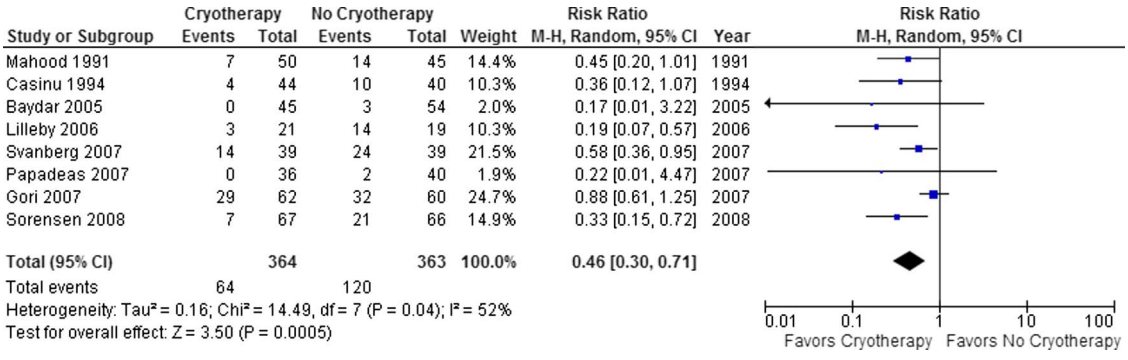

Figure 1 Cryotherapy versus no cryotherapy for the reduction of severe oral mucositis in patients receiving treatment for cancer or undergoing haematopoietic stem cell transplantation. Forest plot of incidence of severe (grade 3 or 4) mucositis in adults and children randomised to cryotherapy, versus no cryotherapy in patients with cancer and those receiving haematopoietic stem cell transplantation. Squares to the left of the vertical line indicate that the intervention reduces mucositis. Horizontal lines through the squares represent CIs. The size of the squares reflects each study's relative weight, and the diamond represents the aggregate risk ratio and 95% CI.

vasoconstriction of the oral tissues may influence local anticancer activity, although this issue has not been noted in the adult studies.

Recommendation 1.2: We suggest that LLLT may be offered to cooperative children receiving chemotherapy or HSCT conditioning with regimens associated with a high rate of mucositis.

Remarks: This recommendation places high value on the possible reduction in mucositis with an intervention with a low risk of harm. It is a weak recommendation because this strategy requires specialised equipment and expertise, and it is unknown whether it is feasible to deliver this therapy modality in routine clinical practice, particularly in a paediatric population. The ideal treatment parameters and cost-effectiveness of this approach are unknown.

LLLT is based on the physiological effects of low-energy light without thermal generation. The main effects of phototherapy are anti-inflammatory, influence on wound healing and analgesic. While the precise mechanism of action of LLLT in preventing oral mucositis is not fully understood, a number of biological effects have been well characterised at the molecular, cellular and tissue-based levels.[22] It is typically administered intraorally, although there is some experience with external application. In the systematic review by Oberoi *et al*,[23] 18 prophylactic LLLT studies were identified; online supplementary appendix 7 summarises the type of laser, wavelength, energy and laser schedule. LLLT significantly reduced the incidence of severe mucositis (RR 0.37, 95% CI 0.20 to 0.67; p=0.001). LLLT also reduced the incidence of severe pain (RR 0.26, 95% CI 0.18 to 0.37; p<0.0001). Two studies included children and there was no difference in the effect of LLLT by age (p for interaction=0.90). One study included adults and children receiving autologous or allogeneic HSCT[24] while the second study included children receiving chemotherapy or autologous HSCT.[25] There was no difference in the effect of LLLT by underlying condition (patients with head and neck cancer receiving radiotherapy or chemoradiotherapy versus patients receiving chemotherapy or HSCT; p for interaction=0.85).

The review identified a significant interaction by allocation concealment, with the effect of LLLT to prevent severe mucositis being RR 0.61 (95% CI 0.30 to 1.25) in studies with adequate concealment and RR 0.16 (95% CI 0.07 to 0.41) for studies with unclear or inadequate concealment (p for interaction=0.03). There was also evidence of publication bias with four outlying studies in the funnel plot. When the 'trim and fill' technique[26] was used to account for publication bias, the effect of LLLT remained significant (RR 0.51, 95% CI 0.29 to 0.90; p=0.0197).

In summary, LLLT is effective in reducing severe mucositis in patients receiving treatment for cancer and undergoing HSCT, although methodological concerns and potential publication bias may mean that the treatment effects observed in these trials are exaggerated.

Recommendation 1.3: We suggest that KGF may be offered to children receiving HSCT conditioning with regimens associated with a high rate of severe mucositis.

Remarks: This recommendation places high value on the evidence of efficacy of KGF in adult populations. It is a weak recommendation because of the lack of efficacy and toxicity data in children, a theoretical concern that young children may be at increased risk of adverse effects related to mucosal thickening and the lack of long-term follow-up data in paediatric cancers.

KGF is an epithelial growth factor; it is a 28 kD, heparin-binding member of the family of fibroblast growth factors. The most commonly studied KGF is palifermin, a recombinant human KGF. It is contraindicated in patients with known hypersensitivity to *Escherichia coli* derived proteins. Online supplementary appendices 8–10 describe the 11 RCTs conducted of KGF; they included 1470 randomised patients. Ten studies evaluated palifermin while one study evaluated repifermin (no longer available). Use of KGF was evaluated in the context of HSCT conditioning (5 studies); chemoradiotherapy for head and neck cancer (3 studies); and chemotherapy alone (3 studies). Of the 11 studies, 9 reported a benefit of KGF.

Figure 2 illustrates that KGF significantly reduced severe oral mucositis (RR 0.81, 95% CI 0.67 to 0.97; p=0.02) in the eight studies reporting this outcome. Primary toxicities were related to the pharmacological properties of the agent with thickening of the oral mucosa and altered taste sensation. The quality of these studies was high and all studies were placebo controlled. All 11 trials were sponsored by a pharmaceutical company. Only one study included children, and it evaluated KGF for the prevention of GVHD following allogeneic HSCT in a mixed adult and paediatric sample.[27] Mucositis severity was evaluated as a secondary outcome and a significant reduction in the mean severity of oral mucositis with KGF compared with placebo was observed (WHO 2.3 vs 2.8; p=0.01). In a long-term follow-up of this study, no difference in invasive fungal infection, chronic GVHD, or overall survival between the KGF and placebo cohorts was evident at 2 years.[28] However, relapse rates were not described, few patients had solid tumours (number not specified) and outcomes were not specifically reported for paediatric patients.

In the systematic review of any primary study type of KGF in paediatric populations, four non-randomised studies were identified, all in the HSCT setting. First, a phase 1 allogeneic HSCT study evaluated doses of 40, 60 and 90 µg/kg/day given 3 days before conditioning and 3 days after stem cell infusion in children 2–18 years of age.[29] Six children received 90 µg/kg/day; no dose-limiting toxicities were

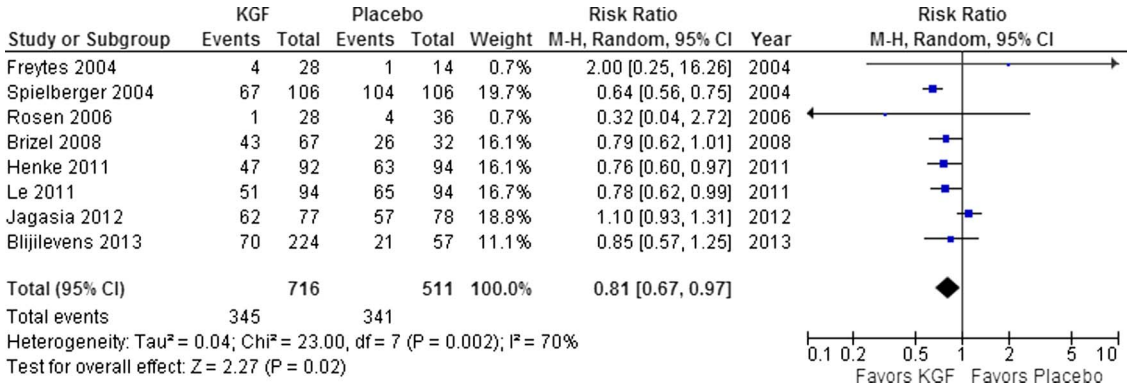

Figure 2 Keratinocyte growth factor (KGF) versus no KGF for the reduction of severe oral mucositis in patients receiving treatment for cancer or undergoing haematopoietic stem cell transplantation. Forest plot of incidence of severe (grade 3 or 4) mucositis in adults and children randomised to KGF versus no KGF in patients with cancer and those receiving haematopoietic stem cell transplantation. Squares to the left of the vertical line indicate that the intervention reduces mucositis. Horizontal lines through the squares represent CIs. The size of the squares reflects each study's relative weight, and the diamond represents the aggregate risk ratio and 95% CI.

observed. Of the 12 patients enrolled, grade 2 or lower skin rash was observed in 67% and 25% experienced mucositis. Second, an allogeneic HSCT study evaluated 20 children with acute lymphoblastic leucaemia[30] who were 7–16 years of age. Participants received KGF 60 μg/kg/day for 3 days before and 3 days after myeloablative therapy. Grade 2 or higher oral mucositis was observed in 60% of KGF-treated participants compared with 86% of historical control patients (p=0.032). Toxicities of KGF were skin rash (60%), skin erythema (60%), altered taste (10%) and severe pain in the tongue, buccal mucosa and palate (10%). Third, an autologous HSCT study included 25 children treated with KGF 60 μg/kg/day for 3 days before conditioning and 3 days following the last dose of chemotherapy.[31] Severe mucositis occurred in 20% of KGF-treated patients versus 42% of historical control patients (p=0.072). Toxicities of KGF were not described. Finally, a case report described a 19-year-old patient who received KGF 60 μg/kg/day for 3 days before and after allogeneic HSCT. He developed transient non-severe hyperplastic gingivitis with a concomitant papulopustular skin rash.[32]

We made a weak recommendation that KGF may be considered for children undergoing HSCT if the benefits of mucositis prevention outweigh the risks and costs. If used, KGF should be administered at a dose of 60–90 μg/kg/day for 3 days prior to conditioning and 3 days following stem cell infusion.

Other interventions as prophylaxis for oral mucositis

There were 21 paediatric RCTs of interventions to reduce oral mucositis identified by the search strategy (see online supplementary appendices 11–13). The most common intervention evaluated was growth factors, more specifically subcutaneous or intravenous granulocyte colony-stimulating factor (GCSF), granulocyte macrophage colony-stimulating factor and pegfilgrastim in seven studies. In all of these studies, mucositis was a secondary end point. In the four studies that compared GCSF with no therapy,[33–35] one showed a reduction in grade 2–4 NCI-CTCAE mucositis (2% vs 6%; p=0.002),[33] two showed no decrease in mucositis[34 36] and the fourth study showed inconsistent results depending on the specific chemotherapy cycle evaluated.[35]

Other growth factors, glutamine and Traumeel S, were not consistently effective in reducing mucositis in paediatric patients in more than one study. Single studies of topical vitamin E,[37] transforming growth factor-β2-enriched feeding,[38] chewing gum,[39] chlorhexidine gluconate,[40] sucralfate[41] and a preventive oral disease protocol[42] were not effective in reducing mucositis. Given that our focus was on the identification of effective interventions to prevent or reduce mucositis, we did not make strong or weak recommendations against the use of any of these agents. Recommendations against the use of an agent would require adult and paediatric systematic reviews and the development of specific criteria on which to make such a recommendation. However, the identification of ineffective interventions is an important area for future research and is identified as a research gap.

DISCUSSION

Considerations for implementation

Clinical assessment for the presence and severity of oral mucositis should be a component of routine care for children receiving treatment for cancer and undergoing HSCT. Validated screening and assessment tools are important. A screening tool that includes mucositis has been developed but has not yet been validated.[43 44] Validated mucositis assessment tools in paediatric patients include the Children's International Mucositis Evaluation Scale (ChIMES),[45] the Oral Assessment Guide,[46] the Oral Mucositis Assessment Scale[47] and the Oral Mucositis Daily Questionnaire.[48]

In this guideline, we identified three interventions that may be appropriate for mucositis prevention in children. Figure 3 illustrates an algorithm for strategy implementation consideration. All three specific interventions (cryotherapy, LLLT and KGF) evaluated in this clinical practice guideline were associated with a weak recommendation for use. Since all systematic reviews compared the intervention against placebo or no therapy, it may be helpful to compare the RRs to gain insight into prioritisation. The RR against placebo or no therapy for LLLT, cryotherapy and KGF were 0.37, 0.46 and 0.81, respectively. In evaluating all three interventions, KGF is an intervention associated with high costs and a potential for harm. In contrast, cryotherapy is associated with very few costs and little risk of harm. On balance, if all three interventions are available, and clinically relevant, cryotherapy or LLLT should likely be prioritised for implementation whereas KGF should be used carefully in individual patients after weighing risks and benefits. There may also be important organisational and cost barriers to the adoption of LLLT since it requires specialised equipment and training for those who will administer therapy.

Dissemination of this guideline will be an important step in effective knowledge translation. We plan to disseminate this guideline through peer-reviewed publication, presentation at conferences and through paediatric oncology and dental organisations.

Research gaps

Research gaps are highlighted in box 1 and include identification of chemotherapeutic agents appropriate for cryotherapy. Important research gaps related to LLLT include better mechanistic information on how the modality could be effective, determination of ideal treatment parameters and comprehensive long-term adverse-effect evaluation, since enhanced bone growth has been reported in preclinical studies.[49 50] For KGF, research is needed to identify the optimal KGF dose and its short-term and long-term toxicities in paediatric patients. Data related to compliance and cost-

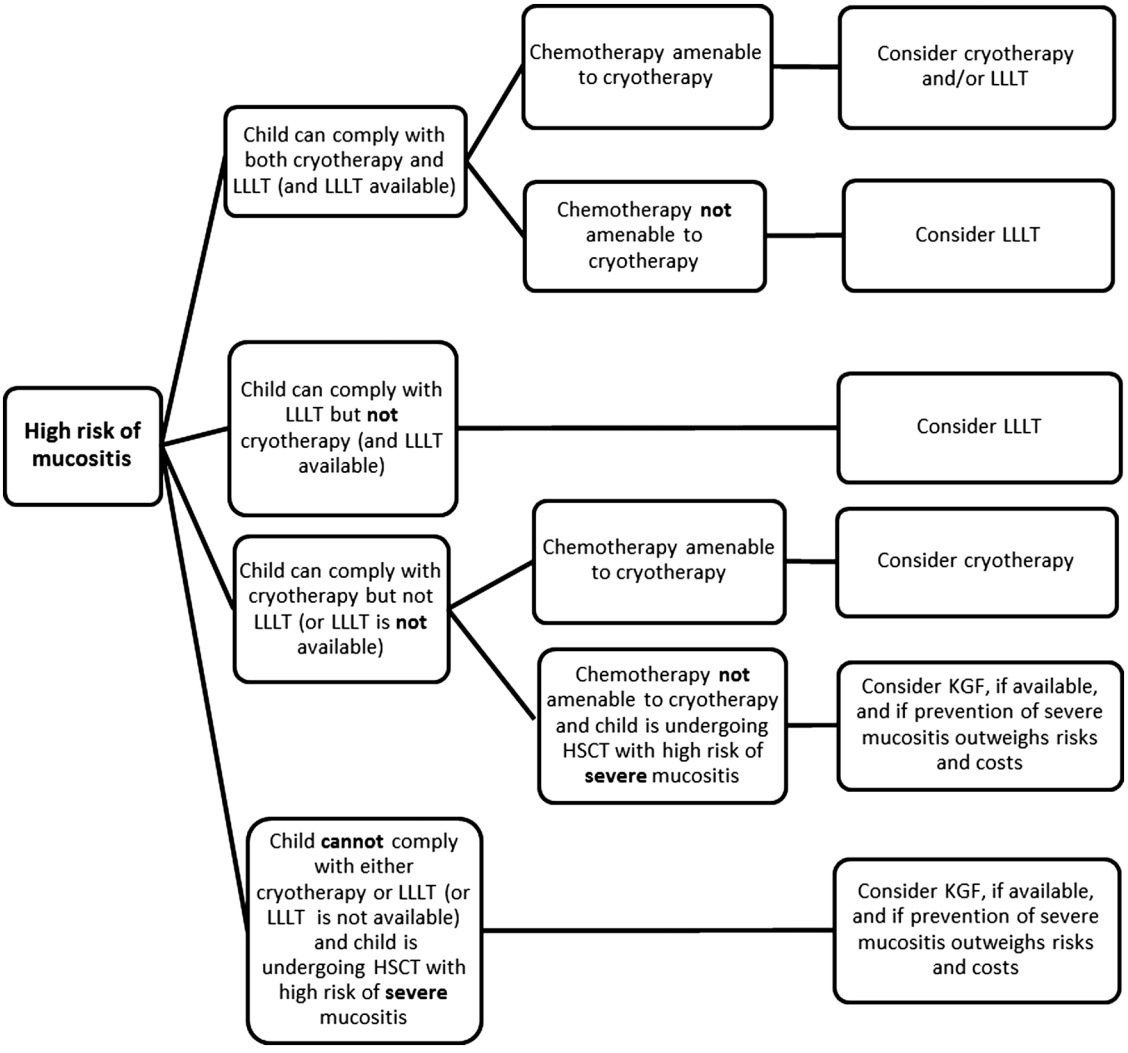

Figure 3 Suggested implementation approach for the prevention of oral mucositis guideline recommendations (HSCT, haematopoietic stem cell transplantation; KGF, keratinocyte growth factor, LLLT, low level light therapy).

Box 1 Key research gaps

Key Research Gaps

- The epidemiology of mucositis is poorly understood in children. Consensus-based approaches should be used to define what cumulative incidence of mucositis constitutes 'high risk'. Observational studies are required to describe the proportion of children receiving specific chemotherapeutic agents and regimens expected to experience any mucositis and severe mucositis
- Development of risk stratification schemas for paediatric mucositis
- Identification of paediatric anticancer treatment protocols appropriate for cryotherapy
- Determination of mechanistic information on mode of action, ideal treatment parameters and comprehensive long-term adverse-effect evaluation for low level light therapy
- Identification of the optimal paediatric dose of keratinocyte growth factor, and its short and long-term toxicities in paediatric patients with cancer
- Cost-effectiveness analysis of different approaches to mucositis prevention
- Evaluation of the feasibility of each of the recommended interventions to prevent mucositis in clinical practice
- Identification of new effective prophylactic strategies to prevent mucositis in paediatric patients, particularly for infants and very young children
- Identification of ineffective interventions to prevent mucositis in children

effectiveness are needed for these strategies. More paediatric evidence is required to evaluate existing and new interventions to prevent or reduce the severity of mucositis particularly since some children at risk for mucositis, especially infants and very young children, will not be eligible for any of the interventions identified in this guideline.

Another important gap is the identification of ineffective interventions to prevent mucositis in children. In randomised trials, equivalence trials require larger sample sizes than superiority trials because the minimal clinically important difference (in superiority trials) is larger than the margin of clinical equivalence. In synthesising trial results, it is unclear how much information is required before concluding equivalence in efficacy outcomes. Similarly, it is unclear how much information demonstrating lack of benefit is required before panels can recommend against use of an agent for interventions without meaningful harms or costs. Finally, how panels should weigh indirect adult evidence in making paediatric recommendations against use of an intervention is another question. Among these research gaps, research priorities that should be addressed early include the identification of paediatric anticancer treatment protocols appropriate for cryotherapy, feasibility of cryotherapy and LLLT in clinical practice, and child preferences for these strategies.

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Correction notice This article has been corrected since it published Online First. The Open Access licence has now been added.

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APPENDIX 1: GUIDELINE DEVELOPMENT PANEL MEMBERS

Panel Member	Role	Institution and Country
Lillian Sung, MD, PhD	Pediatric hematologist/oncologist (chair)	The Hospital for Sick Children *(Canada)*
Paula Robinson, MD, MSc	Guideline methodologist	POGO and C17 *(Canada)*
L. Lee Dupuis, RPh, ACPR, FCSHP, PhD	Pediatric oncology pharmacist	The Hospital for Sick Children *(Canada)*
John Wiernikowski, BScPhm, PharmD, FISOPP	Pediatric oncology pharmacist	McMaster Children's Hospital *(Canada)*
Paul Gibson, MD	Pediatric hematologist/oncologist	Children's Hospital, London Health Sciences Centre *(Canada)*
Wim Tissing, MD, PhD	Pediatric hematologist/oncologist	Beatrix Kinderziekenhuis / Universitair Medisch Centrum Groningen *(The Netherlands)*
Nathaniel Treister, DMD, DMSc	Pediatric oral medicine specialist	Brigham and Women's Hospital *(USA)*
Christina Baggott, RN, PhD, PPCNP-BC, CPON	Pediatric oncology nurse	Stanford University *(USA)*
Jennifer Brinklow, RN, BScN	Pediatric oncology nurse	Children's Hospital of Eastern Ontario *(Canada)*

APPENDIX 10: RANDOMIZED CONTROLLED TRIALS OF KERATINOCYTE GROWTH FACTOR FOR THE PREVENTION OF ORAL MUCOSITIS IN ADULT AND PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION – OUTCOMES

First Author (Year)	**COMPARISONS**	**OUTCOMES**				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Blijilevens (2013) [1]	KGF (pre-post) versus placebo	224	57	No significant difference in maximum severity of oral mucositis between placebo and KGF given either pre-/post HSCT (OR 0.7, 95% CI 0.4 to 1.3) or pre-HSCT (OR 1.2, 95% CI 0.6 to 2.4)	Area under curve for MTS not significantly different between placebo and pre-/post HSCT or pre-HSCT	17/224 adverse events leading to KGF discontinuation vs 1/57 with placebo. 1 fatal adverse event with KGF vs 0 with placebo
Jagasia (2012) [2]	KGF (pre-post) versus placebo	77	78	Incidence of grade 3-4 oral mucositis (73% placebo vs 81% KGF) similar between groups	Not reported	Study drug-related adverse events 23 (32%) placebo vs 31 (40%) KGF. Most commonly reported treatment-related adverse events: skin/subcutaneous such as rash, pruritus and erythema
Le (2011) [3]	KGF versus placebo	94	94	Incidence of severe oral mucositis significantly lower for KGF than placebo (54% vs 69%; P=0.041)	Average MTS scores in KGF vs. placebo arms (mean 1.7 vs 1.9) (NS)	Adverse events similar between arms (98% KGF, 93%, placebo). Most common study drug–related adverse events rash, flushing and dysgeusia
Henke (2011) [4]	KGF versus placebo	92	94	Incidence of severe oral mucositis significantly lower for KGF than placebo (51% vs 67%; P=0.027)	No difference in MTS between groups	Adverse events with difference in incidence of at least 5% between KGF and placebo arms: dysphagia (35% and 21%), dehydration (6% and 14%), leukopenia (13% and 21%), insomnia (5% and 13%), fatigue (8% and 15%), diarrhea (12% and 5%), mucosal inflammation (4% and 11%), asthenia (14% and 8%), headache (10% and 4%), abdominal pain (8% and 2%), and back pain (6% and 1%)
Vadhan Raj (2010) [5]	KGF versus placebo	32	16	KGF reduced cumulative incidence of grade 2 or higher WHO mucositis (44% vs 88%; P<0.001) and grade 3 or 4 mucositis (13% vs 51%; P=0.002)	Mouth pain scores significantly lower with KGF (1 vs 5; P=0.002)	Main adverse effects thickening of oral mucosa (72% KGF vs 31% placebo; P=0.007) and altered taste
Brizel (2008) [6]	KGF versus placebo	67	32	Median duration grade 2 or higher mucositis non-significantly shorter for KGF than placebo (6.5 vs 8.1 weeks; P=0.157)	Not reported	Type, incidence, and severity of adverse events similar between treatment groups
Rosen (2006) [7]	KGF versus placebo	28	36	During first chemotherapy cycle, incidence of WHO grade 2 or higher mucositis lower with KGF than with placebo (29% vs 61%; P=0.016)	Cycle 1, MTS scores significantly lower with KGF (P=0.005)	Oral-related adverse events more frequent in KGF vs placebo. During cycle 1, 50% KGF patients oral-related adverse event vs 33% placebo (P=0.13)

First Author (Year)	COMPARISONS	OUTCOMES				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Blazar (2006) [8]	KGF versus placebo	69	31	Difference in mean severity of oral mucositis significantly lower with KGF than with placebo (2.8 vs 2.3; P=0.01)	Not reported	Most adverse events similar frequencies in two groups. Skin reactions significantly more common with KGF (94% vs 68%; P<0.01)
Freytes (2004) [9]	KGF versus placebo	28	14	Grade 2 to 4 mucositis 100% for placebo, 64% for 25 mcg/kg (P=0.041 vs placebo), and 50% for 50 mcg/kg (P=0.006 vs placebo). Worst OMAS scores 14.0, 14.1, and 9.6 respectively for placebo, 25 mcg/kg and 50 mcg/kg groups (NS)	Mean worst pain on swallowing score 4.6, 4.8, and 2.1 for the placebo, 25 mcg/kg, and 50 mcg/kg groups, respectively. Difference between 50 mcg/kg and placebo significant (P=0.044)	Adverse events similar for KGF and placebo groups
Spielberger (2004) [10](companion paper: [11])	KGF versus placebo	106	106	Incidence of WHO grade 3 or 4 mucositis 63% with KGF and 98% with placebo (P<0.001). Median duration of mucositis 3 days (range 0 to 22) with KGF vs 9 days (range 0 to 27) with placebo (P<0.001)	KGF associated with significant reduction in MTS (P<0.001)	Adverse events more often with KGF: skin and oral epithelium effects such as rash, pruritus, erythema, paresthesia, mouth and tongue disorders, and taste alteration
Meropol (2003) [12]	KGF versus placebo	54	27	Frequency grade 2 to 4 mucositis 43% with KGF compared with 67% with placebo (P=0.06)	Area under the curve for mouth soreness: Placebo (mean 35.9; SE 7.6) vs. KGF (mean 30.3; SE 4.8)	Skin and oral events occurred in 13 of 18 patients treated with 60 and 80 mcg/kg of KGF and three of 11 patients treated with 40 mcg/kg

Abbreviations: KGF – keratinocyte growth factor; HSCT – hematopoietic stem cell transplantation; OR – odds ratio; CI – confidence interval; MTS – Mouth and Throat Soreness; WHO – World Health Organization; OMAS – Oral Mucositis Assessment Scale; NS – not significant

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APPENDIX 11: RANDOMIZED CONTROLLED TRIALS OF ANY INTERVENTION FOR THE PREVENTION OF ORAL MUCOSITIS IN PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION – STUDY CHARACTERISTICS

STUDY CHARACTERISTICS AND PARTICIPANTS

First Author (Year)	Enrollment Year		Country of Patient Enrollment	Pharma Sponsorship Declared	Total N Randomized	Age Range	Specific Cancer Diagnosis	Population Type (Cancer, HSCT, Both)	Transplant Type	Treatment (Chemo alone, Radiation alone, Both, Not specified)	Treatment Regimen in Related to Intervention
	Start	End									
Patte (2002) [1]	1994	1996	France	No	149	NR	NHL	Cancer	NA	Chemo	COPADM
Michel (2000) [2]	1993	1998	France	No	67	NR	High risk ALL	Cancer	NA	Chemo	R3 and COPADM for 6 cycles total
Lehrnbecher (2007) [3]	1998	2003	Germany	No	317	0 to 18	AML	Cancer	NA	Chemo	Induction AML
Ladenstein (2010) [4]	2002	2005	16 European countries	Yes	239	1 to 17	High risk neuroblastoma	Cancer	NA	Chemo	Rapid COJEC
Cesaro (2013) [5]	2007	2011	Italy	No	61	1.1 to 16.8	Various	HSCT	Auto	Both	Various
Fox (2009) [6]	2000	2005	US	Yes	34	3.8 to 25.8	Sarcoma	Cancer	NA	Both	VDC and IE
Wexler (1996) [7]	NR	NR	US	No	37	1 to 24	Sarcoma	Cancer	NA	Both	NCI protocol 86C 169
Uderzo (2011) [8]	2005	2008	Italy	No	120	0.4 to 18.6	Hem malignancy	HSCT	Allo	Both	Timing based on HSCT, not conditioning
Aquino (2005) [9]	1998	2002	US	No	130	NR	Various	HSCT	Auto, allo	Both	Various
Ward (2009) [10]	1999	2005	UK	Yes	76	1 to 22	Various	Cancer	NA	Chemo	Various
Sencer (2012) [11]	2004	2006	US, Israel	No	195	3 to 25	Various	HSCT	Auto, allo	Not specified	Timing based on HSCT, not conditioning
Oberbaum (2001) [12] (companion paper: [13])	NR	NR	Israel	No	32	3 to 25	Various	HSCT	Auto, allo	Not specified	Various
Abramoff (2008) [14]	2003	2003	Brazil	Yes	22	7 to 23	Osteosarcoma and ALL	Cancer	NA	Chemo	Various
Cruz (2007) [15]	2003	2005	Brazil	Yes	62	3 to 18	Various	Both	Unclear	Chemo	Various
Raether (1989) [16]	1986	1987	US	Yes	47	1.6 to 21.5	Various	HSCT	Auto, allo	Both	Various
Cheng (2004) [17] (companion papers:[18] [19])	2000	2001	Hong Kong	No	40	6 to 16	Various	Cancer	NA	Chemo	Various
Shenep (1988) [20]	1983	1987	US	Yes	48	NR	AML	Cancer	NA	Chemo	Induction AML
Sung (2007) [21]	2001	2004	Canada	Yes	45	6.4 to 15.1	Various	Cancer	NA	Chemo	Doxorubicin

STUDY CHARACTERISTICS AND PARTICIPANTS											
First Author (Year)	Enrollment Year		Country of Patient Enrollment	Pharma Sponsorship Declared	Total N Randomized	Age Range	Specific Cancer Diagnosis	Population Type (Cancer, HSCT, Both)	Transplant Type	Treatment (Chemo alone, Radiation alone, Both, Not specified)	Treatment Regimen in Related to Intervention
	Start	End									
de Koning (2007) [22]	2001	2004	Netherlands	Yes	30	1 to 14	Various	Cancer	NA	Chemo	Various
Gandemer (2007) [23]	1999	2002	France	Yes	145	5.2 to 18.7	Various	Both	Auto, allo	Chemo	Various
Rojas de Morales (2001) [24]	1998	1999	Venezuela	Yes	16	5 to 12	ALL or lymphoma	Cancer	NA	Chemo	Not stated

Abbreviations: NR - not reported; NA - not applicable; pharma – pharmaceutical company; N – number; HSCT - hematopoietic stem cell transplantation; chemo – chemotherapy; NHL – non-Hodgkin's lymphoma; ALL - acute lymphoblastic leukemia; AML – acute myeloid leukemia; auto – autologous; allo – allogeneic; hem – hematological; COPADM - cyclophosphamide, vincristine, prednisone, doxorubicin and methotrexate; R3 - high-dose cytarabine, etoposide and dexamethasone; COJEC - cisplatin, vincristine, carboplatin, etoposide and cyclophosphamide; VDC - vincristine, doxorubicin and cyclophosphamide; IE – ifosphamide and etoposide; NCI – National Cancer Institute; US – United States; UK – United Kingdom

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APPENDIX 12: RANDOMIZED CONTROLLED TRIALS OF ANY INTERVENTION FOR THE PREVENTION OF ORAL MUCOSITIS IN PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION – METHODOLOGY

METHODOLOGY					RISK OF BIAS FOR RANDOMIZED CONTROL TRIALS					
First Author (Year)	RCT or quasi-RCT	Study Design: (Parallel group, Cross-over, N-of-1)	Scales Used to Measure Mucositis	Frequency and Timing of Mucositis Assessment	Adequate sequence generation?	Adequate allocation concealment?	Participants and personnel blinded?	Outcome assessors blinded?	Loss to follow-up is less than 20% and/or equally distributed between both interventions?	Study free of selective reporting?
Patte (2002) [1]	RCT	Parallel	Unclear	Unclear	Unclear	Unclear	No	No	Yes	Yes
Michel (2000) [2]	RCT	Parallel	Not reported	Unclear	Unclear	Unclear	No	No	Yes	Yes
Lehrnbecher (2007) [3]	RCT	Parallel	CTCAE v3.0	Unclear	Unclear	Yes	No	No	Yes	Yes
Ladenstein (2010) [4]	RCT	Parallel	CTCAE v2.0	Unclear	Yes	Yes	No	No	Yes	Yes
Cesaro (2013) [5]	RCT	Parallel	WHO	Unclear	Yes	Yes	No	No	Yes	Yes
Fox (2009) [6]	RCT	Parallel	CTCAE v2.0	Unclear	Unclear	Yes	No	No	Yes	Yes
Wexler (1996) [7]	RCT	Parallel	CTCAE	Unclear	Unclear	Unclear	No	No	Yes	Yes
Uderzo (2011) [8]	RCT	Parallel	WHO	Unclear	Yes	Yes	Yes	Yes	Yes	No
Aquino (2005) [9]	RCT	Parallel	Modified Walsh scale	Daily until day 28 post HSCT or discharge	Yes	Yes	Yes	Yes	Yes	Yes
Ward (2009) [10]	Quasi-RCT	Cross-over	CTCAE v2.0	Days 1 to 21, frequency unclear	No	No	No	No	No	Yes
Sencer (2012) [11]	RCT	Parallel	Modified Walsh scale, WHO	Daily from day -1 to day 20 post HSCT	Unclear	Unclear	Yes	Yes	Yes	Yes
Oberbaum (2001) [12] (companion paper: [13])	RCT	Parallel	WHO	Every 2 days until no symptoms for 2 days, 14 days minimum after the start of study agent	Unclear	Yes	Yes	Yes	Yes	Yes
Abramoff (2008) [14]	RCT	Parallel	CTCAE v2.0	Before and after each laser application	Unclear	Unclear	Yes	Yes	Yes	No
Cruz (2007) [15]	RCT	Parallel	CTCAE v2.0	Days 1, 8 and 15	Unclear	Unclear	No	Yes	Yes	Yes
Raether (1989) [16]	RCT	Parallel	Percentage of ulcerated mucosa	Twice weekly from 8 days prior to HSCT until day 35 or discharge	Unclear	Unclear	Yes	Yes	Yes	Yes
Cheng (2004) [17] (companion papers:[18], [19])	RCT	Cross-over	Modified Oral Assessment Guide, WHO, VAS	Twice weekly	Unclear	Unclear	No	No	Yes	Yes
Shenep (1988) [20]	RCT	Parallel	Study-specific ulceration scale	Twice weekly	Yes	Yes	Yes	Yes	Yes	Yes

METHODOLOGY					RISK OF BIAS FOR RANDOMIZED CONTROL TRIALS					
First Author (Year)	RCT or quasi-RCT	Study Design: (Parallel group, Cross-over, N-of-1)	Scales Used to Measure Mucositis	Frequency and Timing of Mucositis Assessment	Adequate sequence generation?	Adequate allocation concealment?	Participants and personnel blinded?	Outcome assessors blinded?	Loss to follow-up is less than 20% and/or equally distributed between both interventions?	Study free of selective reporting?
Sung (2007) [21]	RCT	N-of-1	OMAS, VAS, WHO	Days 7, 10, 14, and 17 of each study cycle.	Yes	Yes	Yes	Yes	Yes	Yes
de Koning (2007) [22]	RCT	Cross-over	WHO	2 days before start of chemotherapy cycle daily until full recovery of patient's condition.	Unclear	Yes	No (personnel not blinded)	Yes	Yes	Yes
Gandemer (2007) [23]	RCT	Parallel	WHO	Daily for 3 weeks starting at beginning of chemotherapy	Yes	Yes	No	No	Yes	Yes
Rojas de Morales (2001) [24]	RCT	Parallel	Rutkauskas Index	Twice a week when in hospital	Unclear	Unclear	No	No	No	No

Abbreviations: RCT – randomized controlled trial; WHO – World Health Organization; CTCAE – Common Terminology Criteria for Adverse Events; VAS – visual analogue scale; HSCT – hematopoietic stem cell transplantation

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First Author (Year)	COMPARISONS	OUTCOMES				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Patte (2002) [1]	Lenograstim versus no lenograstim	75	73	Incidence grade 3 and 4 mucositis similar between arms	Not reported	Not reported
Michel (2000) [2]	Lenograstim versus no lenograstim	34	33	GCSF reduced incidence mucositis (6% vs 19%; P=0.04) after R3 but not after COPADM (65% vs 75%; P=NS)	Not reported	Not reported
Lehrnbecher (2007) [3]	GCSF versus no GCSF	161	156	GCSF no impact on incidence grades 3 and 4 mucositis (26.6% with GCSF vs 23.6% without GCSF; P=0.59)	Not reported	Not reported
Ladenstein (2010) [4]	Filgrastim versus no filgrastim	110	114	Grade 2 to 4 mucositis significantly less with GCSF (2%) compared with no GCSF (6%; P=0.002)	Not reported	Tolerance to GCSF good, only expected adverse effects reported
Cesaro (2013) [5]	Pegfilgrastim versus filgrastim	32	29	No significant difference in Grade 2 to 4 mucositis with GCSF (76%) vs pegfilgrastim (59%). No significant difference in severity or duration between groups	Not reported	Both pegfilgrastim and filgrastim well tolerated, no significant adverse effects
Fox (2009) [6]	Pegfilgrastim versus filgrastim	17	17	Grade 2 to 4 mucositis occurred in 4 patients with pegfilgrastim and 7 patients with GCSF, respectively, during cycles 1 to 4	Not reported	Pegfilgrastim and GCSF well tolerated, adverse events similar between arms
Wexler (1996) [7]	GMCSF versus no GMCSF	19	18	No significant differences in mucositis grade in cycles 1-2 and 3-18 between GMCSF and control groups	Not reported	Not reported
Uderzo (2011) [8]	Glutamine enriched versus standard nutrition	60	58	Mucositis in the first 3 to 4 weeks from HSCT in 94.8% and 96.7% in standard and glutamine enriched groups (P=0.68)	Not reported	Not reported
Aquino (2005) [9]	Glutamine versus glycine	57	63	Mean mucositis score 3.0±0.3 vs 3.9±0.4 (P=0.07) in glutamine and glycine groups. No difference in maximum mucositis score (P=0.7)	Not reported	No statistically significant difference in toxicity between groups
Ward (2009) [10]	Enteral glutamine versus no glutamine	50	50	No significant difference in severe mucositis (P=0.942) or duration of severe mucositis	Not reported	No adverse effects attributed to glutamine
Sencer (2012) [11]	Traumeel S versus placebo	98	92	Mean Walsh area under curves similar in two groups: 71.7 (SE 7.2) with Traumeel S and 69.8 (SE 8.2) with placebo. No difference in WHO scores.	Not reported	No significant difference in adverse events between group
Oberbaum (2001) [12] (companion paper: [13])	Traumeel S versus placebo	15	15	33% with Traumeel S did not develop mucositis vs 7% with placebo. Mean area under curve mucositis scores 10.4 with Traumeel S vs 24.3 with placebo (P<0.01).	5 in Traumeel S group had any oral pain vs 14 in placebo group	High incidence of serious complications but no significant difference between the groups

First Author (Year)	COMPARISONS	OUTCOMES				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Abramoff (2008) [14]	Low level light therapy versus placebo	11	11	At the third evaluation, 73% prophylactic laser group did not have mucositis vs 27% placebo (P=0.03)	Not reported	Not reported
Cruz (2007) [15]	Low level light therapy versus no low level light therapy	29	31	No significant difference in mucositis grade on day 8 (P=0.234) or day 15 (P=0.208)	Not reported	Not reported
Raether (1989) [16]	Chlorhexidine versus placebo	23	24	No significant difference in severity of oral ulceration between chlorhexidine and placebo groups (P=0.18)	Not reported	Not reported
Cheng (2004) [17] (companion papers:[18] , [19])	Benzydamine versus chlorhexidine	40	40	Ulcerative lesions in 27% (chlorhexidine) and 59% (benzydamine) (P<0.05). 26% and 48% using chlorhexidine and benzydamine had WHO grade 2 mucositis (P<0.05)	Significant difference in mean area under the curve of mouth pain (chlorhexidine 1.35±2.26 vs benzydamine 3.09±3.21; P=0.05)	Not reported
Shenep (1988) [20]	Sucralfate versus placebo	24	24	Objective observers noted more moderate and severe oral ulceration in placebo vs sucralfate groups (38% vs 12%; P=0.12)	58% patients sucralfate reported no oral pain vs 25% placebo (P=0.06)	8 in placebo and 4 in sucralfate experienced rashes (P=0.18). One placebo patient had unexplained papilledema
Sung (2007) [21]	Topical vitamin E versus placebo	22	23	No difference in objective mucositis scores with mean score 0.2 with vitamin E vs 0.3 with placebo .	Vitamin E did not reduce pain VAS scores, mean scores of 0.9 (on a scale of 0–10) in each group	No unexpected toxicity with topical vitamin E. Many children complained study solution difficult to use because of oily texture
de Koning (2007) [22]	TGF-b2-enriched feeding versus placebo	25	25	Grade 3 or 4 mucositis occurred in 40% with TGF-b2-treatment vs 32% with placebo	Not reported	No significant difference between the TGFb2 and placebo arms for any of toxicity parameters
Gandemer (2007) [23]	Chewing gums versus no chewing gum	73	72	No overall reduction in severe oral mucositis in gum (51%) vs control arms (44%; P=0.67)	Unable to assess pain because too few evaluations	Proportion of patients experiencing adverse events did not differ between arms
Rojas de Morales (2001) [24]	Oral disease preventive protocol versus oral physiotherapy	5	7	No significant difference in mucositis (P>0.05)	Not reported	Not reported

Abbreviations: GCSF – granulocyte colony stimulating factor; GMCSF – granulocyte-macrophage colony stimulating factor; NS – not significant; HSCT – hematopoietic stem cell transplantation; SE – standard error; VAS – visual analogue scale

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APPENDIX 2: SEARCH STRATEGIES, SELECTION CRITERIA AND APPRAISAL

a) Randomized Controlled Trials of Cryotherapy

i. **Search Strategy:** The following databases were searched and included articles indexed as of April 1, 2014: Ovid in MEDLINE, EMBASE, and EBM Reviews – Cochrane Central Register of Controlled Trials.

ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. We included fully-published papers that were randomized controlled trials (RCTs) or quasi-RCTs of cryotherapy for the prevention of mucositis in patients receiving treatment for cancer or undergoing hematopoietic stem cell transplantation (HSCT). There was no restriction by language. Two reviewers compiled the evidence summary table.

MEDLINE: The search strategy for OvidSP MEDLINE (1946 to **April 1, 2014**)

Set	History
1	mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab.
2	exp neoplasms/ or exp Antineoplastic Agents/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation dosage/ or dose-response relationship, radiation/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or rt.fs. or radiotherapy/ or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	1 and 2
4	cryotherapy/ or hypothermia, induced/ or cryosurgery/ or (((cryosurg* or cryogenic*) adj2 (treat* or therap*)) or cryothermy or cryotreat* or (cold adj2 therap*) or cryotherap* or (Oral adj2 cooling)).mp.
5	3 and 4

EMBASE: The search strategy for OvidSP Embase Classic+Embase <1947 to 2014 Week 13>

Set	History
1	mucosa inflammation/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp antineoplastic agent/ or exp transplantation/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	1 and 2
4	cryotherapy/ or cryoablation/ or cryosurgery/ or cryosurgery device/ or cryoprobe/ or (((cryosurg* or cryogenic*) adj2 (treat* or therap*)) or cryothermy or cryotreat* or (cold adj2 therap*) or cryotherap* or (Oral adj2 cooling)).mp.
5	3 and 4

EBM Reviews – CCTR: The search strategy for OvidSP EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>

Set	History
1	mucosa inflammation/ or mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab. or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp neoplasms/ or exp antineoplastic agent/ or exp Antineoplastic Agents/ or exp transplantation/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiation dosage/ or dose-response relationship, radiation/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	1 and 2
4	cryotherapy/ or hypothermia, induced/ or cryoablation/ or cryosurgery/ or cryosurgery device/ or cryoprobe/ or (((cryosurg* or cryogenic*) adj2 (treat* or therap*)) or cryothermy or cryotreat* or (cold adj2 therap*) or cryotherap* or (Oral adj2 cooling)).mp.
5	3 and 4

(b) Randomized Controlled Trials of Low Level Light Therapy (LLLT): A systematic review of RCTs evaluating LLLT to prevent mucositis in adults and children was recently published.[1]

i. **Search Strategy:** The following databases were searched and included articles indexed as of February 17, 2014: Ovid in MEDLINE, EMBASE, EBM Reviews – Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS and LILACS. The search strategies may be found in Oberoi et al.[1]

ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. Studies were included if the population consisted of patients with cancer or undergoing HSCT and patients were randomly assigned to receive prophylactic LLLT versus placebo, no therapy or usual care. Studies were excluded if: (1) allocation not randomly assigned; (2) absence of a placebo or no treatment group; (3) randomized chemotherapy cycles or left and right buccal mucosa within a patient rather than randomizing patients (as episodes would not be independent); and (4) duplicate publication. Studies included in the meta-analysis were not restricted by language or publication status.

(c) Randomized and Non-Randomized Trials of Keratinocyte Growth Factor (KGF)

Randomized Studies of KGF in Adult and Pediatric Populations:

i. **Search Strategy:** The following databases were searched and included articles indexed as of April 1, 2014: Ovid in MEDLINE, EMBASE, and EBM Reviews – Cochrane Central Register of Controlled Trials.

ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. We included fully-published papers that were RCTs or quasi-RCTs of KGF for the prevention of mucositis in patients receiving treatment for cancer or undergoing HSCT. There was no restriction by language. Two reviewers compiled the evidence summary table.

Non-Randomized Studies of KGF Conducted in Pediatric Populations:

i. **Search Strategy:** The same search strategy to identify RCTs of KGF was used since a filter for trial design was not added.

ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. We included fully-published papers of any study design that evaluated KGF for the prevention of mucositis in pediatric patients (≤ 25 years of age) receiving treatment for cancer or undergoing HSCT. There was no restriction by language.

MEDLINE: The search strategy for OvidSP MEDLINE (1946 to **April 1, 2014**)

Set	History
1	mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab.
2	exp neoplasms/ or exp Antineoplastic Agents/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation dosage/ or dose-response relationship, radiation/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or rt.fs. or radiotherapy/ or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	("fibroblast growth factor*" or fgf1 or "hbgf-1" or "fgf-1").mp. or ("fgf 2" or "fgf-2" or fgf2 or prostatropin or hbgf-2).mp. or ("FGF 7" or KGF or "7 fibroblast growth factor" or (keratinocyte adj2 growth) or palifermin or kepivance or "cg 53135" or cg53135 or "recombinant FGF 20" or velafermin).mp. or fibroblast growth factors/ or fibroblast growth factor 1/ or fibroblast growth factor 2/ or fibroblast growth factor 7/ or fibroblast growth factor 10/ or ("recombinant fibroblast growth factor 10" or "KGF 2" or repifermin).mp. or ("FGF 10" or FGF10).mp.
4	1 and 2 and 3

EMBASE: The search strategy for OvidSP Embase Classic+Embase <1947 to 2014 Week 13>

Set	History
1	mucosa inflammation/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp antineoplastic agent/ or exp transplantation/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	growth factor/ or fibroblast growth factor/ or fibroblast growth factor 1/ or fibroblast growth factor 10/ or fibroblast growth factor 2/ or keratinocyte growth factor/ or repifermin/ or ("recombinant fibroblast growth factor 10 " or KGF 2 or repifermin).mp. or velafermin/ or ("cg 53135" or cg53135 or "recombinant FGF 20" or velafermin).mp. or palifermin/ or (palifermin or kepivance).mp. or ("FGF 7" or KGF or "7 fibroblast growth factor" or (keratinocyte adj2 growth)).mp. or ("fibroblast growth factor*" or fgf1 or "hbgf-1" or "fgf-1").mp. or ("fgf 2" or "fgf-2" or fgf2 or prostatropin or hbgf-2).mp. or repifermin/ or ("recombinant fibroblast growth factor 10 " or "KGF 2" or kgf2 or repifermin).mp. or ("FGF 10" or FGF10).mp.
4	1 and 2 and 3

EBM Reviews – CCTR: The search strategy for OvidSP EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>

Set	History
1	mucosa inflammation/ or mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab. or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp neoplasms/ or exp antineoplastic agent/ or exp Antineoplastic Agents/ or exp transplantation/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiation dosage/ or dose-response relationship, radiation/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	("fibroblast growth factor*" or fgf1 or "hbgf-1" or "fgf-1" or ("fgf 2" or "fgf-2" or fgf2 or prostatropin or hbgf-2) or ("FGF 7" or KGF or "7 fibroblast growth factor" or (keratinocyte adj2 growth) or palifermin or kepivance or "cg 53135" or cg53135 or "recombinant FGF 20" or velafermin)).mp. or fibroblast growth factors/ or fibroblast growth factor 1/ or fibroblast growth factor 2/ or fibroblast growth factor 7/ or fibroblast growth factor 10/ or ("recombinant fibroblast growth factor 10" or "KGF 2" or repifermin).mp. or ("FGF 10" or FGF10).mp. or growth factor/ or fibroblast growth factor/ or fibroblast growth factor 1/ or fibroblast growth factor 10/ or fibroblast growth factor 2/ or keratinocyte growth factor/ or repifermin/ or ("recombinant fibroblast growth factor 10 " or KGF 2 or repifermin).mp. or velafermin/ or ("cg 53135" or cg53135 or "recombinant FGF 20" or velafermin).mp. or palifermin/ or (palifermin or kepivance).mp. or ("FGF 7" or KGF or "7 fibroblast growth factor" or (keratinocyte adj2 growth)).mp. or ("fibroblast growth factor*" or fgf1 or "hbgf-1" or "fgf-1").mp. or ("fgf 2" or "fgf-2" or fgf2 or prostatropin or hbgf-2).mp. or repifermin/ or ("recombinant fibroblast growth factor 10 " or "KGF 2" or kgf2 or repifermin).mp. or ("FGF 10" or FGF10).mp.
4	1 and 2 and 3

(d) Randomized Controlled Trials of Any Intervention in Pediatric Patients

i. **Search Strategy:** The following databases were searched and included articles indexed as of April 1, 2014: Ovid in MEDLINE, EMBASE, and EBM Reviews – Cochrane Central Register of Controlled Trials.

ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. We included fully-published papers that were RCTs or quasi-RCTs of any intervention for the prevention of mucositis in pediatric patients (≤ 25 years of age) receiving treatment for cancer or undergoing HSCT. There was no restriction by language. Two reviewers compiled the evidence summary table.

MEDLINE: The search strategy for OvidSP MEDLINE (1946 to **April 1, 2014**)

Set	History
1	mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab.
2	exp neoplasms/ or exp Antineoplastic Agents/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation dosage/ or dose-response relationship, radiation/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or

	Radiotherapy, Adjuvant/ or rt.fs. or radiotherapy/ or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	randomized controlled trial.pt. or controlled clinical trial.pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.
4	exp animals/ not humans.sh.
5	3 not
6	1 and 2 and 5
7	limit 6 to "all child (0 to 18 years)"
8	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
9	7 or (6 and 9)

EMBASE: The search strategy for OvidSP Embase Classic+Embase <1947 to 2014 Week 13>

Set	History
1	mucosa inflammation/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp antineoplastic agent/ or exp transplantation/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	ct.fs. or controlled clinical trial.pt. or controlled clinical trial/ or randomized controlled trial.pt. or randomized controlled trial/ or randomized.ab. or placebo.ab. or dt.fs. or randomly.ab. or trial.ab. or groups.ab.
4	1 and 2 and 3
5	limit 4 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
6	infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
7	5 or (4 and 6)

EBM Reviews – CCTR: The search strategy for OvidSP EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>

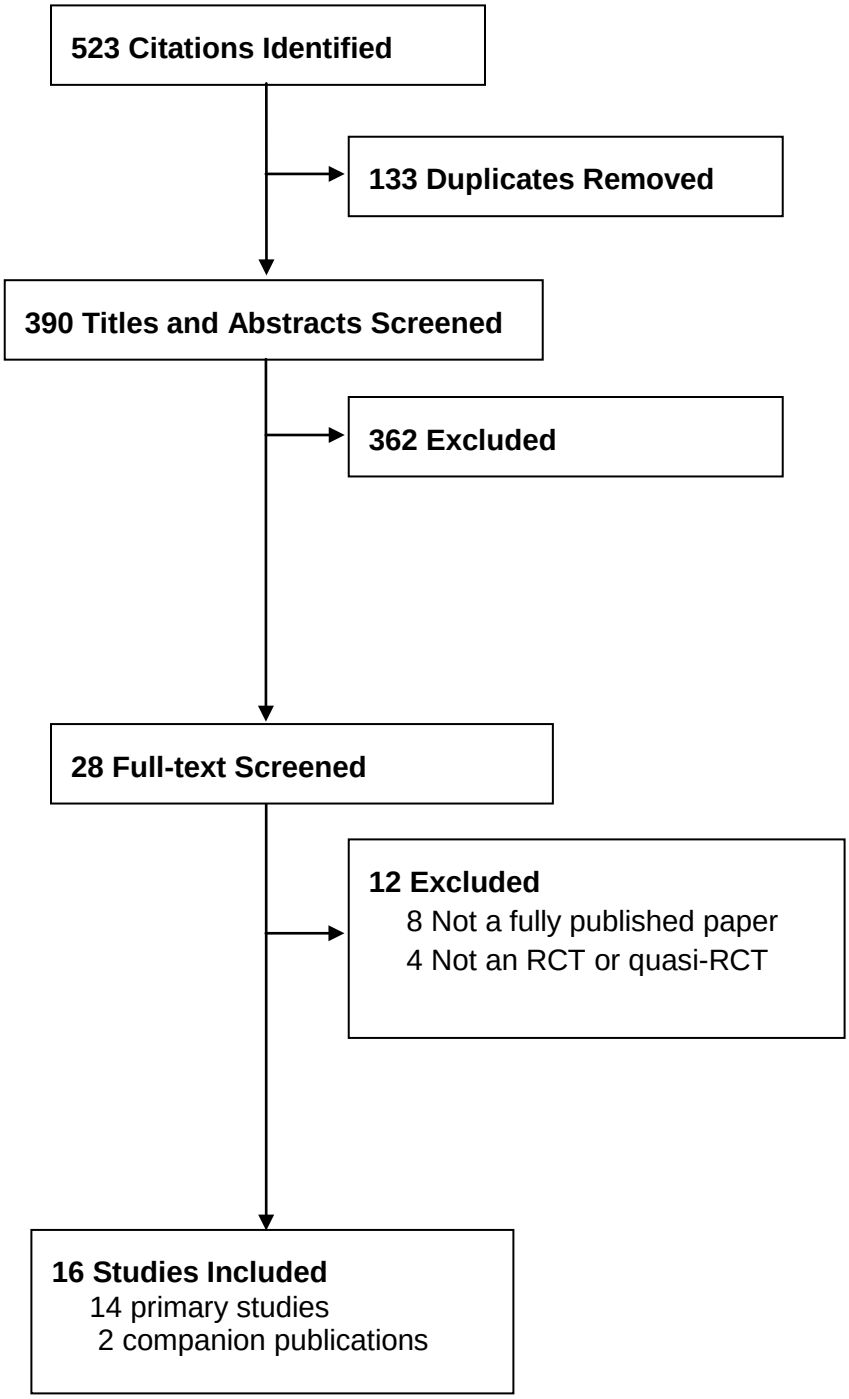
Set	History
1	mucosa inflammation/ or mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab. or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp neoplasms/ or exp antineoplastic agent/ or exp Antineoplastic Agents/ or exp transplantation/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiation dosage/ or dose-response relationship, radiation/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
4	1 and 2 and 3

REFERENCES

1. Oberoi S, Zamperlini–Netto G, Beyene J, Treister N, Sung L. Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014;**PlosOne (in press)**

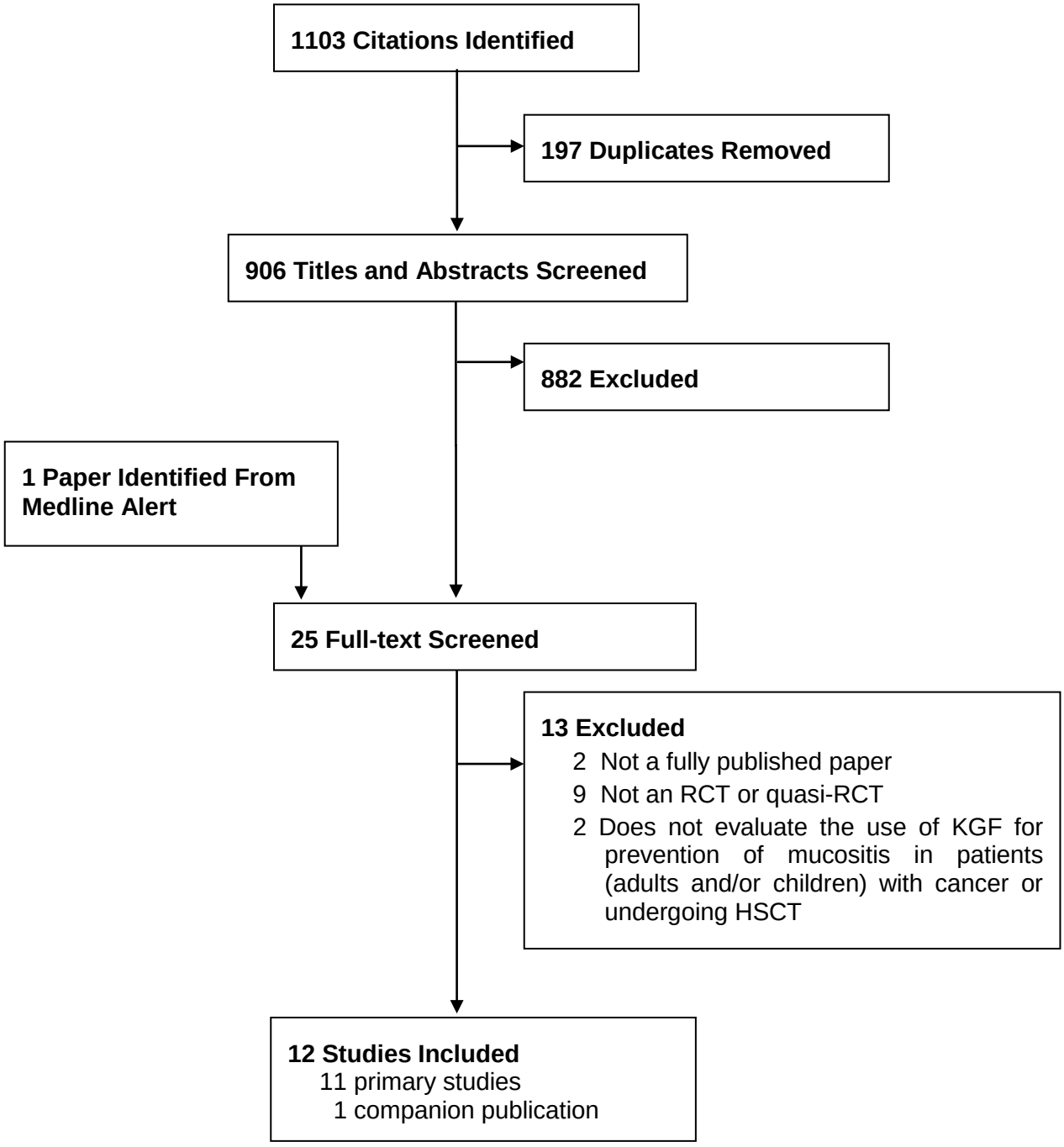
APPENDIX 3: RESULTS OF THE SEARCH STRATEGIES AND FLOW CHARTS OF STUDY IDENTIFICATION, SELECTION AND REASONS FOR EXCLUSION

(a) Randomized Controlled trials of Cryotherapy to Prevent Oral Mucositis in Adults and Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation: A total of 390 references were identified from the search strategy. After screening titles and abstracts, 28 were retrieved in full and 16 satisfied the eligibility criteria (14 primary and 2 companion papers).

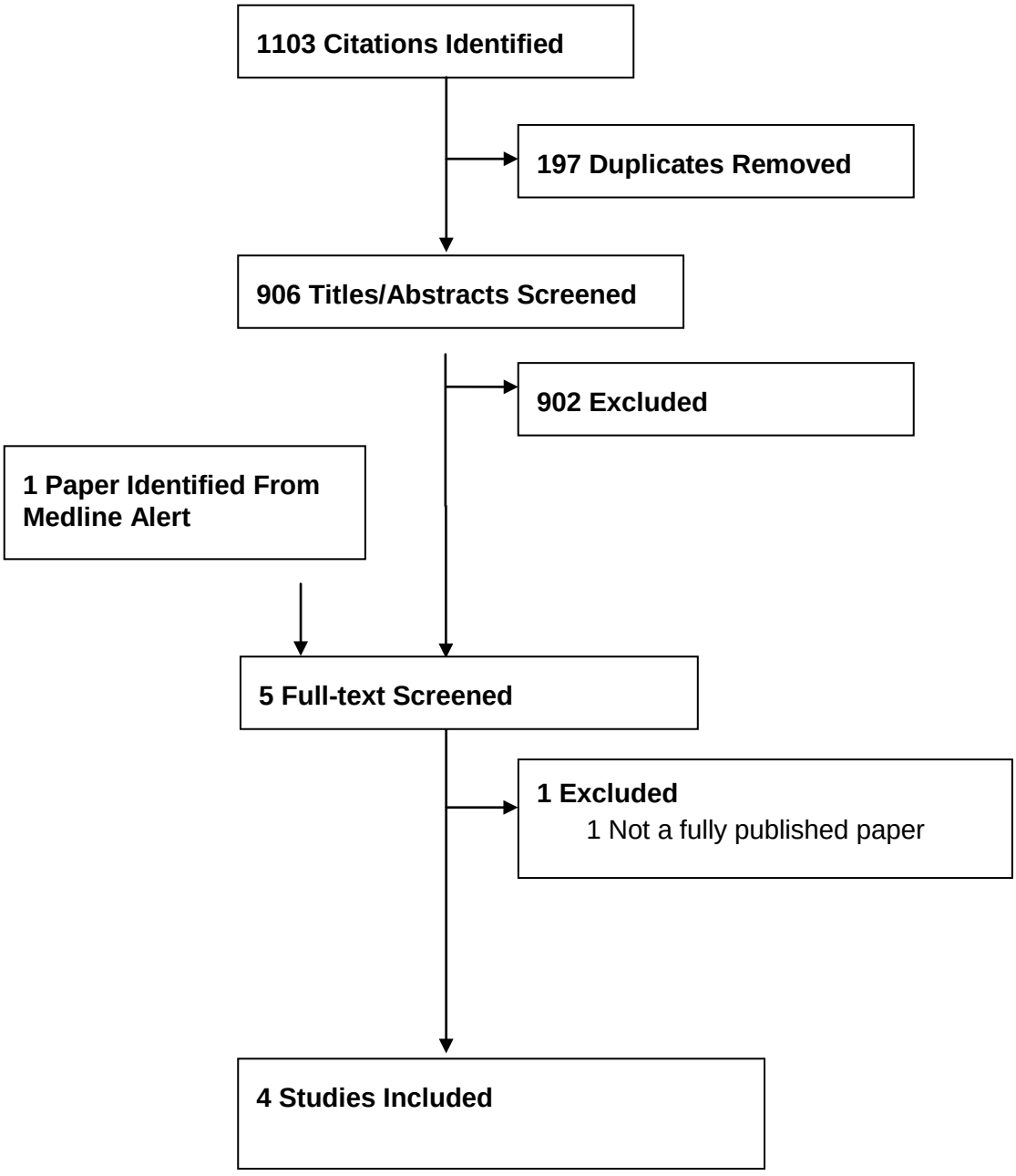


(b) Randomized Controlled trials of Low Level Light Therapy to Prevent Oral Mucositis in Adults and Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation: A total of 2,446 references were identified from the search strategy. After screening titles and abstracts, 57 were retrieved in full and 18 satisfied the eligibility criteria (Details available in Oberoi et al.[1]).

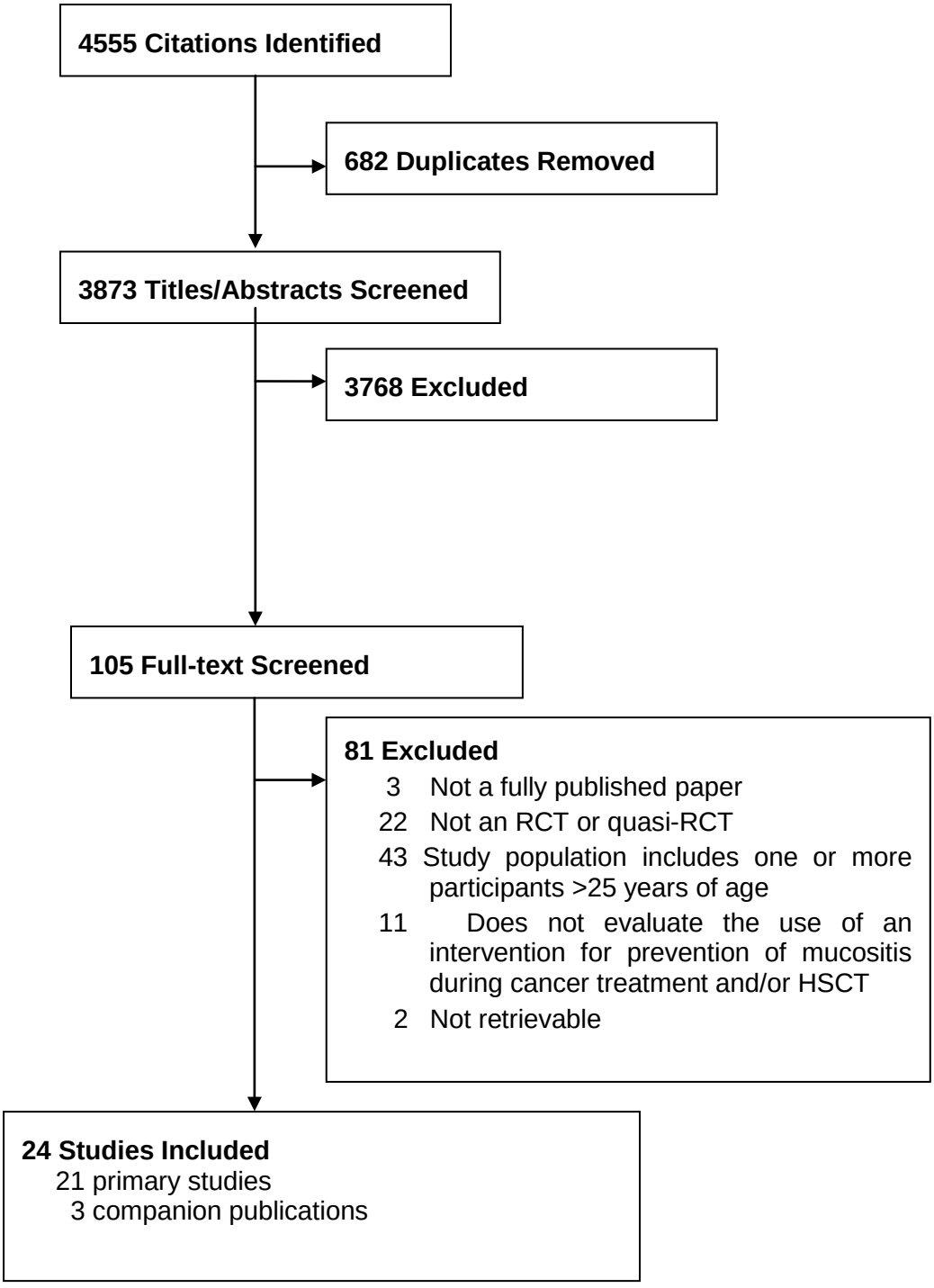
(c) Randomized Controlled trials of Keratinocyte Growth Factor to Prevent Oral Mucositis in Adults and Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation: A total of 906 references were identified from the search strategy. After screening titles and abstracts, 25 were retrieved in full and 12 satisfied the eligibility criteria (11 primary and 1 companion paper).



Non-Randomized Controlled trials of Keratinocyte Growth Factor to Prevent Oral Mucositis in Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation: As the search for RCTs of keratinocyte growth factor did not use trial design as a filter, the same 906 references were evaluated. After screening titles and abstracts, 5 were retrieved in full and 4 satisfied the eligibility criteria.



(d) Randomized Controlled trials of Any Intervention to Prevent Oral Mucositis in Children Receiving Treatment for Cancer or Undergoing Hematopoietic Stem Cell Transplantation: A total of 3,873 references were identified from the search strategy. After screening titles and abstracts, 105 were retrieved in full and 24 satisfied the eligibility criteria (21 primary and 3 companion papers).



Abbreviations: RCT – randomized controlled trial; HSCT – hematopoietic stem cell transplantation

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1. Oberoi S, Zamperlini–Netto G, Beyene J, Treister N, Sung L. Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014;**PlosOne (in press)**

APPENDIX 4: RANDOMIZED CONTROLLED TRIALS OF CRYOTHERAPY FOR THE PREVENTION OF ORAL MUCOSITIS IN ADULT AND PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION – STUDY CHARACTERISTICS

STUDY CHARACTERISTICS AND PARTICIPANTS

First Author (Year)	Enrollment Year		Country of Patient Enrollment	Pharma Sponsorship Declared	Total N Randomized	Age (Pediatric, Adult, Both)	Specific Cancer Diagnosis	Population Type (Cancer, HSCT, Both)	Transplant Type	Treatment Related to Cryotherapy	Duration of Cryotherapy	Radiotherapy in Oral Area
	Start	End										
Katranci (2012) [1]	NR	NR	Turkey	No	60	Adult	Various	Cancer	NA	5-FU, leukovorin	30 minutes	No
Salvador (2012) [2]	2007	2007	Canada	No	46	Adult	Multiple myeloma	HSCT	Auto	Melphalan	60 minutes	No
Sorensen (2008)[3]	2001	2005	Denmark	No	225	Adult	Gastro-intestinal cancer	Cancer	NA	5-FU, leukovorin	45 minutes	No
Svanberg (2007) [4] (companion papers: [5], [6])	2002	2004	Sweden	No	78	Adult	Various	HSCT	Auto, allo	Various	Throughout chemotherapy session	Sometimes
Gori (2007) [7]	2004	2006	Italy	No	130	Both	Hem diagnosis	HSCT	Allo	Methotrexate	At least 1 hour	Sometimes
Papadeas (2007) [8]	NR	NR	Greece	No	85	Adult	Unclear	Cancer	NA	5-FU, leukovorin	50 minutes	No
Lilleby (2006) [9]	2003	2005	US	No	41	Adult	Multiple myeloma	HSCT	Auto	Melphalan	7 hours	No
Baydar (2005) [10]	NR	NR	Turkey	No	99	Adult	Various	Cancer	NA	5-FU, leukovorin	From start of 5-FU until 10 minutes after	No
Karagozoglu (2005) [11]	2000	2001	Turkey	No	60	Adult	Various	Cancer	NA	Etoposide, cisplatin, mitomycin-C, vinblastine	Throughout chemotherapy infusion	No
Nikoletti (2005) [12]	NR	NR	Australia	No	79	Adult	Various	Cancer	NA	5-FU, leukovorin	30 minutes	No
Cascinu (1994) [13]	NR	NR	Italy	NR	84	Adult	Various	Cancer	NA	5-FU, leukovorin	30 minutes	No
Rocke (1993) [14]	NR	NR	US	No	179	Adult	Unclear	Cancer	NA	5-FU, leukovorin	60 minutes	No
Mahood (1991) [15]	NR	NR	US	No	95	NR	Unclear	Cancer	NA	5-FU, leukovorin	30 minutes	No
Kakoei (2013) [16]	NR	NR	Iran	No	40	Adult	Head and neck cancer	Cancer	NA	Radiotherapy	10 minutes	Yes

Abbreviations: NR - not reported; NA - not applicable; pharma – pharmaceutical company; N – number; hem – hematological; HSCT - hematopoietic stem cell transplantation; auto – autologous; allo – allogeneic; 5-FU – 5-fluorouracil; US – United States

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APPENDIX 5: RANDOMIZED CONTROLLED TRIALS OF CRYOTHERAPY FOR THE PREVENTION OF ORAL MUCOSITIS IN ADULT AND PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION - METHODOLOGY

METHODOLOGY					**RISK OF BIAS FOR RANDOMIZED CONTROL TRIALS**					
First Author (Year)	RCT or quasi-RCT	Study design: (Parallel group, Cross-over, N-of-1)	Scales Used to Measure Mucositis	Frequency and Timing of Mucositis Assessment	Adequate sequence generation?	Adequate allocation concealment?	Participants and personnel blinded?	Outcome assessors blinded?	Loss to follow-up is less than 20% and/or equally distributed between both interventions?	Study free of selective reporting?
Katranci (2012) [1]	RCT	Parallel group	WHO	Days 7, 14 and 21 after chemotherapy	Yes	Unclear	No	No	Yes	Yes
Salvador (2012) [2]	RCT	Parallel group	WHO	Days 3, 6, 9, and 12 after stem cell infusion	Yes	Unclear	No	Yes	Yes	Yes
Sorensen (2008) [3]	RCT	Parallel group	CTCAE v2.0	Day 14 and 28	Unclear	Unclear	No	No	Yes	Yes
Svanberg (2007) [4] (companion papers: [5], [6])	RCT	Parallel group	OMAS, WHO	Start of chemotherapy daily until day 21	Unclear	Unclear	No	No	Yes	Yes
Gori (2007) [7]	RCT	Parallel group	WHO	Day stem cell infusion until day 20	Unclear	Unclear	No	No	Yes	Yes
Papadeas (2007) [8]	Quasi-RCT	Parallel group	4 point grading scale	Once, one month after treatment	No	No	No	Yes	No	Yes
Lilleby (2006) [9]	RCT	Parallel group	CTCAE v2.0	Daily from day 2 to day 28 post stem cell infusion	Unclear	Unclear	No	No	Yes	Yes
Baydar (2005) [10]	Quasi-RCT	Extended cross-over	WHO	Days 5, 10, 15 and 21 from chemotherapy start	No	Unclear	No	No	Yes	Yes
Karagozoglu (2005) [11]	Quasi-RCT	Parallel group	Patient-judged mucositis grading and physician-judged mucositis grading	Patient report: Daily from day 1 of chemotherapy until day 21; Physician report - days 1 and 21, and days 2 and 3 if patient in clinic	No	Unclear	No	No	Yes	Yes
Nikoletti (2005) [12]	RCT	Cross-over	Oral Assessment Guide and Western Consortium Cancer Nursing Research Scale	Baseline and day 15 of each chemotherapy course	Unclear	Unclear	No	No	No	Yes

METHODOLOGY					RISK OF BIAS FOR RANDOMIZED CONTROL TRIALS					
First Author (Year)	RCT or quasi-RCT	Study design: (Parallel group, Cross-over, N-of-1)	Scales Used to Measure Mucositis	Frequency and Timing of Mucositis Assessment	Adequate sequence generation?	Adequate allocation concealment?	Participants and personnel blinded?	Outcome assessors blinded?	Loss to follow-up is less than 20% and/or equally distributed between both interventions?	Study free of selective reporting?
Cascinu (1994) [13]	RCT	Parallel group	Global assessment of the physicians' judgment and patients' description of mucositis severity graded O-4	Once weekly until start of next course	Unclear	Unclear	No	No	Yes	Yes
Rocke (1993) [14]	RCT	Parallel group	Physician and patient judged mucositis graded 0 to 4	Physician: Approximately 1 month after treatment initiation; Patient: 2 to 3 weeks after treatment initiation	Unclear	Unclear	No	No	Yes	Yes
Mahood (1991) [15]	RCT	Parallel group	Physician and patient judged mucositis graded 0 to 4	Physician: Approximately 1 month after treatment initiation; Patient: 2 to 3 weeks after treatment initiation	Unclear	Unclear	No	No	Yes	Yes
Kakoei (2013) [16]	RCT	Parallel group	Physician and patient judged mucositis graded 0 to 4	Days 1, 7 and 14	Unclear	Unclear	No	No	Yes	No

Abbreviations: RCT – randomized controlled trial; WHO – World Health Organization; OMAS – Oral Mucositis Assessment Scale; CTCAE – Common Terminology Criteria for Adverse Events

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APPENDIX 6: RANDOMIZED CONTROLLED TRIALS OF CRYOTHERAPY FOR THE PREVENTION OF ORAL MUCOSITIS IN ADULT AND PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION – OUTCOMES

First Author (Year)	COMPARISONS	OUTCOMES				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Katranci (2012) [1]	Cryotherapy versus no cryotherapy	30	30	For day 21, 1/30 in cryotherapy arm vs 6/30 in control group had severe mucositis	Not measured	No toxicity and no discomfort
Salvador (2012) [2]	Cryotherapy versus no cryotherapy	23	22	Overall mean (SE) of oral mucositis severity for the cryotherapy arm significantly lower than that for the control group: 0.43 (0.12) vs 1.14 (0.12); P<0.001 on a 0-4 scale	Overall mean (SE) mucositis-related pain score for the cryotherapy arm significantly lower than that for the control group: 0.30 (0.23) vs 1.64 (0.24); P < 0.001 on a 0-10 scale	Four participants experienced teeth sensitivity and complained of chills during cryotherapy, did not deter completion of therapy
Sorensen (2008) [3]	Cryotherapy versus oral rinse	67	66	Frequency of grade 3 or 4 oral mucositis was 10% in cryotherapy arm and 32% in saline rinse control group (P<0.005)	Not reported	No significant differences with respect to compliance or to side effects such as headache or taste disturbances. No effects on teeth
Svanberg (2007) [4] (companion papers: [5], [6])	Cryotherapy versus no cryotherapy	39	39	Auto: Cryotherapy significantly lower mucositis score on day 10 (1.6±1.9 vs 4.3±5.7; P=0.042) Allo: Cryotherapy significantly lower mucositis score on day 16 (3.7±1.8 vs 11.6±6.8; P=0.021)	No significant difference in pain between cryotherapy and control arms for either auto or allo group	Seven patients (18%) found oral cryotherapy unpleasant, and among those, four (10%) found it very unpleasant, mostly because of shooting pain from teeth
Gori (2007) [7]	Cryotherapy versus no cryotherapy	62	60	Incidence of grade 3–4 oral mucositis comparable (47% in cryotherapy arm vs. 53% in control group; P=0.46). Maximum mean mucositis score comparable (1.98±1.12 in cryotherapy arm vs 2.13±1.24 in control group; P=0.56). Duration of mucositis among patients with either grade 3–4 or grade 2–4 mucositis was comparable	Not reported	Not reported
Papadeas (2007) [8]	Cryotherapy versus no cryotherapy	36	40	Percentage patients free from oral toxicity higher in cryotherapy arm (P<0.01) according to physicians' evaluation in all three chemotherapy cycles	Not reported	Mouth numbness or headache (n=6); did not deter cryotherapy
Lilleby (2006) [9]	Cryotherapy versus warm saline rinses	21	19	Cryotherapy group experienced less grade 3–4 mucositis than normal saline group (14 vs 74%, P=0.0005). Average number of days with grade 3 mucositis: 0.5 in cryotherapy group vs 4.6 in normal saline group (P=0.0001). Mean of average daily mucositis scores for cryotherapy vs. normal saline groups: 0.41 vs 1.06; P=0.0005	Mean of average mouth pain scores 2.7 for normal saline vs 0.6 for cryotherapy groups (P=0.003)	Some patients complained of coldness and stopped using ice chips
Baydar (2005) [10]	Cryotherapy versus no cryotherapy	45	54	Development of mucositis correlated only with cryotherapy in logistic regression: OR=11.5; 95% CI=3.2 to 41.9; P=0.001	Not reported	No local or systemic side effects due to cryotherapy

First Author (Year)	**COMPARISONS**	**OUTCOMES**				
		Number Received Intervention Group 1	Number Received Intervention Group 2	Description of Main Mucositis Findings	Description of Main Pain Findings	Description of Adverse Events
Karagozoglu (2005) [11]	Cryotherapy versus no cryotherapy	30	30	Patient-judged: Rate of mucositis 36.7% with cryotherapy and 90.0% in control group; P<0.05. Physician-judged: Rate of mucositis 10.0% with cryotherapy and 50.0% in control group; P<0.05	Not reported	Not reported
Nikoletti (2005) [12]	Cryotherapy versus no cryotherapy	NR	NR	Standard care vs cryotherapy: OAG: OR 3.26, 95% CI 1.55 to 6.90; P=0.002. WCCNR: OR 3.23, 95% CI 1.19 to 9.09; P=0.021	Cryotherapy more effective than standard care in reducing average reported pain (P=0.009)	Nausea, sensitivity and headache with cryotherapy (n = 5)
Cascinu (1994) [13]	Cryotherapy versus no cryotherapy	44	40	Mucositis significantly reduced by cryotherapy with first cycle of therapy (mean score for cryotherapy 0.59 vs 1.1 for control group; P<0.05) and all chemotherapeutic courses (mean score for cryotherapy 0.36 vs 0.69 for control group; P< 0.05)	Not reported	Cryotherapy well tolerated by most patients. Two patients reported an “ice cream” headache resulting in cryotherapy refusal
Rocke (1993) [14]	Cryotherapy 60 versus 30 min	89	88	Mean physician-judged mucositis grades 0.58 and 0.79 for 30 vs 60 minutes of cryotherapy (P=0.37). Mean patient-graded mucositis scores were 0.73 and 1.00 (P=0.09)	Not reported	Few subjects discontinued cryotherapy prematurely because of nausea, headache, or chill
Mahood (1991) [15]	Cryotherapy versus no cryotherapy	50	45	Mean physician-judged mucositis grade for cryotherapy 0.9 vs 1.9 for control (P=0.0002). Mean patient-graded toxicity 1.1 for cryotherapy vs 2.4 for control (P=0.0001)	Not reported	Cryotherapy well tolerated by most. Few patients noted mild, temporary mouth numbness or “ice cream headache" which rapidly resolved after cessation of cryotherapy. Some ascribed nausea to cryotherapy
Kakoei (2013) [16]	Cryotherapy versus no cryotherapy	NR	NR	Mean pain intensity in the control group significantly increased with time (P<0.001), whereas cryotherapy group showed no significant change with time (P>0.05)	Patients’ self-assessment in control group significantly higher oral discomfort with time (P=0.012) vs cryotherapy group with no significant changes during study (P>0.05)	Not reported

Abbreviation: SE – standard error; auto- autologous; allo – allogeneic; OAG – Oral Assessment Guide; WCCNR - Western Consortium Cancer Nursing Research Scale; OR – odds ratio; CI – confidence interval

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APPENDIX 7: RANDOMIZED CONTROLLED TRIALS OF LOW LEVEL LIGHT THERAPY FOR THE PREVENTION OF ORAL MUCOSITIS IN ADULT AND PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION - STUDY CHARACTERISTICS

First Author (reference)	Year Pub	Age	Underlying Condition	Setting	N Randomized	Type of Laser	Wavelength (nm)	Energy (J/m2)	Laser Schedule
Antunes[1 2]	2013	Adults	Head and neck cancer	Chemo-radio	94	InGaAlP	660	4	5 sessions/week during radiation
Arbabi-Kalati[3]	2013	Adults	Oncologic disorders	Chemo	48	Mustang	630	5	Prior to chemotherapy
Gautam (a)[4 5]	2012	Adults	Head and neck cancer	Chemo-radio	239	He-Ne	632.8	3	5 sessions/week x 45 days
Gautam (b)[6]	2012	Adults	Oral carcinoma	Chemo-radio	121	He-Ne	632.8	3.5	5 sessions/week during radiation
Gouvea de Lima[7]	2012	Adults	Head and neck cancer	Chemo-radio	75	GaAlAs	660	2.5	5 sessions/week during radiation
Hodgson (a)[8]	2012	Both	Hematologic, oncologic disorders	HSCT (allo, auto)	40	Infrared LED	670 ± 10	4	Daily from day 0 to day +14
Hodgson (b)[8]	2012	Adults	Multiple myeloma	HSCT (auto)	40	Infrared LED	670 ± 10	4	Daily from day 0 to day +14
Oton-Leite[9 10]	2012	Adults	Head and neck cancer	Radio or Chemo-radio	60	InGaAlP	685	2	5 sessions/week during radiation
Pires-Santos[11]	2012	Adults	Breast cancer	Chemo	12	NA	NA	NA	Day 0 to day +7 q 48 hours
Silva[12]	2011	Both	Hematologic, oncologic disorders	HSCT (allo, auto)	42	InGaAlP	660	4	Daily from day -4 to day +4
Chor[13]	2010	Adults	NA	HSCT (auto)	34	AsGaAl	660	NA	Daily from day -7 to day 0
Khouri[14]	2009	Both	Hematologic disorders	HSCT (allo)	22	InGaAlP and GaAlAs laser	660 and 780	6.3	Daily until day +15 or day of engraftment
Antunes[15]	2007	Adults	Hematologic Disorders	HSCT (allo, auto)	38	InGaAlP	660	4	Daily from day -7 until neutrophil recovery
Cruz[16]	2007	Children	Hematologic and solid malignancies	Chemo or HSCT (auto)	62	NA	780	4	Daily from start of chemo x 5 days
Schubert[17]	2007	Both	Hematologic, oncologic disorders	HSCT (allo, auto)	47	GaAlAs	650	2	Daily from day -1 of conditioning to day +2
Arun Maiya[18]	2006	Adults	Oral carcinoma	Radio	50	He-Ne	632.8	1.8	5 sessions/week during radiation
Lopes[19]	2006	Adults	Head and neck cancer	Chemo-radio	60	InGaAlP	685	2	NA
Bensadoun[20 21]	1999	Adults	Head and neck cancer	Radio	30	He-Ne	632.8	2	5 sessions/week during radiation
Cowen[22]	1997	Adults	Hematologic malignancies	HSCT (auto)	30	He-Ne	632.8	1.5	Daily from day -5 to day -1

Adapted from Oberoi et al. For more detailed information and outcomes, see [23]
Abbreviations: N – number; allo - allogeneic; auto-autologous; chemo – chemotherapy; GaAlAs/AsGaAl – gallium-aluminium-arsenide/arsenate; He-Ne- helium-neon; HSCT – hematopoietic stem cell transplantation; InGaAlP – indium-gallium-aluminium phosphide; LED – light emitting diode; NA – not available; pub – published; radio- radiotherapy

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APPENDIX 8: RANDOMIZED CONTROLLED TRIALS OF KERATINOCYTE GROWTH FACTOR FOR THE PREVENTION OF ORAL MUCOSITIS IN ADULT AND PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION – STUDY CHARACTERISTICS

STUDY CHARACTERISTICS AND PARTICIPANTS

First Author (Year)	Enrollment Year		Country of Patient Enrollment	Pharma Sponsorship Declared	Total N Randomized	Age (Pediatric, Adult, Both)	Specific Cancer Diagnosis	Population Type (Cancer, HSCT, Both)	Transplant Type	Treatment (Chemo alone, Radiation alone, Both, Not specified)	Treatment Related to KGF
	Start	End									
Blijilevens (2013) [1]	2006	2009	Europe	Yes	281	Adult	Multiple myeloma	HSCT	Auto	Chemo alone	Melphalan
Jagasia (2012) [2]	2005	2008	US and Australia	Yes	155	Adult	Hem malignancy	HSCT	Allo	Both	Variable
Le (2011) [3]	2005	2007	North America and Europe	Yes	188	Adult	Advanced head and neck cancer	Cancer	NA	Both	Cisplatin, radiotherapy (no surgery)
Henke (2011) [4]	2005	2007	Australia, Canada, Europe	Yes	186	Adult	Advanced head and neck cancer	Cancer	NA	Both	Cisplatin, radiotherapy (post-operative)
Vadhan-Raj (2010) [5]	2005	2008	US	Yes	48	Both	Sarcoma	Cancer	NA	Chemo alone	Doxorubicin
Brizel (2008) [6]	1999	2001	Australia, Canada, US	Yes	100	Adult	Advanced head and neck squamous cell carcinoma	Cancer	NA	Both	Cisplatin, 5-FU, radiotherapy
Rosen (2006) [7]	NR	NR	NR	Yes	65	Adult	Metastatic colon cancer	Cancer	NA	Chemo alone	5-FU, leukovorin
Blazar (2006) [8]	NR	NR	US	Yes	100	Both	Hem malignancy	HSCT	Allo	Both	Cyclophosphamide with TBI or busulphan
Freytes (2004) [9]	NR	NR	US	Yes	52	Adult	Hem malignancy	HSCT	Auto	Both	Variable
Spielberger (2004) [10](companion paper: [11])	2001	2002	US	Yes	214	Adult	Hem malignancy	HSCT	Allo	Both	Etoposide, cyclophosphamide, TBI
Meropol (2003) [12]	NR	NR	US	Yes	81	Adult	Metastatic colon or rectal cancer	Cancer	NA	Chemo alone	5-FU, leukovorin

Abbreviations: NR – not reported; NA – not applicable; pharma – pharmaceutical company; N – number; US – United States; HSCT – hematopoietic stem cell transplantation; hem- hematological; auto- autologous; allo – allogeneic; 5-FU – 5-fluorouracil; TBI – total body irradiation; KGF - keratinocyte growth factor

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APPENDIX 9: RANDOMIZED CONTROLLED TRIALS OF KERATINOCYTE GROWTH FACTOR FOR THE PREVENTION OF ORAL MUCOSITIS IN ADULT AND PEDIATRIC PATIENTS RECEIVING TREATMENT FOR CANCER OR UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION – METHODOLOGY

METHODOLOGY					RISK OF BIAS FOR RANDOMIZED CONTROL TRIALS					
First Author (Year)	RCT or quasi-RCT	Study Design: (Parallel group, Cross-over, N-of-1)	Scales Used to Measure Mucositis	Frequency and Timing of Mucositis Assessment	Adequate sequence generation?	Adequate allocation concealment?	Participants and personnel blinded?	Outcome assessors blinded?	Loss to follow-up is less than 20% and/or equally distributed between both interventions?	Study free of selective reporting?
Blijilevens (2013) [1]	RCT	Parallel	WHO	Daily from day 2 to day 32	Yes	Unclear	Yes	Yes	Yes	Yes
Jagasia (2012) [2]	RCT	Parallel	WHO	First day of the conditioning regimen until discharge or day 28	Unclear	Unclear	Yes	Yes	Yes	Yes
Le (2011) [3]	RCT	Parallel	WHO	Twice weekly during chemo-radiotherapy for 15 weeks	Unclear	Yes	Yes	Yes	Yes	Yes
Henke (2011) [4]	RCT	Parallel	WHO	Twice-weekly during radio-chemotherapy for 15 weeks	Yes	Yes	Yes	Yes	Yes	Yes
Vadhan_Raj (2010) [5]	RCT	Parallel	WHO, CTCAE	Before chemotherapy and days 10, 12 and 14	Yes	Yes	Yes	Yes	Yes	Yes
Brizel (2008) [6]	RCT	Parallel	CTCAE v2.0 and RTOG	Once weekly for 12 weeks, weeks 14, 16, 18 and 20	Unclear	Unclear	Yes	Yes	Yes	Yes
Rosen (2006) [7]	RCT	Parallel	WHO, OMDQ	Baseline, days 1, 4, 8, 12, 15, and at the end of both cycles 1 and 2	Unclear	Unclear	Yes	Yes	Yes	Yes
Blazar (2006) [8]	RCT	Parallel	WHO	3 times per week during hospitalization	Unclear	Unclear	Yes	Yes	Yes	Yes
Freytes (2004) [9]	RCT	Parallel	CTCAE, OMAS	Day 0 and three times per week until mucositis resolved	Unclear	Unclear	Yes	Yes	Yes	Yes
Spielberger (2004) [10] (companion paper: [11])	RCT	Parallel	WHO, RTOG, Western Consortium Cancer Nursing Research Scale	Daily for 28 days after HSCT	Unclear	Unclear	Yes	Yes	Yes	Yes
Meropol (2003) [12]	RCT	Parallel	WHO	Days 1, 4, 8, 15, and 28 after chemotherapy	Unclear	Unclear	Yes	Yes	Yes	Yes

Abbreviations: RCT – randomized controlled trial; WHO – World Health Organization; CTCAE – Common Terminology Criteria for Adverse Events; RTOG – Radiation Therapy Oncology Group; OMDQ – Oral Mucositis Daily Questionnaire; HSCT – hematopoietic stem cell transplantation

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