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Review

Clinical practice guideline for the prevention of oral and oropharyngeal mucositis in pediatric cancer and hematopoietic stem cell transplant patients: 2021 update

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Abstract ***Purpose:*** To update the 2015 clinical practice guideline for the prevention of oral mucositis in pediatric cancer or hematopoietic stem cell transplant (HSCT) patients.
Methods: We performed seven systematic reviews of mucositis prevention. Three reviews included randomized controlled trials (RCTs) conducted in pediatric and adult patients evaluating cryotherapy, keratinocyte growth factor (KGF) or photobiomodulation therapy with a focus on efficacy. Three reviews included studies of any design conducted in pediatric patients evaluating these same interventions with a focus on adverse events and feasibility. One review included all RCTs of any intervention for mucositis prevention in pediatric patients. Primary outcome was severe oral mucositis.

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Results: We included 107 unique studies of cryotherapy (22 RCTs and 4 pediatric studies); KGF (15 RCTs and 12 pediatric studies); photobiomodulation therapy (29 RCTs and 8 pediatric studies) and any intervention (31 pediatric RCTs). Effects on severe mucositis reduction from RCTs were cryotherapy risk ratio (RR) 0.49 and 95% confidence interval (CI) 0.31–0.76; palifermin RR 0.81 and 95% CI 0.69–0.95 and photobiomodulation therapy RR 0.40 and 95% CI 0.27–0.60. Cryotherapy was not feasible in young children while photobiomodulation therapy was feasible across age groups. Palifermin was associated with adverse effects.
Conclusions: Cryotherapy should be used for older cooperative pediatric patients who will receive short infusions of melphalan or 5-fluorouracil. Intraoral photobiomodulation therapy (620–750 nm spectrum) should be used in pediatric patients undergoing autologous or allogeneic HSCT and for pediatric head and neck carcinoma patients undergoing radiotherapy. Palifermin should not be used routinely in pediatric cancer or HSCT patients.

1. Introduction

Oral mucositis is a common toxicity of intensive chemotherapy and radiotherapy in pediatric cancer and hematopoietic stem cell transplant (HSCT) patients [1]. It is important because it is painful, impairs the ability to eat or drink, limits cancer treatment delivery, reduces quality of life, increases costs and may predispose patients to bacteremia [2–4]. We previously developed a clinical practice guideline (CPG) in 2015 for mucositis prevention in this population [5].

All CPGs require updating on a regular basis, and given that the 2015 CPG was created five years ago, an update was required. As in the initial CPG, we considered maintenance of good oral hygiene a good practice statement [6]. The objective was to update the 2015 CPG for mucositis prevention in pediatric cancer and HSCT patients.

2. Methods

2.1. Panel constitution

The panel included representatives from pediatric hematology/oncology, pediatric HSCT, oral medicine and dentistry, nursing, pharmacy, two patient advocates and a CPG methodologist (Appendix 1). Members were selected based on expertise, discipline and geographic location. Panel members completed conflict of interest forms; no members had conflicts that precluded participation in any aspect of this panel (Appendix 2).

2.2. General approach

We used the Appraisal of Guidelines for Research & Evaluation II tool to direct development of this CPG [7,8]. While CPG conduct was financially supported by the Pediatric Oncology Group of Ontario, the CPG was editorially independent from the funder.

The key clinical question remained unchanged from the 2015 CPG and was 'What prophylactic interventions are effective at preventing or reducing the severity of oral and oropharyngeal mucositis in pediatric patients (0–18 years) receiving treatment for cancer or undergoing HSCT?' The target population was pediatric patients receiving chemotherapy or radiotherapy for cancer or undergoing HSCT who are at risk for developing oral mucositis. The target users were physicians, nurses, nurse practitioners, pharmacists, oral medicine specialists and dentists who manage mucositis in the target population. Administrators responsible for allocation of resources in pediatric oncology care settings may also find the CPG useful.

2.3. Searching and selecting the evidence

The 2015 CPG consisted of five systematic reviews. We reasoned that interventions effective for adults would likely be applicable to children and adolescents and, thus, decided to conduct systematic reviews of randomized controlled trials (RCTs) in both pediatric and adult populations. However, we made pragmatic choices so that the number and conduct of the systematic reviews would be feasible. At that time, there were two recent publications focused on mucositis prevention in primarily adult patients, namely a Cochrane Collaboration systematic review [9] and recommendations from The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) [10–18]. We focused on interventions that were recommended or suggested by MASCC/ISOO for the prevention of oral mucositis and showed evidence of benefit in the Cochrane Collaboration systematic review. These interventions were cryotherapy, keratinocyte growth factor (KGF) and low-level light therapy (nomenclature updated to photobiomodulation therapy). Three systematic reviews of RCTs of these interventions were conducted in pediatric and adult populations. For the

2015 CPG, we were also concerned about KGF adverse effects and, thus, conducted a fourth systematic review including publications of any study design evaluating KGF in pediatric patients. Finally, the fifth systematic review included all RCTs of mucositis prevention in pediatric populations to ensure directly applicable studies were evaluated. The 2015 CPG made three conditional recommendations for use of cryotherapy, KGF and photobiomodulation therapy [5].

The strategy for the 2021 CPG update consisted of seven systematic reviews that followed the same general approach but expanded the evaluation of adverse effects and feasibility in pediatric patients (Appendix 3). Three systematic reviews included RCTs of mucositis prevention examining cryotherapy, KGF and photobiomodulation therapy in pediatric and adult populations, with a focus on evaluating intervention efficacy overall and among pediatric patients where possible. Three systematic reviews included studies of any design examining these same three interventions but restricted to pediatric patients, with a focus on describing adverse effects and feasibility of the intervention. The final systematic review included all RCTs of mucositis prevention conducted in pediatric populations.

The literature searches were facilitated by a library scientist in the following databases: MEDLINE, MEDLINE in-process, MEDLINE epubs ahead of print and Embase. Appendix 4 consists of the full search strategies for all seven systematic reviews. Across all reviews, inclusion criteria were fully published studies that evaluated an intervention as prophylaxis for mucositis where at least 90% of study participants were patients undergoing treatment for cancer or HSCT recipients. There was no restriction by language. The search included studies published from January 1, 1980, to August 31, 2020. For the three all-ages systematic reviews of RCTs, randomized trials with a parallel group design were included if the intervention focused on cryotherapy, KGF or photobiomodulation therapy without restriction by age. For the three pediatric systematic reviews of studies of any design, studies were included if they examined cryotherapy, KGF or photobiomodulation therapy; the study population was younger than 25 years and the mean or median age was less than 19 years without restriction by study design. The last systematic review included RCTs of mucositis prevention with a parallel group design conducted in patients younger than 25 years if the mean or median age was less than 19 years without restriction by intervention. We included studies from the original CPG to improve our ability to evaluate secondary end-points, to perform stratified analysis and to more comprehensively describe cancer treatments associated with applied interventions. In addition, the two new systematic reviews that focused on adverse effects and feasibility in pediatric patients were not included in the original CPG, necessitating inclusion of studies across the time span.

For all systematic reviews, titles and abstracts of articles identified by the search strategies were screened, and the full text of potentially eligible articles were evaluated. Articles that were identified in the 2015 CPG publication, but no longer indexed in the databases searched, were also brought forward.

Screening of abstracts and full-text reviews were performed in duplicate (P.P. and P.D.R.). Disagreements were resolved by a third reviewer (L.S.). Agreement in study inclusion was described using the Kappa statistic [19].

2.4. Outcomes

The panel identified and categorized important outcomes by consensus. Outcomes considered critical for decision-making were severe mucositis, mucositis of any severity, pain, fever and neutropenia (FN), intervention adverse effects and feasibility of the intervention in pediatric populations. Outcomes considered important were enteral or parenteral nutrition and receipt of opioid analgesia. Fever alone was not considered important.

As in the 2015 CPG, the primary outcome was severe oral mucositis; this categorization was based on the mucositis scale used in the primary publication. World Health Organization (WHO), National Cancer Institute Common Toxicity Criteria v2·0 or Radiation Therapy Oncology Group scales range from 0 to 4; severe was defined as a score of 3 or 4. The National Cancer Institute Common Terminology Criteria for Adverse Events v3·0 and v4·0 mucositis scales range from 1 to 5; severe was defined as a score of 3–5. As the timing of mucositis onset varies by treatment regimen, in the event of multiple reported mucositis time points, we chose the time point with the highest proportion of severe mucositis across the intervention and control groups.

Other outcomes abstracted for synthesis were any mucositis, any mucositis-related pain (for example, visual analogue scale [0–10] score $\geq$1 or WHO Pain Assessment Scale score $\geq$1), FN, supplemental enteral nutrition such as nasogastric feeds, administration of total parenteral nutrition and opioid use. These were recorded as dichotomous variables. Intervention-associated adverse effects and feasibility were described qualitatively.

2.5. Study demographics and risk of bias

Demographic information included study sample size, population age (adult, pediatric or both), cancer or HSCT cohort (cancer only, HSCT only or both cancer and HSCT), cancer treatment (chemotherapy, radiotherapy, both or not specified), specific chemotherapy related to the mucositis prevention intervention, pharmaceutical sponsorship, year of publication ($<$2012 or $\geq$2012, approximate median), intervention details, control details and mucositis assessment scale.

For the RCTs, the Cochrane Collaboration's tool for assessing risk of bias was used [20]. These items assess adequate sequence generation, adequate allocation concealment, participant and personnel blinded, outcome assessors blinded, lack of attrition bias and free of selective reporting.

2.6. Statistical analysis

Synthesis of quantitative data was performed when there were at least three studies with available outcome data. All syntheses used the risk ratio (RR) with the 95% confidence interval (CI) as the effect measure, where an RR less than 1 suggests that the intervention is better than control. As we anticipated heterogeneity, the Mantel-Haenszel random effects model in Review Manager 5·3[20] was used to estimate treatment effects.

Stratified analysis focused only on the primary outcome, severe mucositis, and evaluated whether heterogeneity in effects could be explained by age and risk of bias. For risk of bias, adequate sequence generation and adequate allocation concealment were examined as they have the largest association with exaggerated treatment effects [21]. Stratified analysis was performed when there were at least two studies with outcome data in each stratum. The P value for interaction (P int) was used to determine if heterogeneity in the effect could be explained by these covariates [20].

We used funnel plots to explore the possibility of publication bias when at least 10 studies were available for the primary outcome of severe mucositis [20]. Funnel plots are figures with the effect measure on the x-axis and precision on the y-axis. An absence of studies in the right lower quadrant may indicate publication bias. In this event, we used the trim and fill technique to describe its potential impact. With this approach, outlying studies are removed (trim), and hypothetical negative studies with equal weight are added (fill) [20]. Analysis used Review Manager 5·3 (Cochrane Collaboration, Nordic Cochrane Centre) [20].

2.7. Formulating recommendations, assigning quality of evidence and manuscript preparation

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the level of evidence and to formulate the recommendations [22]. The level of evidence reflects the certainty of intervention effects in our target population, namely pediatric patients receiving cancer treatments or undergoing HSCT. Evidence level was rated as high, moderate, low or very low. Level designation was based on study design limitations, imprecision, inconsistency and indirectness. Recommendations were either strong or conditional. A strong recommendation was made where benefits clearly outweighed the harms and burdens, or vice versa. Conversely, a conditional recommendation was made when the benefits and harms or burdens were either closely matched or uncertain. Efficacy, adverse effects, feasibility and resources influenced recommendation formulation.

Evidence tables based on the systematic reviews were created and distributed. Recommendations were developed during a series of online meetings. A plan to manage conflicts of interest was created. If a member had a conflict of interest with a manufacturer of a product under consideration, that member was recused from deliberations and did not participate in that recommendation formulation. The remaining panel members voted on each recommendation, and consensus was required to adopt the recommendations. Draft versions of the recommendations and manuscript were circulated until approved by all authors. The peer-review mechanism was used as an efficient alternative to external review. We plan to update the 2021 CPG in five years or earlier in the event of important new information.

3. Results

Table 1 summarizes the health question, recommendations, strength of recommendations, level of evidence and remarks. The search strategy identified 107 unique trials across the seven systematic reviews. Agreement in study inclusion between reviewers was perfect (Kappa = 1·00). The flow diagram of study identification, selection and reasons for exclusion for each of the seven systematic reviews are shown in Appendix 5. Table 2 summarizes the number of studies in the 2015 CPG, the number of new studies added in this 2021 update and the characteristics of studies by age group, cancer or HSCT cohort, cancer therapy, pharmaceutical sponsorship, year of publication and risk of bias. Across the seven reviews, 50 new unique studies were added to the 57 identified in the 2015 CPG, and 48 (44·9%) were conducted in a pediatric population. All KGF studies evaluated palifermin except for one study of repifermin [23]. As this product was never brought to market, outcomes and recommendations focused only on palifermin.

Table 3 summarizes syntheses of cryotherapy, palifermin and photobiomodulation therapy RCTs for outcomes in which a sufficient number of studies reported data. Appendices 6–13 provide details of the pediatric and adult RCTs and pediatric studies of any design for these three interventions. Appendix 14 illustrates stratified analyses for cryotherapy, palifermin and photobiomodulation therapy RCTs by age, adequate sequence generation and adequate allocation concealment where a sufficient number of studies per stratum were available. Appendix 15 shows details of RCTs of any intervention conducted in pediatric populations. Three interventions were examined in more than one

Table 1
Summary of recommendations for mucositis prophylaxis in children and adolescents with cancer and pediatric HSCT recipients.

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 pediatric patients (0 to 18 years) receiving treatment for cancer or undergoing HSCT?	
1. Use cryotherapy for older, cooperative pediatric patients receiving treatment for cancer or undergoing HSCT who will receive short infusions of melphalan or 5-fluorouracil.	Strong recommendation High-quality evidence
Remarks: The panel valued the absence of documented adverse effects, low costs and consistent benefits associated with cryotherapy. The duration of melphalan and 5-fluorouracil administration in the included trials was 30 min or less where infusion duration was described. The panel did not believe that cryotherapy would be feasible for chemotherapy administrations longer than 1 h.	
2. Consider using cryotherapy for older, cooperative pediatric patients receiving treatment for cancer or undergoing HSCT who will receive short infusions of chemotherapy associated with mucositis other than melphalan or 5-fluorouracil.	Conditional recommendation Moderate-quality evidence
Remarks: The panel hypothesized that the efficacy of cryotherapy is likely generalizable to chemotherapy other than melphalan and 5-fluorouracil. However, the indirectness of the data lowered the panel's certainty and resulted in a conditional recommendation. It is important to counsel families and patients that mucositis may develop even with diligent cryotherapy use, and the efficacy of cryotherapy may vary depending on the chemotherapy regimen administered.	
3. Do not administer palifermin routinely to pediatric patients with cancer receiving treatment for cancer or undergoing HSCT.	Strong recommendation High-quality evidence
Remarks: While the panel acknowledged the significant reduction in severe mucositis associated with palifermin, the observed effect size was relatively modest. Based on its known short-term adverse effects, its potential for long-term negative effects on cancer outcomes, high costs and restricted availability, the panel made a strong recommendation against its routine use.	
4. Use intraoral photobiomodulation therapy in the red light spectrum (620–750 nm) for pediatric patients undergoing autologous or allogeneic HSCT and for pediatric patients who will receive radiotherapy for head and neck carcinoma.	Strong recommendation High-quality evidence
Remarks: The panel valued the consistent benefits of photobiomodulation therapy and data regarding feasibility in pediatric patients. The ability to deliver photobiomodulation therapy requires specialized equipment, training and protective eyewear for the patient and those in attendance. The panel believed these requirements to be acceptable given the magnitude of benefit and the restricted patient populations included in the recommendation based on direct data. The ability to deliver photobiomodulation therapy to very young children requires assistance and support from family members and may not always be successful.	
5. Consider using intraoral photobiomodulation therapy in the red light spectrum (620–750 nm) for pediatric patients who will receive radiotherapy for head and neck cancers other than carcinoma.	Conditional recommendation Moderate-quality evidence
Remarks: Although direct data were not available, the panel hypothesized that the efficacy of photobiomodulation therapy for head and neck carcinoma patients receiving radiotherapy is likely generalizable to pediatric patients who will receive radiotherapy for other head and neck cancers such as rhabdomyosarcoma. However, the indirectness of the data lowered the panel's certainty and resulted in a conditional recommendation.	
6. Do not administer GCSFs to pediatric patients receiving treatment for cancer or undergoing HSCT for the purpose of mucositis prevention.	Strong recommendation High-quality evidence
Remarks: While the panel recognized that patients receive GCSFs for other indications including shortening the duration of neutropenia, the absence of benefit, adverse effects and costs led the panel to make a strong recommendation against its use for the purpose of mucositis prevention.	

HSCT, hematopoietic stem cell transplantation; GCSF, granulocyte colony-stimulating factor.

Table 2
Demographic characteristics of included studies overall and by the seven systematic reviews.

	Unique studies overall	Individual systematic reviews						
		Cryotherapy		Keratinocyte growth factor		Photobiomodulation therapy		Any intervention
		Adult + Pediatric RCTs	Pediatric All study designs	Adult + Pediatric RCTs	Pediatric All study designs	Adult + Pediatric RCTs	Pediatric All study designs	Pediatric RCTs
Total number of studies								
Original	57	12	N/A	11	3	15	N/A	17
New studies in update	50	10	4	4	9	14	8	14
Age group								
Adult	53	19	0	11	0	23	0	0
Pediatric	48	2	4	3	12	2	8	31
Both	6	1	0	1	0	4	0	0
Cancer or HSCT cohort								
Cancer only	56	13	1	8	2	18	2	18
HSCT only	48	9	3	7	10	10	4	11
Cancer and HSCT	3	0	0	0	0	1	2	2
Cancer treatment								
Chemotherapy	51	18	2	6	4	7	4	18
Radiotherapy	5	1	0	0	0	4	0	0
Both	48	3	2	8	7	18	4	10
Not specified	3	0	0	1	1	0	0	3
Pharmaceutical sponsor								
Yes	24	0	0	11	2	3	3	7
No	83	22	4	4	10	26	5	24
Year of publication								
<2012	46	9	1	9	0	13	3	15
≥2012	61	13	3	6	12	16	5	16
Risk of bias								
Adequate sequence generation	41	8	1	6	3	17	0	14
Adequate allocation concealment	23	1	1	6	2	5	0	14
Participants, personnel blinded	29	0	0	14	2	4	1	14
Outcome assessors blinded	49	3	0	15	3	21	2	15
Lack of attrition bias	82	21	2	15	3	23	2	30
Free of selective reporting	79	18	2	13	1	26	1	26
Not applicable (non-RCT)	17	0	2	0	9	0	6	0

HSCT, hematopoietic stem cell transplantation; N/A, not applicable; RCT, randomized clinical trial.

study, namely granulocyte colony-stimulating factors (GCSFs), glutamine and Traumeel®. Only GCSFs had sufficient number of studies for synthesis (Table 3). Appendix 16 shows results of trim and fill sensitivity analysis where publication bias was suggested in the funnel plots. Table 4 summarizes identified research gaps.

Recommendation 1: Use cryotherapy for older, cooperative pediatric patients receiving treatment for cancer or undergoing HSCT who will receive short infusions of melphalan or 5-fluorouracil (strong recommendation, high-quality evidence).

Explanation: Table 2 shows that there were 22 RCTs of cryotherapy (10 added in the 2021 update; Appendices 6 and 7) and 4 pediatric studies of any design (Appendix 8). Cryotherapy significantly reduced severe mucositis (RR 0.49, 95% CI 0.31–0.76) and any mucositis (RR 0.62, 95% CI 0.46–0.83) compared with no prophylaxis (Table 3). Appendix 7 shows the population, diagnosis and specific chemotherapy associated with cryotherapy administration. The most commonly evaluated chemotherapies infused concurrently with cryotherapy were melphalan (n = 4) and 5-fluorouracil (n = 8). The chemotherapy infusion duration was 30 min or less for studies in which it was described. Appendix 7 also shows when cryotherapy was started and stopped relative to chemotherapy infusion.

Two pediatric RCTs were performed. One study of 53 patients included those aged 4–17 years and attempted cryotherapy for multiple chemotherapy regimens with varying infusion times, some lasting greater than 12 h [24]. Severe mucositis was similar among intervention (15/26, 58%) and control (11/23, 48%) groups although only 15 of 26 (58%) intervention patients complied with cryotherapy on at least 70% of study days. A second RCT included 40 patients aged 6–18 years and noted severe mucositis in 0 of 20 (0%) of intervention (flavored cryotherapy) and 5 of 20 (25%) of control (plain cryotherapy) patients [25]. No adverse effects were reported in these two RCTs or the other

Table 3
Synthesis of intervention versus no prophylaxis among pediatric and adult randomized trials of cryotherapy, palifermin and photobiomodulation therapy and among pediatric randomized trials of any intervention.

Comparison and outcome	No. trials	N	RR	95% CI	I^2	P
Pediatric and adult RCT meta-analysis						
Cryotherapy versus no prophylaxis						
Severe mucositis	11	960	0.49	0.31–0.76	70%	0.001
Mucositis, any severity	11	942	0.62	0.46–0.83	92%	0.002
Palifermin versus no prophylaxis						
Severe mucositis	9	1434	0.81	0.69–0.95	66%	0.008
Mucositis, any severity	7	1182	0.93	0.84–1.02	87%	0.11
Total parenteral nutrition	3	648	0.96	0.58–1.60	87%	0.88
Any photobiomodulation therapy vs. no prophylaxis						
Severe mucositis	19	1078	0.40	0.27–0.60	66%	<0.00001
Mucositis, any severity	14	763	0.84	0.71–1.00	94%	0.05
Pain	4	260	0.74	0.40–1.40	95%	0.36
Opioid use	6	514	0.47	0.37–0.59	0%	<0.00001
Enteral nutrition	5	337	0.56	0.24–1.34	57%	0.19
Intraoral red light spectrum (620–750 nm) photobiomodulation therapy versus no prophylaxis						
Severe mucositis	16	970	0.42	0.27–0.63	69%	<0.0001
Mucositis, any severity	10	636	0.84	0.70–1.01	95%	0.07
Pediatric RCT meta-analysis						
GCSFs versus no prophylaxis						
Severe mucositis	3	520	0.95	0.75–1.21	15%	0.68

CI, confidence interval; GCSFs, granulocyte colony stimulating factors; RCT, randomized controlled trials; RR, risk ratio.

pediatric studies (Appendix 8). In terms of feasibility, two studies suggested compliance was worse in younger patients, specifically in those younger than 7 years [24,26].

In stratified analysis (Appendix 14), heterogeneity in the effect of cryotherapy was not explained by adequate sequence generation. The funnel plot of severe mucositis suggested the potential for publication bias (data not shown) although sensitivity analysis using the trim and fill approach did not show substantially different effects compared with the base analysis (Appendix 16).

The panel made a strong recommendation to use cryotherapy for older, cooperative patients who were receiving regimens evaluated in the RCTs, namely short infusions of melphalan or 5-fluorouracil. The strong recommendation was based on the absence of documented adverse effects, low costs and consistent benefits associated with cryotherapy. Cryotherapy is typically delivered by asking patients to suck on ice in the form of cubes, chips or flavored ice pops for the duration of the chemotherapy infusion. Ice pops may be more palatable for pediatric patients. Ideal start and end times are not clear, but a reasonable strategy would be to start 5 min before infusion start and continue cryotherapy for 5–30 min after infusion completion.

Recommendation 2: Consider using cryotherapy for older, cooperative pediatric patients receiving treatment for cancer or undergoing HSCT who will receive short infusions of chemotherapy associated with mucositis other than melphalan or 5-fluorouracil (conditional recommendation, moderate-quality evidence).

Explanation: The panel believed it was reasonable to generalize the efficacy of cryotherapy to short infusions of chemotherapy associated with mucositis other than melphalan or 5-fluorouracil. However, the indirectness of the data lowered the quality of evidence to moderate and resulted in a conditional recommendation. The panel also recognized that the effect of cryotherapy may vary depending on the chemotherapy regimen administered. Consequently, they felt it was important to

Table 4
Key knowledge gaps related to mucositis prophylaxis among children and adolescents with cancer and pediatric hematopoietic stem cell transplant recipients.

Key Knowledge Gaps
Determine efficacy of cryotherapy associated with chemotherapies other than melphalan and 5-fluorouracil
Identify approaches to improve the feasibility of cryotherapy administration in young pediatric patients
Determine the efficacy of intraoral photobiomodulation when used outside of HSCT and when used for pediatric patients receiving radiotherapy for head and neck cancers other than carcinomas
Determine the efficacy of extraoral photobiomodulation therapy in pediatric patients
Identify new effective approaches to prevent mucositis in pediatric patients
Determine approaches to improve implementation of strategies to reduce mucositis
Identify patient-related and treatment-related factors that increase risk of severe mucositis

HSCT, hematopoietic stem cell transplantation.

counsel families and patients that mucositis may develop even with diligent cryotherapy use.

Recommendation 3: Do not administer palifermin routinely to pediatric patients with cancer receiving treatment for cancer or undergoing HSCT (strong recommendation, high-quality evidence).

Explanation: Table 2 shows that there were 15 RCTs of KGF (4 added in the 2021 update; Appendix 9) and 12 pediatric studies of any design (9 added in the 2021 update; Appendix 10). Palifermin significantly reduced severe mucositis (RR 0.81, 95% CI 0.69–0.95) but did not significantly reduce any mucositis (RR 0.93, 95% CI 0.84–1.02) or total parenteral nutrition administration (RR 0.96, 95% CI 0.58–1.60) compared with no prophylaxis (Table 3). Three pediatric RCTs were performed [27,28], but only one had synthesisable primary outcome data; it compared palifermin to chlorhexidine [28]. Adverse effects significantly associated with palifermin in pediatric patients were rash, erythema and white film coating of the tongue or mouth (Appendix 10). One second malignancy with squamous cell carcinoma of the oral epithelium was noted in a patient with chronic oral graft-versus-host disease [29]. In terms of accessibility, palifermin is not currently routinely available in Canada or Europe but is available in the United States (verbal communication, Dr. James Scrivens, Sobi Canada Inc., September 14, 2020).

In stratified analysis, heterogeneity in the effect of palifermin on severe mucositis was not explained by either adequate sequence generation or adequate allocation concealment (Appendix 14). There was no suggestion of publication bias in the funnel plot (data not shown).

In making a strong recommendation against the routine use of palifermin in pediatric patients, the panel acknowledged the significant reduction in severe mucositis but noted the observed effect size was relatively modest. Other factors contributing to the strong recommendation against routine use were the known short-term adverse effects of palifermin, its potential for long-term negative effects on cancer outcomes, high costs and restricted availability in some jurisdictions. However, the panel noted that there may be rare cases in which palifermin could be considered, such as repeated episodes of debilitating mucositis.

Recommendation 4: Use intraoral photobiomodulation therapy in the red light spectrum (620–750 nm) for pediatric patients undergoing autologous or allogeneic HSCT and for pediatric patients who will receive radiotherapy for head and neck carcinoma (strong recommendation, high-quality evidence).

Explanation: Table 2 shows that there were 29 RCTs of photobiomodulation therapy (14 added in the 2021 update; Appendices 11 and 12) and 8 pediatric studies of any design (Appendix 13). All except two studies [30,31] used intraoral photobiomodulation therapy exclusively. Photobiomodulation therapy reduced severe mucositis (RR 0.40, 95% CI 0.27–0.60), any mucositis (RR 0.84, 95% CI 0.71–1.00) and opioid use (RR 0.47, 95% CI 0.37–0.59) when compared with no prophylaxis (Table 3). Photobiomodulation therapy did not significantly reduce pain or enteral nutrition (Table 3).

The most common approach was intraoral therapy in the red light spectrum (620–750 nm) (n = 24 RCTs). Intraoral photobiomodulation therapy in the red light spectrum had a similar effect to the overall analysis related to reduction in severe mucositis (RR 0.42, 95% CI 0.27–0.63) and any mucositis (RR 0.84, 95% CI 0.70–1.01) versus no prophylaxis. The most common settings in which photobiomodulation therapy in the red light spectrum was evaluated were among autologous and allogeneic HSCT recipients (n = 8) and among adults receiving radiotherapy for head and neck cancer or carcinoma (n = 10; Appendix 12).

Among the pediatric studies of photobiomodulation therapy, no adverse effects were noted (Appendix 13). Issues with compliance were not observed even though the youngest patients were 0–7 years of age across the studies. One study included infants younger than one year of age. Its authors noted that intraoral photobiomodulation therapy could be executed in all patients although for infants and young children, there could be the need to wait for the child to fall asleep or to distract the child with entertainment, increasing the time required [32].

In stratified analysis, heterogeneity in the effect of photobiomodulation therapy on severe mucositis was not explained by age group, adequate sequence generation or adequate allocation concealment (Appendix 14). The funnel plot of severe mucositis suggested the potential for publication bias (data not shown) although sensitivity analysis using the trim and fill approach did not show substantially different effects compared with the base analysis (Appendix 16).

The strong recommendation for photobiomodulation therapy was influenced by consistent benefits and data regarding feasibility in pediatric patients. The panel believed it was important to specify the approach most commonly used in the RCTs, namely intraoral therapy in the red light spectrum (620–750 nm). The panel considered whether age and cooperativity should be added to the recommendation but, based on the published pediatric experience, preferred that therapy should be used across the age spectrum. Successful utilization in very young children will require assistance and support from family members.

Recommendation 5: Consider using intraoral photobiomodulation therapy in the red light spectrum (620–750 nm) for pediatric patients who will receive radiotherapy for head and neck cancers other than carcinoma (conditional recommendation, moderate-quality evidence).

Explanation: The panel believed it was reasonable to generalize the efficacy of red light spectrum

photobiomodulation therapy for adults with head and neck carcinoma receiving radiotherapy to pediatric patients with non-carcinoma head and neck cancers such as rhabdomyosarcoma. However, the indirectness of the data lowered the quality of evidence to moderate and resulted in a conditional recommendation.

Recommendation 6: Do not administer GCSFs to pediatric patients receiving treatment for cancer or undergoing HSCT for the purpose of mucositis prevention (strong recommendation, high-quality evidence).

Explanation: There were 5 RCTs evaluating GCSFs versus no GCSF (1 added to the 2021 update; Appendix 15). Products evaluated were lenograstim, filgrastim and pegfilgrastim. GCSFs did not significantly reduce severe mucositis (RR 0.95, 95% CI 0.75–1.21) compared with no prophylaxis. The strong recommendation against the use of GCSFs for the purpose of mucositis prevention was influenced by the absence of benefit, adverse effects and costs.

4. Discussion

In this pediatric mucositis prevention CPG 2021 update, a large number of new studies were identified since the conduct of our 2015 CPG, resulting in modification of previous recommendations and the addition of new recommendations. In contrast to the 2015 CPG, which made three conditional recommendations, the 2021 CPG update made two strong recommendations for the use of cryotherapy and photobiomodulation therapy in specific clinical circumstances and two strong recommendations against the routine use of palifermin and GCSFs for mucositis prevention. The factors facilitating strong recommendations included additional RCTs, more direct pediatric evidence and a more thorough evaluation of adverse effects and feasibility in pediatric patients. The 2021 CPG update also increased the specificity of its recommendations related to associated diagnoses and treatment regimens. This specificity may improve implementation.

The strength of this CPG was the seven separate systematic reviews, which provided the depth of evidence required to make fully informed recommendations. The utilization of an interdisciplinary and multinational group of experts with two patient advocates is another strength. However, a limitation of this CPG is that we did not conduct systematic reviews of all interventions examined in adult patients. Our approach presumes that the most promising interventions in adults will be studied in pediatric populations and, thus, will be included in the analysis. A second limitation is that we could not provide specificity around a lower age limit for cryotherapy utilization as this age is likely to vary by cognitive ability and cooperativeness.

In conclusion, cryotherapy should be used for older cooperative pediatric patients who will receive short infusions of melphalan or 5-flurouracil. Intraoral photobiomodulation therapy (620–750 nm spectrum) should be used in pediatric patients undergoing autologous or allogeneic HSCT and for pediatric head and neck carcinoma patients undergoing radiotherapy. Palifermin and GCSFs should not be used routinely in pediatric cancer or HSCT for the purpose of mucositis prevention. Tools for implementation will be important for the successful translation of these CPG recommendations to practice.

Authors' contributions

All the authors contributed to study concepts and design, data interpretation and drafting the manuscript or revising it critically for important intellectual content; gave final approval of version to be published and agreed to be accountable for all aspects of the work. P.P., P.D.R. and S.C. contributed to data acquisition. P.P. and P.D.R. performed data analysis.

Ethical approval

As this guideline is a systematic review of primary studies, no ethics committee/institutional review board approval was required.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: G.O.: Part-time employment at K-Laser d.o.o. company (Sezana, Slovenia); contract ended February 1, 2020, before her participation on the guideline panel. RP: Principal investigator for two mucositis trials and previous publication related to the objects of study. N.T.: Midatech Pharma, served as principal investigator for a single-site clinical trial that ended early. C.B., S.C., L.L.D., P.G., G.L., N.M., P.P., P.D.R., G.R.-R., L.S. and M.W. declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.05.013.

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